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THE ILLUSTRATED DICTIONARY OF TOXICOLOGIC PATHOLOGY AND SAFETY SCIENCE



PRITAM S. SAHOTA | ROBERT H. SPAET
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The Illustrated Dictionary of Toxicologic Pathology and Safety Science



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The Illustrated Dictionary of Toxicologic Pathology and Safety Science

Edited by
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Preface

There has been a growing interest in toxicologic pathology, particularly as related to its impact on the safety assessment of pharmaceuticals and chemicals, and in general drug development. The language of toxicologic pathology is unfamiliar to a broad range of safety scientists involved in the safety evaluation of pharmaceuticals and chemicals. Thus, there is a growing need for an Illustrated Dictionary of Toxicology Pathology and Safety Science (IDTP) that this publication aims to fill. The IDTP format provides the brevity, clarity, and conciseness that the user is unlikely to receive in a toxicologic pathology textbook, even if adequately indexed. With the inclusion of descriptions of terms used in general toxicology, drug metabolism/pharmacokinetics, safety pharmacology, genotoxicity, reproductive toxicology, and regulatory science, the scope of the IDTP is considerably broadened and decidedly unique in its appeal to all safety scientists. It is meant to be a one-stop, ready reference within arm's reach as a textbook, or as an e-book.

At over 600 pages and with more than 800 color images to provide visual context, an important aim of the IDTP is to present pathological changes as reference examples of terminology, nomenclature, and descriptions for all safety scientists including the entry-level as well as seasoned toxicologic pathologists. It will also aid non-pathology specialists such as study directors, contributing scientists, senior toxicology report reviewers, scientific management of contract research organizations, regulatory agencies, and drug development companies to better understand the biological significance of tissue changes. These users are often left with the task of translating pathology findings to Maximum Tolerated Doses (MTD), No Observed Adverse Effect Level (NOAEL), and Highest Non-Severely Toxic Dose (HNSTD) levels, and are then asked to justify these designations. The IDTP provides a single reference volume for these users to further their understanding and appreciation of biologically significant pathology findings in toxicology studies.

The IDTP will also be of interest to students in the biomedical sciences as well as non-scientists (e.g., individuals serving on animal care committees) to better understand the terminology used by the toxicologic pathologist and safety scientist, particularly as related to risk assessment. Students in the pharmaceutical and medical sciences have for generations referred to medical dictionaries, but essentially have had nowhere to go for practical toxicologic pathology and safety science terminology—until now.

The IDTP consists of four major areas:

1. A–Z Dictionary of Toxicologic Pathology (~70%) encompassing all organ systems, and non-pathology (~30%) terms supported by references in a "For Further Reading" section.
2. Appendix 1: Overview of Drug Development, Nonclinical Safety & Toxicologic Pathology, and Important/Special Topics with emphasis on the role of toxicologic pathology and current topics of interest (e.g., Adversity/NOAEL, Digital Pathology, Image Analysis, Developing Biologics, Vaccines).
3. Appendix 2: Diagnostic Criteria of Proliferative Lesions in Rodents (Rat and Mouse) and Selected Non-Rodent Laboratory Species with illustrations, detailed references, and links to source material.
4. Appendix 3: Mini-Atlas of Organ System Anatomy and Histology by organ system to help re-acquaint the non-pathology safety scientist with normal histology.

All rodent and non-rodent terms are described in the main alphabetized section of the book. In addition, rodent lesions and diagnostic criteria for proliferative lesions (neoplastic and non-neoplastic) are included in Appendix 2. Published international guidelines for diagnostic criteria for proliferative lesions are currently only available for rodents (e.g., International Harmonization of Nomenclature and Diagnostic Criteria [INHAND]); thus, there are no published international guidelines for non-rodents. As such, non-rodent proliferative terms described herein are based upon a review of the scientific literature.

Any book of this nature is only as good as the contributors who prepare the specific sections; thus, their selection was given careful consideration. Contributors were chosen for their knowledge, expertise, and focused interest on a topic or organ system. While multiple potential authors may be able to develop a treatise on a topic based on literature reviews, extensive knowledge and expertise based on the personal experience of navigating tough toxicologic pathology issues that often do not appear in the literature add a critical dimension. Therefore, the IDTP was designed to present important information, both published and unpublished, as gained through personal experience, so this knowledge can be used by others to improve the quality of drug safety evaluation. The IDTP editors and over 70 contributing scientists (board-certified veterinary pathologists, board-certified toxicologists, allied health safety scientists, health regulatory representatives) have experience from bench-level pathology and other safety sciences to managing global preclinical safety units in leading pharmaceutical companies. They all have considerable experience mentoring pharmaceutical industry project team members, interacting with industry clinicians and representatives of decision-making bodies within the industry, as well as with global health authorities, such as the FDA and EMA. These activities convinced the editors of the necessity for and usefulness of the IDTP. As experts in their field, they have undertaken the hard work of writing and compiling the information,

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making the IDTP a one-of-a kind resource. We are indebted to all the contributors for organizing and summarizing the most current information available in the literature, for sharing their expertise and knowledge on the subject matter, and for incorporating all this into this one volume, the IDTP.

All procedures used to prepare macroscopic and microscopic images of animal specimens for the IDTP were performed in accordance with regulations and established guidelines for humane treatment of research animals, and were reviewed and approved in advance by an institutional animal care and use committee.

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Robert H. Spaet
Philip Bentley
Zbigniew W. Wojcinski

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Acknowledgments

The editors wish to acknowledge and extend heartfelt thanks to the more than 70 individuals who made valuable contributions toward the writing of *The Illustrated Dictionary of Toxicologic Pathology and Safety Science* (IDTP), and without whom it would never have been possible. Through their expertise and long experience in the field of toxicologic pathology and safety science, their efforts have ensured the scientific accuracy and comprehensiveness of the text and quality of the photomicrographic material.

As a seminal work in the area of toxicologic pathology and the allied safety sciences, the IDTP required careful thought and planning in collating the vast amount of necessary information. Moreover, it was essential that the material be presented in a clear and concise manner that would best suit a broad readership. In this regard, the editors would like to formally recognize the IDTP Advisors who provided the guidance to achieve this goal: Shayne C. Gad, Peter Greaves, Ramesh C. Gupta, Jerry F. Hardisty, Charlotte M. Keenan, and James A. Popp. These individuals provided sage advice on developing general guidelines for the contributors who generated the A–Z term descriptions, and on preparing guidance in the preparation of the Appendices. In particular, the editors would like to acknowledge Shayne C. Gad for his contributions in the writing of Appendix 1 and to Charlotte M. Keenan for sharing her expert advice on the use of INHAND and Standard for Exchange of Nonclinical Data (SEND) terminology with the IDTP contributors and editors. The editors would also like to thank Charlotte M. Keenan for her support in obtaining photomicrographic material of proliferative lesions from various external sources; review of several sections of the IDTP, and valuable contributions to the General Pathology and Appendix 2 teams. We additionally want to thank Dr. Phil Long for his expert review of the Bone/Muscle/Tooth terms and descriptions. We are grateful to all our advisors for making themselves available to the editors during planning, preparation, and finalization stages of the IDTP.

As one can imagine, suitable illustrative material is critical to this type of work. In this regard, we would like to especially thank Gregory Argentieri for his outstanding contributions as Illustrations Editor, Dropbox Administrator, and Content Liaison to CRC Press/Taylor & Francis, as well as his skillful contributions to the post processing of images, photocomposition, and photo layout. A special thanks goes to Oliver C. Turner for carefully reviewing the figures and legends from an experienced pathologist's perspective. The successful completion of IDTP with over 800 images would not have been possible without the unwavering dedication of Gregory and Oliver, and their willingness to devote considerable time to this formidable project. We are deeply indebted to Ron Herbert, Head, Pathology Support Group, Cellular and Molecular Pathology Branch, National Toxicology Program for guiding the IDTP contributors to the critical image resources provided by that agency, as well as, Emily Singletary, Digital Image Supervisor at EPL who helped get the process rolling.

The editors want to extend a special acknowledgement to Stacey Fossey who assumed the responsibility as Lead Contributor for two major "Organ Systems": General Pathology and Bone/Muscle/Tooth. Dr. Fossey repeatedly stepped up to the plate to fill the vacuum at critical stages during the writing of this book. The editors wish to acknowledge the excellent working relationship we have had with the CRC Press/Taylor & Francis staff, especially Laura Piedrahita, Danielle Zarfati, Jonathan Achorn, and Stephen Zollo that resulted in expert advice and timely responses to their many inquiries. We also want to thank Ms. Annie Lubinsky, Project Manager at Nova Techset, who helped bring the IDTP project over the finish line. Lastly, we also want to acknowledge Tom Curtis of Plus Equals Media for creating the IDTP cover art, and Ms. Carolyn Frank, aspiring young medical illustrator, who created Figure 8 in Appendix 3 of the Nervous System pictorially describing cerebrospinal fluid circulation in the brain of a cynomolgus macaque.

Finally, the editors acknowledge the ongoing work of all INHAND (International Harmonization of Nomenclature and Diagnostic Criteria) working groups. This global effort involves teams of expert pathologists from around the world convened to consider the most appropriate diagnoses and terminologies to be used by toxicologic pathologists. Working groups were subdivided by species and organ system to recommend harmonized and appropriate diagnoses of proliferative and nonproliferative lesions, requiring considerable effort and communication to create each manuscript. Going forward, the INHAND publications will enable better communication and understanding globally for diagnostic terms that have precise meanings but remain subject to context of use. The organization and framework of the IDTP relied heavily on the expertise and recommendations made by the various INHAND working groups. Short descriptions of the INHAND-preferred proliferative terms appear in the A–Z section, while the corresponding comprehensive descriptions of these terms, many accompanied by representative photomicrographs, appear in Appendix 2. Citations for all INHAND publications currently available as of the publication date of the IDTP, can be found under "For Further Reading by Organ System." New manuscripts produced by INHAND working groups will become available at the following link: https://www.toxpath.org/inhand.asp.

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Editors

Pritam S. Sahota, Global ToxPath, LLC, Kennewick, Washington, has extensive experience in toxicologic pathology and drug development within the framework of nonclinical safety assessment of pharmaceuticals, He was Executive Director and Head of Pathology, Preclinical Safety, Novartis Pharmaceuticals, East Hanover, New Jersey (2004–2010). Dr. Sahota obtained his veterinary medicine (BVSc) and veterinary pathology degrees (MSc and PhD) from Punjab Agricultural University, India. He is a Diplomate of the American Board of Toxicology. After receiving his PhD in 1976, Dr. Sahota started working as a toxicologic pathologist at Dawson Research Corporation (DRC), Orlando, Florida; a contract research organization involved in the preclinical safety evaluation of drugs and chemicals. In DRC, he received increasing responsibilities over the next 10 years [Pathologist→Senior Pathologist→Scientific Director]. As Scientific Director, he assumed overall responsibility for pathology and toxicology at DRC. While working briefly for Dynamac Corporation, Research Triangle Park, North Carolina (1986–1987), Dr. Sahota conducted retrospective scientific audits of over 20 rodent carcinogenicity studies of National Toxicology Program (NTP) and participated in discussions with the representatives of the NTP, FDA, and EPA in reviewing the results of scientific audits of >200 NTP carcinogenicity studies. In 1987, Dr. Sahota joined Ciba-Geigy Pharmaceuticals in New Jersey as Manager of Pathologists in Preclinical Safety and was responsible for establishing pathology peer review, quality control, and scheduling systems. He continued to work primarily in this position with increasing responsibilities at CIBA and then Novartis Pharmaceuticals (after Ciba-Sandoz merger in 1996) to become Director and eventually Executive Director/Head of pathology. During this time, he also served as an International Project Team Representative for a number of successfully marketed CNS, immunosuppression, diabetes, and cardiovascular drugs, including Diovan, which eventually became one of 15 all-time best-selling prescription drugs. Dr. Sahota also held an adjunct academic appointment at the University of Medicine and Dentistry, New Jersey, for 8 years. He successfully led several global preclinical safety initiatives at Novartis, including patient centricity, review of best practices in cardio and ocular toxicity, and as well as evaluation of rodent carcinogenicity potential of early developmental compounds based on non-carcinogenicity data to minimize future delays in regulatory submissions. As Lead Editor of *Toxicologic Pathology – Nonclinical Safety Assessment* (CRC Press), he participated in the submission of a manuscript for the second edition in 2018.

Robert H. Spaet is Principal Consultant for RSPathologics, LLC, Granby, Colorado. He obtained his BS and MS degrees in zoology from Eastern Illinois University (1971, 1973). He began his career as a Sr. Research Technician at the Franklin McClean Memorial Research Institute, University of Chicago, before joining GD Searle Laboratories in Skokie, Illinois, as a Parapathologist (1973–1976). He became a Research and Teaching Assistant at the University of Oklahoma Health Sciences Center in Oklahoma City, Oklahoma, and completed the coursework toward a PhD in anatomic and experimental pathology (1975–1977) before joining Ciba-Geigy Pharmaceuticals in June 1977 as a Scientist II in Pathology, Preclinical Safety. He also completed his oral and written exams for a PhD degree in anatomic pathology at University of Medicine and Dentistry of New Jersey, Newark, New Jersey (UMDNJ), in 1984 while working for CIBA. His core training and expertise lies in toxicologic pathology within the framework of drug safety evaluation. He has also had full-time experience as a Study Director and is certified as a Diplomate, American Board of Toxicology. He has written many scientific papers in the field of toxicology and toxicologic pathology and holds full membership in several prominent professional societies including the Society of Toxicologic Pathologists (U.S. and Europe), Society of Toxicology, American College of Toxicology, and is a member of the Roundtable of Toxicology Consultants. Dr. Spaet has more than 40 years of experience in toxicologic pathology and regulatory toxicology. During his tenure with CIBA and Novartis (merger of CIBA and Sandoz), he held a series of positions of increasing responsibility to eventually become Director, Translational Sciences, Preclinical Safety, Department of Pathology. His professional experience was broadened as an Exchange Scientist with CIBA in Basel, Switzerland (1987–1988). Among other professional activities, he participated in the team teaching of pathology as Adjunct Instructor in the School of Allied Health Sciences at UMDNJ. Since 1986, he served as an International Project Team Preclinical Safety representative for a number of compounds in development, including several medically significant marketed pharmaceuticals. Within this capacity he has authored extensive safety summaries in support of IND/NDA/CTX drug submissions and represented the company as a preclinical safety expert before regulatory agencies such as the FDA and EMEA. Dr. Spaet is a member of several high-profile groups including the Society of Toxicologic Pathology's Science and Regulatory Policy Committee, the STP Membership Committee, and the European Society of Toxicologic Pathology Committee on Future Technologies in Toxicologic Pathology.

Philip Bentley is Principal Consultant at Toxicodynamix International LLC, Hendersonville, North Carolina. He studied biochemistry at the University of Hull, UK, graduating with a BSc in 1970 and a PhD in 1974. He had postdoctoral fellowships at the Universities of Basel, Switzerland and Mainz, Germany. His postdoctoral research centered on the

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formation and inactivation of reactive metabolites and the enzymes involved in the metabolism of foreign compounds. In 1979, he joined the Investigative Toxicology group (Cell Biology) in the Toxicology Department of Ciba-Geigy, Basel, Switzerland and remained with the company, later Novartis, until 2014. In these 35 years he held various management positions in Europe and the United States with responsibility for Investigative Toxicology; Drug Metabolism; Drug Metabolism and Toxicology; Preclinical Safety Europe; Drug Metabolism and Pharmacokinetics; Toxicology/Pathology USA; Preclinical Safety USA and Global Preclinical Safety. In these positions, he contributed to the registration of more than 45 marketed drug products and the preparation of several hundred INDs. He has vast experience in the areas of drug metabolism and disposition, toxicology/pathology, genetic toxicology, pharmacokinetics/toxicokinetics, and all aspects of investigative toxicology. He is well grounded in biochemistry, cell biology, molecular biology, and pharmacology with the ability to integrate data from the different preclinical disciplines to enable translation to determine the clinical relevance of the findings. He is very familiar with global drug registration requirements and working on global projects.

He has authored more than 80 scientific publications, has lectured in toxicology at the University of Basel for more than 30 years, and is a Past President of the European Society of Biochemical Pharmacology and the Swiss Society of Toxicology. He was a member of the PhRMA/IQ Preclinical Leadership (DruSafe) Committee for 16 years, a member of the advisory board of the PSTC Biomarker consortium, and a member of the expert working group for revision of the ICH S2 guidance on genotoxicity testing and the PhRMA expert group on genotoxic impurities.

Zbigniew W. Wojcinski is President of Toxicology & Pathology Consulting, LLC, in Ann Arbor, Michigan and has over 30 years of experience in drug development. Dr. Wojcinski received his undergraduate degree (BSc) in zoology from the University of Toronto and his DVM and DVSc. (pathology) degrees from the Ontario Veterinary College, University of Guelph. He is a certified Diplomate of the American Board of Toxicology and a Diplomate of the American College of Veterinary Pathologists. He is also recognized as a Specialist in Veterinary Pathology by the Canadian Veterinary Medical Association. Dr. Wojcinski gained experience in drug development and toxicologic pathology during his 22-year tenure with Parke-Davis\Warner-Lambert and Pfizer Global Research and Development and then more than 3 years with Fulcrum Pharma Developments, Inc. In 2011, he founded Drug Development Pathology Services, LLC, in Ann Arbor, and subsequently grew the organization into Drug Development Preclinical Services, LLC to provide toxicology, pathology, and drug metabolism and pharmacokinetic services. Dr. Wojcinski has extensive experience as a Study Director, Study Pathologist, and Review Pathologist for numerous acute and repeated-dose toxicity studies, including carcinogenicity studies. Throughout his career, he has managed successful cross-functional drug development teams in CNS, metabolic diseases, and dermatology therapeutic areas. As Therapeutic Area Leader for Dermatology at Pfizer, Dr. Wojcinski was responsible for development and implementation of the safety and risk management strategies for, what was then, a new therapeutic area. He has also been directly involved in the preparation of pre-IND documents, Nonclinical Safety Assessments for IND/IMPD/NDA/MAA, Investigators Brochures, and labeling (USPI, SmPC) negotiations in CNS, anti-infective, and dermatology therapeutic areas. He has had numerous interactions with regulatory agencies in the United States, Europe, Canada, and Australia for compounds at various stages of development. He has also provided pathology consultation and histopathology peer review on several projects in various therapeutic areas, including respiratory infections, dermatitis, and ophthalmic disease and served on pathology working groups. Dr. Wojcinski is a full member of numerous professional societies including the American College of Veterinary Pathologists, Society of Toxicologic Pathologists, Society of Toxicology, American College of Toxicology, American Veterinary Medical Association, Canadian Veterinary Medical Association, Canadian Association of Veterinary Pathologists, Regulatory Affairs Professionals Society, and Roundtable of Toxicology Consultants. He has served as President of the Dermal Toxicity Specialty Section of the Society of Toxicology, an Associate Editor for the Society of Toxicologic Pathology, Editor of *The Scope* for the Society of Toxicologic Pathology, and Chair of the Society of Toxicologic Pathology Recruitment Subcommittee. Dr. Wojcinski has lectured at the Ontario Veterinary College and the University of Maryland and authored/co-authored numerous scientific reports, manuscripts, and book chapters.

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As advisors to the plans and subsequent steps in completion of the IDTP, we are delighted to see that the final product has achieved the important objectives established for this book. The authors and editors are to be commended for their dedication to the completion of this monumental effort. The IDTP will undoubtedly be a unique and valuable resource for pathologists and toxicologists as they address safety assessment and regulatory issues for many years in the future.

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AAALAC is an acronym for Association for the Assessment and Accreditation of Laboratory Animal Care, whose duties are to promote the humane treatment of animals in science.

AAAS is an acronym for the American Association for the Advancement of Science.

AACT is an acronym for the American Academy of Clinical Toxicology.

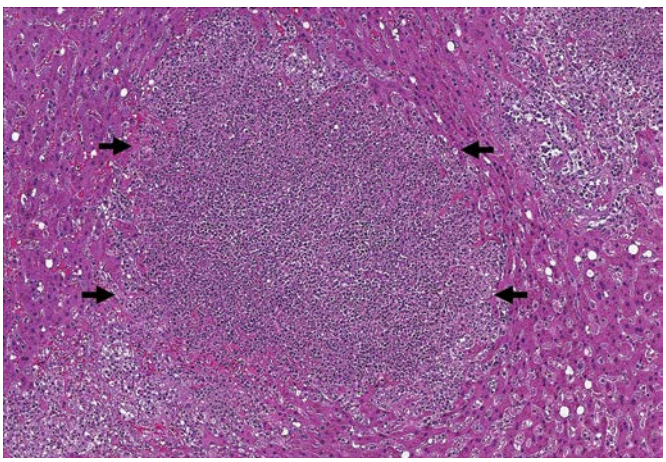
ABC-binding cassette transporters are a family of active transporters that have an ATP binding site (ATP-binding cassette) and are responsible for the transport of drugs both into and out of cells. Effects of the latter on transporters are studied to understand the factors affecting the distribution of a drug candidate and to predict potential drug-drug interactions through effects on transporter activity. Important ABC-binding cassette transporters are MDR1, BCRP, and BSEP. See **Drug transporters** for further information.

Abnormal base analogs are nucleic acid bases that are not the native ones in DNA (adenine, cytosine, guanine, thymine) or RNA (adenine, cytosine, guanine, uridine). These nucleic acid bases can be incorporated during cell replication and lead to mutation or cell death. They are used therapeutically for tumor or viral therapy.

Abnormal embryo-fetal development is related to mortality, dysmorphogenesis (structural abnormalities), alterations to growth (growth retardation) and/or functional impairment (behavioral teratology).

Abrikosoff's tumor, see the preferred term **Accessory male sex organs, granular cell tumor, benign**.

Abscess is a circumscribed accumulation of inflammatory cells with necrotic cell debris and fluid (pus) within a tissue. Abscesses may be visible grossly or may be noted only microscopically (microabscess). Acute abscesses are dominated by neutrophils that arrive within minutes at the site of infection. The combined activity of the pathogen with the release of the neutrophil's lysosomal contents, oxygen-derived free radicals, neuropeptides, and chemokines results in localized tissue damage that may escalate the inflammatory response or may eliminate the infection to allow resolution with restoration of normal tissue function. If the infection is persistent, peripheral fibroblastic proliferation and chronic inflammatory infiltrates (lymphocytes, plasma cells, macrophages) become major components of the lesion. The latter may become isolated within fibrous tissue (walled-off abscess) or may resolve by scar formation. Although abscesses are most commonly associated with infectious agents, sterile abscesses may be associated with irritants, such as subcutaneously applied drugs or foreign material. Abscesses associated with fungal or parasitic infections may have a significant eosinophilic inflammatory cell component in conjunction with the neutrophils.



Abscess in the liver of a nonhuman primate, H&E. There is accumulation of inflammatory cells and necrotic cell debris within the liver as outlined by the arrows.

Absolute bioavailability is the amount of a nonintravenously administered drug (e.g., oral, inhaled, intramuscular, subcutaneous, etc.) which reaches the systemic circulation as active drug compared to the amount of active drug in the circulation following intravenous administration of the same dose. Absolute bioavailability is calculated by dividing the dose-corrected integral drug systemic exposure (area under the plasma concentration time curve [AUC]) via the non-intravenous route, by the integral drug systemic exposure via the intravenous route. For example, for oral administration:

$$F = 100 \times (AUC_{0\text{-}\infty})_{oral}/(AUC_{0\text{-}\infty})_{iv} \times (dose)_{iv}/(dose)_{oral}$$

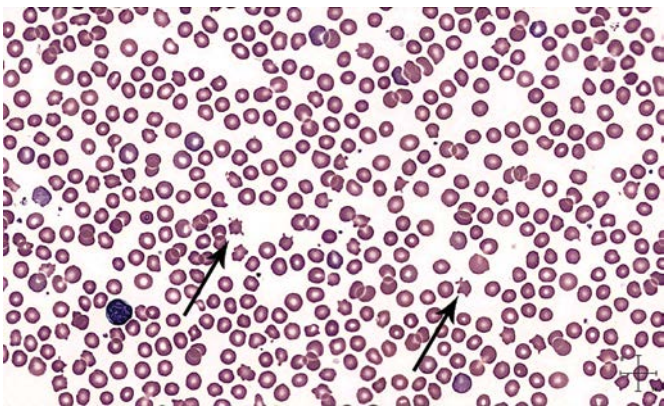
Absorption is the process of uptake of a drug into the systemic circulation from the site of application; for example, uptake from the gastrointestinal tract after oral intake. Passive absorption is a function of the physiochemical properties of the drug (lipophilicity, solubility, etc.). Drugs may also be subject to active uptake, which is also a function of the affinity for the respective drug transporter.

Acanthocyte is an abnormally shaped red blood cell in which the erythrocytes are densely contracted and have irregularly placed horny projections or spikes of varying lengths. They

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have also been called spur cells. The mechanism of acanthocyte formation involves alteration of the red cell membrane lipid composition and fluidity. Classically, they are associated with abetalipoproteinemia (Bassen-Kornzweig syndrome) and spur cell hemolytic anemia of severe liver disease. However, they are less frequently found in a number of other conditions including alcoholic cirrhosis, anorexia nervosa and other malnourished states, vitamin E deficiency in the newborn, hypothyroidism, hypopituitarism, the McLeod phenotype in individuals of the Kell blood group system, and in individuals with the Rhesus (Rh) null blood type. It is important to distinguish true acanthocytes from echinocytes or schistocytes, as they are produced by differing mechanisms.



Acanthocytes, rabbit. The image shows the variable length and width and uneven distribution of spicules found on true acanthocytes (arrows).

Acantholysis is the loss of cell-cell junctional integrity by keratinocytes, resulting in loss of intercellular cohesion. Keratinocytes that have undergone acantholysis are often referred to as acantholytic cells. Acantholysis and the presence of acantholytic cells is a characteristic of immune-mediated dermatoses that disrupt epidermal junctional attachments such as pemphigus vulgaris and pemphigus foliaceous. Acantholysis is also seen in some forms of skin cancer.

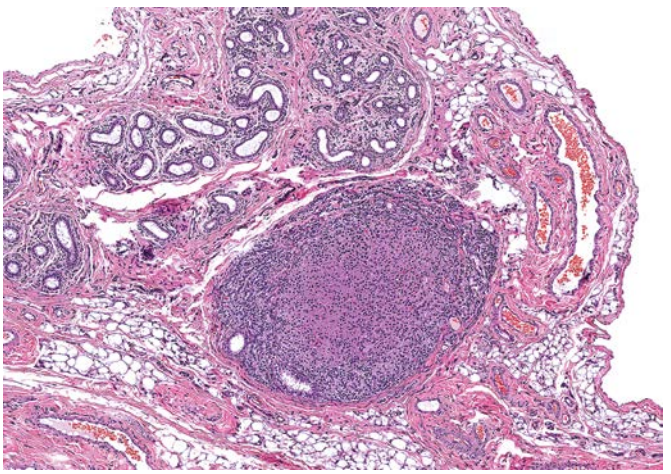
Acanthoma, infundibular, keratinizing, see the preferred term **Keratoacanthoma**.

Acanthosis, see the preferred term **Epidermal hyperplasia**.

Acceptable daily intake (ADI) is the amount of an agent found in food or drinking water which may be consumed per day throughout a lifetime without an appreciable risk to health. The concept was originally developed for food additives that were deliberately included in foodstuffs but was later extended to include residues in the food from pesticides, pharmaceuticals, veterinary drugs, and pollutants in drinking water. The ADI is estimated from the no observed adverse effect level (NOAEL) in toxicity studies. A similar approach is taken for the qualification of impurities in drug substance or drug product in the pharmaceutical industry, where the permitted daily exposure (PDE) is estimated.

Accessory adrenal cortical tissue is the presence of normal adrenal cortical tissue outside of the adrenal gland capsule or in the adjacent tissues. It may be surrounded by a fibrous capsule and may lack the normal zonal arrangement of the adrenal cortex and medullary cells. It is most commonly found in the fat surrounding the adrenal gland and kidney, although may be found anywhere in the peritoneal cavity.

Synonym(s): **Adrenal gland, ectopic**; **adrenal rest**; **adrenocortical tissue, ectopic**; **adrenocortical rest**; **adrenal extracortical nodule**; **adrenocortical choristoma**.



Accessory adrenal gland in the epididymis, cynomolgus monkey, H&E.

Accessory male sex organ acinar cystic dilation, see the preferred term **Accessory male sex organs, acinar/vesicle dilation**.

Accessory male sex organ acinar distension, see the preferred term **Accessory male sex organs, acinar/vesicle dilation**.

Accessory male sex organ acinar/vesicle dilation (prostate, coagulating gland, seminal vesicle, ampullary gland, bulbourethral gland, and preputial gland) is characterized by focal or diffuse acinar/vesicle distension due to the accumulation of secretory fluids. Treatment-related hyperprolactinemia and hyperandrogenism cause diffuse acinar or vesicle dilation due to increased secretory activity accompanied by a varying degree of thinning of acinar/vesicular walls. Changes in organ weight are the most sensitive method to detect treatment-related acinar/vesicular dilation. Acinar/vesicle dilation of the seminal vesicle and coagulating gland is a common age-related finding in rodents, possibly due to the accumulation of secretory contents associated with sexual inactivity, and declining testosterone levels. Acinar/vesicle dilation may be associated with urethral obstruction in rodents, and in mice occurs secondary to ascending urinary tract infections. The modifier "cystic" is used when dilatation is associated with reduction or loss of epithelial papillary folds, flattening of epithelium, and compression of the adjacent structures. Cystic dilation of acini/vesicles has been described in the prostate and bulbourethral gland of aging

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rodents. See **Prostate**, **Coagulating gland**, **Seminal vesicle**, **Ampullary gland**, **Bulbourethral gland**, and **Preputial gland** for further information.

Synonym(s): **Accessory male sex organ acinar distension**; **accessory male sex organ acinar cystic dilation**.



Dilated (cystic) acinus, seminal vesicle, F344/N rat, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

Accessory male sex organ adenoma (prostate, seminal vesicle, coagulating gland) is an uncommon (prostate or seminal vesicle) or rare (coagulating gland) group of benign neoplasms arising from the glandular epithelial cells of these organs. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Accessory male sex organ apoptosis, see the preferred term **Accessory male sex organ single cell epithelial necrosis**.

Accessory male sex organ arteritis, see the preferred term **Accessory male sex organ vascular/perivascular necrosis/inflammation**.

Accessory male sex organ atrophy (prostate, seminal vesicle, coagulating gland, and/or bulbourethral gland) is characterized by the partial or complete absence of secretions in an acinar/vesicle lumen that may be cystic and/or have crowding of acinar/vesicle epithelial folds. The epithelial surface is attenuated or flattened, and epithelial cells have reduced or absent cytoplasmic secretory droplets. Atrophy is generally associated with decreased androgen levels as seen with aging, castration, or chronic androgen depletion. Decreased androgens result in reduced size and weight of the end organ, the latter being a better indicator of atrophy than histologic correlates. Atrophy due to aging is often associated with increased stroma, presence of epithelial lipofuscin pigmentation, acini/ducts with intraluminal proteinaceous fluid and cellular debris, and/or complete absence of secretions.

Differential diagnosis: **Accessory male sex organ hypoplasia**.

Accessory male sex organ concretions (prostate, seminal vesicle, coagulating gland, and/or bulbourethral gland) are a very common, age-related change in rodents associated with acinar atrophy of accessory male sex organs. Concretions are round and homogenous or concentrically laminated bodies that are usually eosinophilic but may be basophilic and mineralized. They form because of compaction of small hyaline masses of degenerate cells. They are more common in the lumen of the prostate.

Synonym(s): **Accessory male sex organ corpora amylacea**.

Accessory male sex organ corpora amylacea, see the preferred term **Accessory male sex organ concretions**.

Accessory male sex organ epithelial vacuolation (prostate, coagulating gland, seminal vesicle, ampullary gland, bulbourethral gland, and preputial gland) may stem from the accumulation of secretory fluids, lipids, phospholipids, or glycoproteins. Vacuolation is characterized as either macro- or microvesicular. Microscopically, the epithelial cell morphology is distorted, and the nucleus is displaced. Phospholipidosis can induce diffuse vacuolation of the seminal vesicles and prostate.

Synonym(s): **Accessory male sex organ vacuolar degeneration**; **accessory male sex organ vesicular or hydropic degeneration**.

Accessory male sex organ hypoplasia (prostate, seminal vesicle, coagulating gland, and/or bulbourethral gland) is a rare congenital abnormality consisting of the underdevelopment of organ(s). It has been observed in transgenic rodent strains such as the 5alpha-reductase type 2 knockout mouse (prostatic hypoplasia), as well as in male Sprague-Dawley rats exposed in utero to di-*n*-butyl) phthalate (prostate and seminal vesicle hypoplasia). There is a macroscopic size reduction relative to the animal's overall body size and state of reproductive maturity. Lobe malformation may occur, as well as reduced secretions.

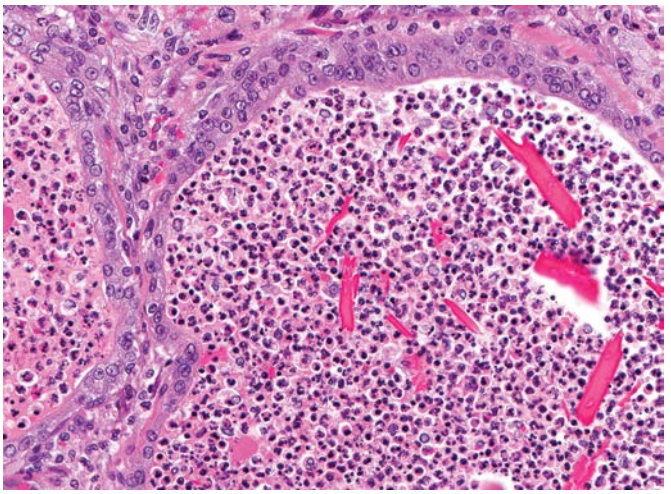
Differential diagnosis: **Accessory male sex organ atrophy**.

Accessory male sex organ inflammation (prostate, coagulating gland, seminal vesicle, bulbourethral gland, and preputial glands) is a common, spontaneous, age-related background finding in rats and mice. It is generally due to tissue injury or necrosis because of ascending bacterial urogenital infections. Underlying causes include fighting with cage mates, and/or infections with *Staphylococcus aureus* or *Pasteurella pneumotropica*. In transgenic mice, urinary stasis and/or immunologic or inflammatory alterations have been known to result in prostatic inflammation. Hyperprolactemia or hyperestrogenemia can result in prostatic inflammation, and the former is sometimes correlated with an increased incidence of pituitary gland tumors in aging rodents. Different accessory glands and regions vary in their susceptibility to inflammation; the dorsolateral prostate lobe is the most susceptible, followed by the ventral lobe, coagulating gland, and then the seminal vesicle. Macroscopically, perineal enlargement may be noted due to swelling of the bulbourethral glands. Microscopic features include focally extensive to diffuse purulent or pyogranulomatous inflammation that may

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be accompanied by epithelial squamous metaplasia or vacuolar degeneration and interstitial fibrosis.

Differential diagnosis: **Accessory male sex organ inflammatory cell infiltrate**.



Neutrophilic inflammation, prostate, rat, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

Accessory male sex organ inflammatory cell infiltrate (prostate, seminal vesicle, coagulating gland) consists of small focal accumulations of inflammatory cells, most commonly composed of lymphocytes, which may reside in the interstitium, perivascularly, and may also be intraluminal. Microabscesses composed of mixed inflammatory cells may be noted as a background finding in the adipose tissue adjacent to the epididymis. The pathogenesis is often unknown, but may represent an early stage of inflammation, and could indicate sperm stasis. Inflammatory cell infiltration is the preferred diagnostic term when other inflammatory changes (degeneration/necrosis, edema/congestion/hemorrhage, fibrosis, regeneration) are not observed.

Differential diagnosis: **Accessory male sex organ inflammation**.

Synonym(s): **Accessory male sex organ lymphocytic infiltrate**; **accessory male sex organs mononuclear cell infiltrate**.

Accessory male sex organ lymphocytic infiltrate, see the preferred term **Accessory male sex organ inflammatory cell infiltrate**.

Accessory male sex organ metaplasia (prostate, seminal vesicle, coagulating gland, and/or bulbourethral gland) is characterized by replacement of the normal secretory epithelium by mucinous, squamous, or transitional cells. Metaplasia may be incidental or result from inflammatory-mediated tissue damage, nutritional deficiencies, or hormonal perturbations. As background lesions, metaplastic changes have been noted most commonly in the prostate of mice, especially transgenics. Treatment with estrogens (e.g., zearalenone) results in squamous metaplasia of the coagulating gland (i.e., anterior prostate), dorsal prostate, and seminal vesicle of rodents, and prostatic squamous metaplasia in dogs. Experimentally induced hypovitaminosis A in rats and mice results in squamous metaplasia of the accessory sex glands, beginning as a layer of squamous epithelium overlying the original luminal epithelium of the seminal vesicle, coagulating gland, ductus deferens, and dorsal prostate.

Accessory male sex organ mononuclear cell infiltrate, see the preferred term **Accessory male sex organ inflammatory cell infiltrate**.

Accessory male sex organ periarteritis, see the preferred term **Accessory male sex organ vascular/perivascular necrosis/inflammation**.

Accessory male sex organ perivascular inflammation, see the preferred term **Accessory male sex organ vascular/perivascular necrosis/inflammation**.

Accessory male sex organ polyarteritis nodosa, see the preferred term **Accessory male sex organ vascular/perivascular necrosis/inflammation**.

Accessory male sex organs include the prostate, coagulating gland or anterior prostate, seminal vesicle, ampullary gland, bulbourethral gland, urethral gland, and preputial gland in mammals. All these glands are present in rats and mice. The prostate and ampullary gland are the accessory sex glands in male dogs. The prostate, seminal vesicles, and bulbourethral glands are the accessory sex glands of male monkeys. The secretions of these glands nourish and activate sperm, clear the urethral tract prior to ejaculation, transport the sperm in the female tract, and create a copulatory plug to help ensure fertilization. The accessory organs are sex-hormone dependent, and their detailed histological examination often reflects changes in spontaneous aging or treatment-related hormone status. See Appendix 3 and **Prostate**, **Coagulating gland**, **Seminal vesicle**, **Ampullary gland**, **Bulbourethral gland**, and **Preputial gland** for further information.

Accessory male sex organs, adaptive hyperplasia, see the preferred term **Accessory male sex organs, hyperplasia, functional**.

Accessory male sex organs, adenocarcinoma (prostate, seminal vesicle, coagulating gland) is an uncommon (prostate or seminal vesicle) or rare (coagulating gland) group of malignant neoplasms arising from the glandular epithelial cells of these organs. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Accessory male sex organs, adenomatous hyperplasia, see the preferred term **Accessory male sex organs, atypical hyperplasia**.

Accessory male sex organs, agenesis, see the preferred term **Accessory male sex organs, aplasia.**

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Accessory male sex organs, angiectasis (prostate, seminal vesicle, coagulating gland, and/or bulbourethral gland) is a spontaneous age-related change characterized by irregularly dilated urethral vessels filled with blood, and lined by a single layer of normal endothelium. These lesions may occur secondary to occlusion, thrombosis, or hypertension.

Accessory male sex organs, aplasia (prostate, seminal vesicle, coagulating gland, and/or bulbourethral gland) is a developmental disorder with the absence of an organ due to failure of the development of its primordium during embryonic development. Congenital aplasia is an uncommon finding in rodents, but reported in some transgenic mice. Examples include prostatic aplasia in 5α-reductase type 2, p63, and Sox9 knockout mice, seminal vesicle aplasia in Pax2 and Emx2 knockout mice, and bulbourethral gland aplasia in Hoxa-10 and Hoxa-11 knockout mice. Heterozygote and homozygote Hoxa-13 knockout mice, and rodents exposed in utero to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and di(*n*-butyl) phthalate (DBP) show aplasia of multiple accessory male sex organs.

Differential diagnosis: **Accessory male sex organ hypoplasia**.

Synonym(s): **Accessory male sex organs, agenesis**.

Accessory male sex organs, atypical hyperplasia (prostate, seminal vesicle, coagulating gland, and/or bulbourethral gland) is the focal or multifocal proliferation of the glandular epithelium in the ventral prostate, dorsolateral prostate, seminal vesicle, or coagulating gland. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Accessory male sex organs, benign myoblastoma, see the preferred term **Accessory male sex organs, granular cell tumor, benign**.

Accessory male sex organs, carcinosarcoma (prostate, seminal vesicle, coagulating gland, and/or bulbourethral gland) is a rare, locally invasive neoplasm composed of spindle cells, pleomorphic cells, and/or homogenous large polygonal, epithelial-like cells within an adenocarcinoma. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Accessory male sex organs, dysplasia, see the preferred term **Accessory male sex organs, atypical hyperplasia**.

Accessory male sex organs, focal hyperplasia, see the preferred term **Accessory male sex organs, atypical hyperplasia**.

Accessory male sex organs, granular cell tumor, benign (prostate, seminal vesicle, coagulating gland) is a rare, benign tumor in the rat and mouse, which may originate from the Schwann or mesenchymal cell. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Accessory male sex organs, granular cell tumor, malignant (prostate, seminal vesicle, coagulating gland) is a rare, malignant tumor in the rat and mouse, which may originate from the Schwann or mesenchymal cell. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Accessory male sex organs, hyperplasia, functional, (prostate, seminal vesicle, coagulating gland) occurs in response to increased functional demand and consists of epithelial hypertrophy and hyperplasia. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Accessory male sex organ single cell epithelial necrosis (prostate, seminal vesicle, coagulating glands, bulbourethral glands) is a form of programmed cell death (i.e., apoptosis) due to a series of intracellular signals and events. It is not accompanied by inflammation. Individual necrotic epithelial cells contain condensed or fragmented nuclei and reduced amounts of hyper-eosinophilic cytoplasm. Acute androgen reduction may be a causative factor. Application of terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) can be employed to confirm the presence of epithelial single cell necrosis.

Synonym(s): **Accessory male sex organ apoptosis**.

Accessory male sex organs, mesenchymal proliferative lesion (prostate, seminal vesicle, coagulating gland, and/or bulbourethral gland) is usually a spontaneous, benign, subepithelial, decidual-like reaction composed of collections of large epithelial cells with peripheral fibrocyte- or smooth muscle-like spindle cells and mononuclear cells. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Accessory male sex organs, mesenchymal tumor, see the preferred term **Accessory male sex organs, mesenchymal proliferative lesion**.

Accessory male sex organs, reactive hyperplasia (prostate, seminal vesicle, coagulating gland) is a particularly common change in dorsolateral lobes of mice prostate and is commonly associated with inflammatory lesions resulting from urogenital infections. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Accessory male sex organs, simple hyperplasia, see the preferred term **Accessory male sex organs, hyperplasia, functional**.

Accessory male sex organs, squamous cell carcinoma (prostate, coagulating gland, preputial gland) is a malignant tumor derived from metaplastic epithelial cells in the glands or ducts. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Accessory male sex organs, squamous cell papilloma (prostate, coagulating gland, preputial gland) is a very rare benign tumor that arises from metaplastic epithelium in the glands or ducts, and can be associated with keratinization. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

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Accessory male sex organ stromal fibrosis (prostate, coagulating gland, seminal vesicle, ampullary gland, bulbourethral gland, and preputial gland) is a relative increase in the ratio of stromal to glandular tissue due to an accumulation of interstitial collagen, or wide bands of dense connective tissue that may completely disrupt normal tissue architecture. In rodents, stromal fibrosis is associated with administration of estrogenic compounds, loss of androgen support, chronic inflammation, or alterations in growth factors and/or extracellular matrix. In the case of chronic estrogen administration, additional findings include decreased secretion, epithelial atrophy, and hyperplasia in the prostate and squamous metaplasia in the prostate and coagulating glands. In older men, stromal fibrosis is associated with benign prostatic hyperplasia and decreasing androgen levels.

Accessory male sex organs, vegetative lesion, see the preferred term **Accessory male sex organs, mesenchymal proliferative lesion**.

Accessory male sex organ vacuolar degeneration, see the preferred term **Accessory male sex organ epithelial vacuolation**.

Accessory male sex organs, vascular/perivascular necrosis/inflammation (prostate, seminal vesicle, coagulating gland, bulbourethral gland, and/or preputial gland) is generally a spontaneous and age-specific progressive degenerative lesion of the vascular walls. Medium-sized vessels are the primary site in the testis, and small arterioles are mainly affected in the prostate, seminal vesicles, coagulating gland, and bulbourethral gland. Affected vessels have a fragmented and hyalinized (referred to as fibrinoid change or necrosis) tunica media which may be thickened (i.e., hypertrophy) and infiltrated by inflammatory cells (usually lymphoplasmacytic). Vascular changes may reflect a systemic condition such as systemic hypertension or immune complex disease. The type and quantity of the diet impacts the incidence of this spontaneous disorder. Vasoactive compounds such as nitrofurantoin may also effect an increased incidence. In beagle dogs, perivascular necrosis/inflammation in the testes and epididymides is observed in idiopathic canine polyarteritis.

Synonym(s): **Accessory male sex organ vasculitis**; **accessory male sex organ arteritis**; **accessory male sex organ perivascular inflammation**; **accessory male sex organ periarteritis**; **accessory male sex organ polyarteritis nodosa**.

Accessory male sex organ vasculitis, see the preferred term **Accessory male sex organ vascular/perivascular necrosis/inflammation**.

Accessory male sex organ vesicular or hydropic degeneration, see the preferred term **Accessory male sex organ epithelial vacuolation**.

Accessory spleen is a small version of a spleen, containing all of the anatomic and functional elements of splenic white pulp and red pulp, which is found in an anatomic location outside the normal anatomic location for the spleen (left anterior quadrant of the abdominal cavity). Common locations for an accessory spleen are within the pancreas, attached to the splenic capsule, and within the gastrosplenic omentum, although accessory spleens may be found nearly anywhere within the peritoneal cavity. An accessory spleen can arise as either a congenital anomaly or secondary to splenic trauma.

Acetylation is the addition of acetyl groups; a reaction catalyzed by liver enzymes belonging to the *N*-acetyl transferase (NAT) family (e.g., NAT-1 or NAT-2). The acetylation reaction uses acetyl CoA as a substrate:

$$\text{R-NH}_2 + \text{CH}_3\text{CO-S-CoA} \rightarrow \text{R-NHCOCH}_3 + \text{CoASH}$$

Acetylation reactions are important in the disposition of amine-containing drugs, particularly aromatic amines and sulfonamides. Some sulfonamide acetyl metabolites are less soluble than the parent drug and may cause toxicity by crystalizing in the kidney upon concentration of the urine. Acetylator phenotype is polymorphically distributed in the population, with approximately 50% of the Caucasian and African American population having a slow acetylator phenotype, which is caused by reduced levels of NAT in the liver. Slow acetylators may have decreased rates of metabolism of some amine-containing drugs (e.g., isoniazid, dapsone, hydralazine, and caffeine).

Acetylator phenotype is a polymorphism that results in either slow or fast acetylation of drugs containing aromatic amines, sulfonamides, and hydrazines, caused by a deficiency of the hepatic enzymes *N*-acetyl transferase. See **Rapid acetylators** and **Acetylation** for further information.

Acetylesterases (EC 3.1.1.6) are enzymes that catalyze the hydrolysis of acetyl esters to acetic acid and the corresponding alcohol. See **Esterases** for further information.

Achlorhydria is a clinical condition where there is absence of hydrochloric acid in the gastric secretions as a result of loss of acid-producing parietal cells, gastrin deficiency, and/or proton pump inhibition. The inhibition of the proton pump in the gastric parietal cell by blocking the final step in the gastric acid secretory pathway causes this condition. Very high doses of omeprazole (a medication that belongs to a group of drugs called proton pump inhibitors is used to treat symptoms of gastroesophageal reflux disease [GERD] and other conditions caused by excess stomach acid) in laboratory animals results in achlorhydria and hypergastrinemia. Achlorhydria also predisposes to bacterial overgrowth, and nitration of dietary components in the presence of nitrite has been linked to gastric carcinogenesis in man.

Acid glycoprotein binding is the non-covalent association of a drug to plasma α-1 acid glycoprotein, an acute-phase protein synthesized mainly by the liver and found in the plasma.

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The protein binds mainly basic, positively charged drugs. See **Plasma protein binding** for further information.

Acid hematin, see the preferred term **Formalin pigment**.

Acidophilic adenoma, see the preferred term **Oncocytoma**.

Acidophilic tumor is an obsolete term once used in rats for renal tubular tumors with eosinophilic staining properties. See the preferred terms **Renal tubular adenoma** and **Renal tubular carcinoma**.

Acidosis occurs when there is too much acid in the body, and blood pH, which is normally regulated at pH 7.4, drops below pH 7.35. Acidosis may result from an inability to clear carbon dioxide via the lungs (respiratory acidosis) or from the production of excess acids (metabolic acidosis). In toxicity studies, acidosis may result if the test article affects pulmonary or renal function, or as a consequence of metabolism of the test article (e.g., methanol at high doses is metabolized to formic acid resulting in a metabolic acidosis).

Acinar-islet cell tumor, benign is a mixed exocrine-endocrine neoplasm that is composed of a mixed cell population of ductal, acinar, and islet cells. Refer to **Endocrine Glands** in Appendix 2 for more information.

Acinar-islet cell tumor, malignant is a mixed exocrine-endocrine neoplasm that is composed of a mixed cell population of ductal, acinar, and islet cells and is invasive with more cellular atypia compared to the benign form, and may metastasize. Refer to **Endocrine Glands** in Appendix 2 for more information.

ACP is an acronym for the American College of Physicians.

Acromegaly is an endocrinopathy due to excessive growth hormone (GH) production by the pituitary gland after closure of the physeal plates of the long bones. The most common cause of excessive GH production is a tumor of the somatotroph cells of the pituitary gland. These pituitary tumors are poorly responsive to the regulatory effects of glucose-induced neuroendocrine suppressive signals. The overproduction of GH results in chronic growth hormone receptor (GHr) stimulation with downstream increased insulin-like growth factor 1 (IGR1) production, increased cell cycling, and abnormal glucose metabolism. There is disproportional bone and organ growth, and increased cardiopulmonary and cerebrovascular dysfunction. Grossly, there is progressive hyperostosis with deformity and thickening of the craniofacial and long bones, and organ growth is excessive resulting in hypertrophy of the liver, heart, and kidneys. Excessive GH leads to insulin resistance and diabetes, cardiac hypertrophy, fluid overload, and renal stress. These changes result in hypertension, arteriosclerosis, and renal failure. Wistar-Furth rats implanted with mammosomatotrophic pituitary tumor cells as juveniles and followed into adulthood have been utilized as a model of acromegaly.

Synonym(s): **Gigantism**.

ACT is an acronym for American College of Toxicology.

Activated macrophage occurs in response to endogenous or exogenous signals, resulting in a physiologic change in normal resting macrophages producing effector macrophages which are larger and metabolically more active. Activation enhances phagocytic, antimicrobial, and antitumor activity and release of macrophage secretory Similar to Th1 and Th2T helper lymphocytes, macrophages exhibit polarized phenotypes that undergo phenotype switching. Originally classical macrophage activation (M1) was thought to be primarily proinflammatory and directed toward host defense to microorganisms with secretion of IL-1, IL-12, IL-23, TNF, reactive oxygen species, MHC class II, and IL-1R. Alternative macrophage activation (M2), with three subsets (a−c) was thought to predominate as an anti-inflammatory response (IL-10 and IL-1 or TGF-β secretion) in immune regulation and wound healing. In vivo and in vitro M1, M2, and other macrophage phenotypes overlap as concurrent activation states that are present after a single inciting event until its resolution. The biology of macrophage activation and applicable nomenclature continues to evolve.

Activation (bioactivation) is the formation of both active and reactive metabolites. See **Active metabolite** and **Reactive metabolite** for further information.

Active avoidance is the use of voluntary motor activity where the individual must act in a specific way to avoid negative internal or external stimuli (e.g., an electric shock). In classic behavioral psychology, it is used as a method of evaluating associative learning and memory.

Active metabolite is a metabolite formed from a drug which also has pharmacological activity, or the pharmacological principal formed from an inactive prodrug. If such metabolites are formed during the disposition of a drug, it is important to characterize the pharmacodynamics and pharmacokinetics of the active metabolite as well as the parent drug.

Active transport is the active uptake or extrusion of a drug through a cell membrane which is facilitated by drug transporters. See **Drug transporters** for further information.

Acute generally refers to a timeframe beginning with the onset of cellular or biochemical change(s), abnormal function, or disease. Changes in form or function that are acute occur rapidly (usually seconds, minutes, or hours); however, the acute timeframe is specific to the type of change and is usually associated with gross and/or microscopic changes that differentiate them from subacute or chronic changes. See **Subacute** and **Chronic** for further information.

Acute gliopathy, see the preferred term **Astrocytic swelling/vacuolation**.

Acute inflammation is characterized by congestion of local blood vessels, exudation of fluid and plasma proteins

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(edema), and influx of polymorphonuclear leukocytes (granulocytes). If the stimulus for inflammation resolves, the inflammatory response is self-limiting due to a coordinated chemical cascade that is initiated during the first few hours after an inflammatory response begins. Once in the tissue, granulocytes stimulate a change from arachidonic acid–derived prostaglandins and leukotrienes to lipoxins, which starts the termination sequence. Granulocyte recruitment stops, and a signal is triggered for programmed death by apoptosis.

Acute-phase (reactant) proteins are a group of proteins (and peptides) that, when present in either increased or decreased plasma levels, are the result of inflammation. These include C-reactive protein, α1-acid glycoprotein, serum amyloids, complement factors, antitrypsin, fibrinogen, ferritin, and prothrombin. Changes in the plasma levels of such proteins during a toxicity study may be used as a clinical biomarker for inflammation.

Acute renal tubular necrosis, see the preferred terms **Renal proximal tubular necrosis**, **Renal distal tubular necrosis**, or **Renal collecting duct necrosis**.

Acute toxicity results from a single exposure to an agent or multiple exposures within less than 24 hours. Acute toxicity testing is now rarely performed in the pharmaceutical industry and is no longer required according to the ICH M3(R2) guidance (International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use). Instead, acute toxic effects are assessed in rising dose studies after the initial dose using a limited number of animals to determine the maximum tolerated dose (MTD) and to establish dose levels for subsequent repeat-dose toxicity studies. In the past, large numbers of animals were used to determine the LD_{50} (lethal dose for 50% of the animals) as a measure of acute toxicity. The latter has been used for potency classification of toxins based on their acute toxicity. If such data is collected today, it is in the form of an ALD_{50} (approximate lethal dose for 50% of the animals) determination, wherein far fewer animals are used.

ACVP is an acronym for the American College of Veterinary Pathologists.

Adaptive clinical trial is a type of clinical trial in which the design may be modified after analysis of results accumulated during the trial. According to the draft FDA Adaptive Design Clinical Trials for Drugs and Biologics (2010) guidance: "An adaptive design clinical study is defined as a study that includes a prospectively planned opportunity for modification of one or more specified aspects of the study design, and hypothesis based on analysis of data (usually interim data) from subjects in the study." Analysis of the accumulating study data are performed at prospectively planned timepoints within the study, can be performed in a fully blinded or unblinded manner, and can occur with or without formal statistical hypothesis testing. It is important that the adaptation is planned and defined in detail prospectively before examination of any data. Such adaptations can cover a range of trial design modifications including, but not limited to, study eligibility criteria, randomization procedure, dose level, dosing schedule, sample size, concomitant treatment, selection of secondary endpoints, and methods of assessing endpoints.

Adaptive responses are common during toxicity studies and, while they may be associated with clinical pathology and/or histopathological changes, they are generally not considered adverse. There are many different kinds of adaptation; one of the most common occurs in liver, particularly in rodent studies due to test substance "overload," resulting in induction of drug metabolism via enzyme induction. This is often accompanied by proliferation of hepatocellular smooth endoplasmic reticulum, histologic hepatocellular hypertrophy, and increased liver weight. Other adaptive changes may result from cellular attempts to overcome the effects of a drug, for example down-regulation of a target protein as an adaptation to agonistic compounds or excess production of the target to overcome inhibition. See **Enzyme induction** for further information.

Adaxonal vacuoles, see the preferred term **Myelin bubbles**.

Addison disease, see the preferred term **Hypoadrenocorticism**.

Adducts, DNA are molecules that are covalently bound to DNA. They are often involved during a premutagenic event.

Adducts, protein are molecules that are covalently bound to proteins.

Adenitis is a general term used for inflammation of a gland. See terms for glandular inflammation in all organ specific chapters for further information.

Adenocarcinoma is a malignant neoplasm of glandular (secretory) epithelial origin and/or glandular appearance that is part of the larger group of tumors of epithelial origin called carcinomas. Adenocarcinomas can be well differentiated, meaning a pathologist can easily distinguish glandular features within the tumor, or poorly differentiated, implying that the tumor lacks these characteristic glandular features. Adenocarcinoma is the malignant counterpart to adenoma, which is the benign form of such tumors. Glandular cells line certain internal organs in the body and make/release substances such as mucus, digestive juices, or other fluids. Most cancers of the breast, pancreas, lung, prostate, and colon are adenocarcinomas. Inherent in the biologic behavior of adenocarcinomas is their propensity to invade the surrounding parenchyma, often including vascular and/or frequently lymphatic invasion. Subsequently, these tumors spread or metastasize to other organs/tissues in

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the body such as the draining lymph nodes, lung, brain, bone (prostatic adenocarcinoma), and liver.

Adenohypophysis, see the preferred term **Anterior pituitary gland**.

Adenoid cystic carcinoma, **primary**, see the preferred term **Eccrine gland carcinoma.**

Adenoma is a benign neoplasm of glandular epithelial origin. Adenomas have well-circumscribed, clear boundaries, and are not invasive or compressive of the adjacent normal tissue. Adenomas are distinguished from adenocarcinomas by the lack of malignant features such as tissue invasion, distant metastasis, and the relative absence of cellular atypia.

Adenomyosis is characterized by the presence of normal-appearing endometrial epithelial and stromal structures within the myometrium. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

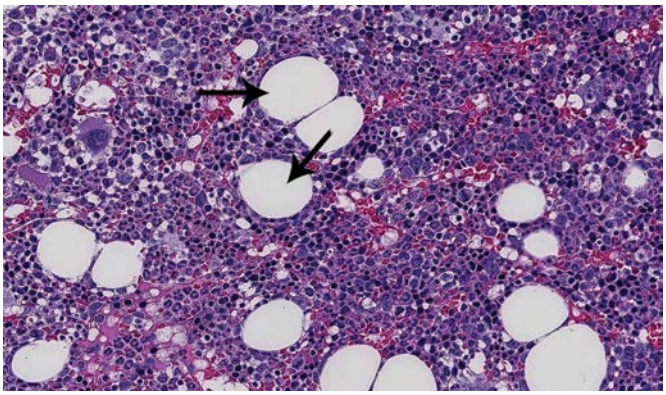
Adenosis is a rare, mouse-specific change affecting predominantly the anterior vagina and cervix. Histologically, the change represents residual Mullerian epithelium forming gland-like structures in the vaginal and cervical uterine stroma. The gland-like structures are formed of a single layer of columnar cells. This change has been associated with long-term estrogen administration.

Differential diagnoses: **Endometrial adenoma**; **Endometrial adenocarcinoma**.

Synonym(s): **Uterine adenomatous differentiation**.

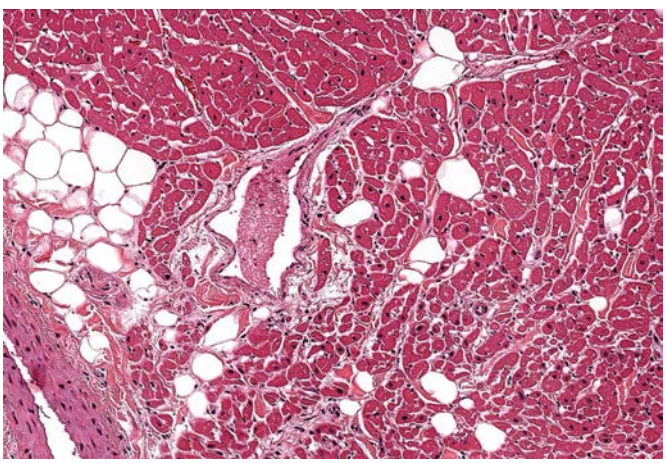
ADI is an acronym for acceptable daily intake. See **Allowable human daily intake** for further information.

Adipocyte in the bone marrow are fat cells characterized by a marginated nucleus with clear cytoplasm composed of a large monolocular lipid droplet specialized for lipid storage and release. Bone marrow adipose is metabolically different from visceral and subcutaneous white fat as these adipocytes are thought to originate from mesenchymal stem cells from the same lineage as osteoblasts. Relative fat content of bone marrow varies greatly with species, age, anatomic site, and activity of hematopoietic elements. Increased hematopoiesis in bone marrow may result in crowding, obstruction, or replacement of fat, and is considered an adaptive response. As hematopoiesis declines in aging, relative fat content of bone marrow increases. Age-related increase of marrow fat in rodents is physiologic and follows a sequential pattern in various marrow cavities. Poor nutritional status may result in decreased fat stores. The overall health and nutritional status of the animal and its systemic body fat reserves should be taken into consideration when evaluating decreased adipose cellularity, as bone marrow fat reserves are among the last to be mobilized. Mice generally have less bone marrow fat than other mammals. Comparison to concurrent control group animals is recommended. Adipose tissue is the most prominent and most easily visualized component of bone marrow stroma. For practical purposes, changes to adipose tissue are addressed separately from other bone marrow stromal elements. Decreases in other stromal elements are generally combined in a single diagnostic category of bone marrow stroma.



Adipocytes (arrows), bone marrow, cynomolgus monkey (H&E).

Adipocyte accumulation is the addition of adipocytes containing lipid to a tissue. Adipocytes are large cells generally containing only one or a few large, clear vacuoles filled with lipid. Their nuclei are marginalized by the cytoplasmic lipid droplet, giving rise to a "signet ring" appearance. Adipocyte accumulation can be due to the division and multiplication of pre-existing adipocytes (hyperplasia), differentiation of adipocytes from local precursors, infiltration of adipocyte precursors with differentiation, transdifferentiation of adipocytes from other pre-existing mesenchymal cell types, or due to physiological mechanisms (obesity). When pathological, this accumulation, infiltration, or metaplastic change is typically a response to injury, including hypoxia. Compare



Adipocyte accumulation in the myocardium of a cat, H&E. Adipocytes are present within the connective tissue surrounding muscle bundles.

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adipocyte accumulation to "fatty infiltration" and "lipomatous." "Fatty infiltration" is frequently misused to mean the process described above; however, it is defined as the abnormal accumulation of fat droplets within the cytoplasm of cells. Similarly, "lipomatous" is not a favored term, as it refers to the features of a lipoma (a benign neoplasm of adipocytes) but is often used incorrectly to describe the presence of adipocytes in an unexpected location. See **Fatty infiltration** and **Lipomatous** for further information.

Adipocyte (fat) atrophy in bone marrow is characterized by decreased size or number of adipocytes (fat cells) relative to an earlier time when both size and number were within normal parameters.

Adipocyte (fat) depletion in bone marrow is a decrease in number or absence of adipocytes (fat cells). Depletion implies that adipocytes are presently decreased compared to the normal parameters by removal or loss of cells.

Adipocyte (fat) hypoplasia in bone marrow is a decrease in number or size of fat cells within bone marrow. Hypoplasia implies a process of decreased or partial development or growth with failure to achieve normal parameters relative to the final number of cells.

Adipocytes (fat) hypocellularity in bone marrow implies fewer than normal numbers of adipocytes (fat cells). This is a descriptive term that has no implications to the dynamics or the process resulting in reduced cell numbers.

Adipose tissue atrophy is the decrease in size of fat- or lipid-containing cells (adipocytes). A decrease in cell size is due to a loss of cell substance and this may be physiologic or pathological. The lesion is characterized by lipolysis, shrunken adipocytes, and accompanying fibrosis. Both white and brown adipose tissue can undergo atrophy. Significant adipose tissue atrophy is seen in cachexia (particularly when cancer related), and peroxisome proliferators may cause a dramatic decrease in adipose tissue weight. Adipose tissue atrophy is occasionally observed as a test article–related effect when xenobiotics cause chronic reduction in feed consumption with resultant starvation or cachexia.

Synonym(s): **Fat atrophy**; **lipoatrophy**.

Adipose tissue hyperplasia is an increase in the number of adipocytes (fat cells).

Differential diagnosis: **Lipoma**.

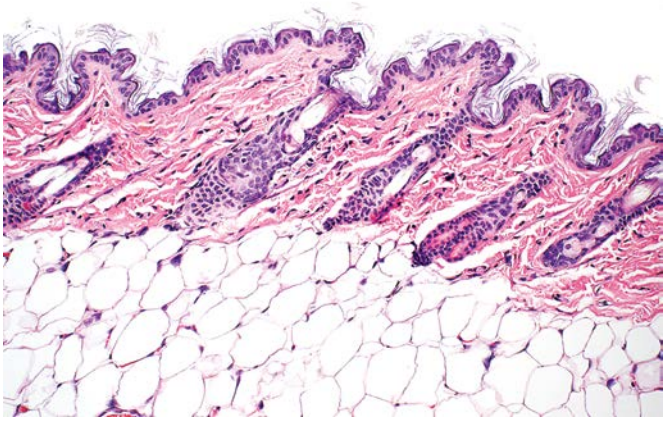
Adipose tissue, polymorphic, see the preferred term **Adipose tissue hyperplasia**.

ADME is an acronym for the processes that define the pharmacokinetics of a drug: **A**bsorption, **D**istribution, **M**etabolism, and **E**xcretion. The term is often used for mass balance studies with radioactive drugs in animals that assess the uptake, plasma/blood kinetics, tissue distribution, and excretion of total drug products (parent drug plus metabolites).

Adnexa are skin appendages that consist of hair follicles and hair shafts with associated arrector pili muscles and sebaceous glands (together referred to as the pilosebaceous unit), as well as apocrine and eccrine sweat glands. Other skin appendages such as horns, claws, and their homologues nails, are also commonly included as skin adnexa. Refer to **Skin** in Appendix 3 for further information.

Adnexal atrophy is a marked reduction in follicular and sebaceous gland size and cell number well beyond that found physiologically during the normal telogen stage of the hair cycle. It is characterized by small remnants of follicles and sebaceous glands that appear as strands of keratinocytes surrounded by a thickened connective tissue sheath. Most hair follicles will have lost their hair shaft, and dermal atrophy or scarring may also be present. Since hair follicles lose cells when they undergo regression in the catagen stage of the hair cycle, hair follicle atrophy must be distinguished from catagen and telogen stages of the hair cycle. Adnexal atrophy can be induced by a number of different agents including corticosteroid hormones and antiproliferative compounds such as bleomycin. Sebaceous gland atrophy may occasionally be present in the absence of follicular atrophy, particularly in genetically engineered mouse models.

Differential diagnosis: **Adnexal dysplasia**.



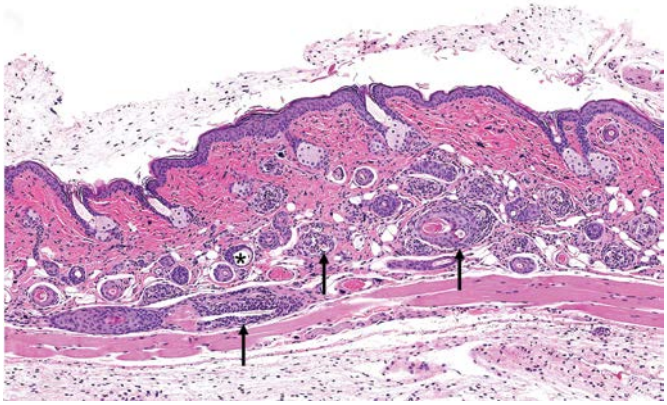
Adnexal (sebaceous gland) atrophy in a CD1 mouse following systemic administration of a compound that inhibits the Notch signaling pathway, H&E.

Adnexal dysplasia primarily affects hair follicles and is characterized by malformation of the follicle affecting the shape of the follicle and/or hair shaft. In addition, the loss of pigmentation from hair follicles, either acquired or congenital, such as occurs in coat color mutants, is considered a form of follicular dysplasia. Unlike dysplasia in many other

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organ systems, adnexal dysplasia is not considered a preneoplastic hyperplastic lesion. Many genetically modified mice exhibit various forms of congenital hair follicle malformation. The primary distinguishing feature of adnexal dysplasia is an obvious reduction in adnexal size, including glands associated with follicles.

Differential diagnosis: **Adnexal atrophy**.

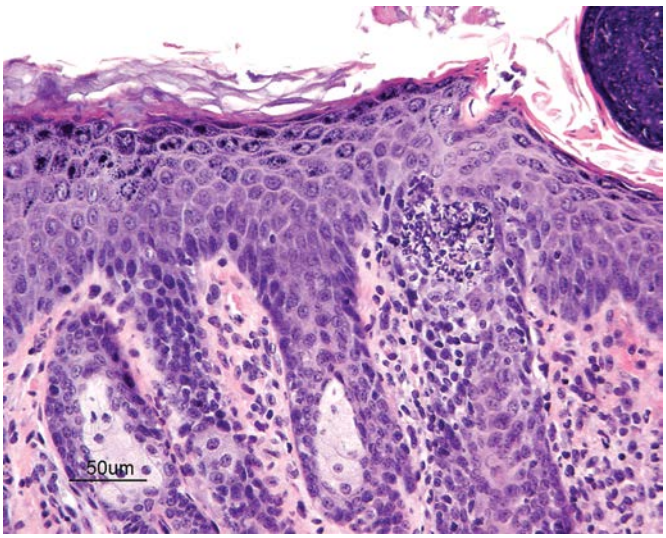


Adnexal dysplasia (follicular dysplasia) in SKH1 hairless mouse, H&E. Hair follicles grow in abnormal orientation to skin surface, resulting in granulomatous folliculitis (arrows) and formation of follicular cysts (*).

Adnexal hyperkeratosis is the result of increased keratinocyte turnover within the hair follicle infundibulum or sebaceous gland duct. The follicular infundibulum is dilated and filled with excessive keratin that resembles epidermal differentiation. The hair follicle canal may be cystic. Ducts of adnexal glands may also become keratin plugged. Keratin plugging can result in retained hairs or secretions. Refer to **Skin** in Appendix 2 for further information.

Adnexal hyperplasia of the cutaneous adnexa mostly affects sebaceous glands. Sebaceous glands are enlarged and show an increased number of sebaceous cells in individual acini with few immature cells, and many mature glandular cells arranged around prominent central ducts. Another form described in some genetically engineered mice is an increase in the overall size of hair follicles with otherwise normal architecture. Refer to **Skin** in Appendix 2 for further information.

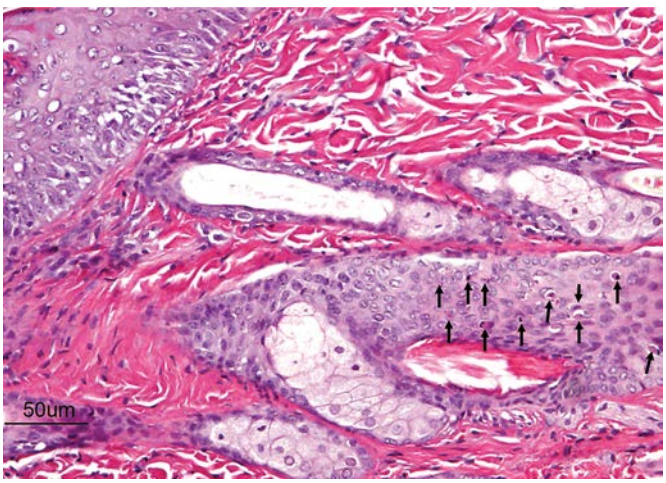
Adnexal inflammation is characterized by infiltration of leukocytes into the cutaneous adnexa, is often associated with epidermal inflammation, and is always found in conjunction with dermal inflammation. Inflammation of the hair follicle is termed folliculitis and may occur anywhere within the follicular epithelial lining, follicular bulb, or follicular lumen. When the inflammatory process results in destruction of the follicular lining epithelium with rupture of the follicle, it is termed furunculosis. Inflammation of the cutaneous adnexa, particularly hair follicles, is a spontaneous, incidental finding often associated with dermatophytosis or demodicosis.



CD45RBHi SCID mouse immune transfer model of psoriasis illustrating peri- and intrafollicular infiltration of inflammatory cells with a predominance of lymphocytes, H&E. (Figure used with permission from Mecklenburg, L. et al. 2013.)

Adnexal necrosis is characterized by degeneration and loss of cellular detail of follicular keratinocytes, either as single cells (single cell type) or as multiple cells (diffuse type). It can be classified as either single cell or full-thickness necrosis. In single cell adnexal necrosis, individual follicular keratinocytes have hypereosinophilic cytoplasm, a pyknotic nucleus, and are often shrunken and surrounded by a clear ring. Necrotic keratinocytes are also sometimes surrounded by infiltrating lymphocytes. Chemotherapeutic agents such as paclitaxel and doxorubicin induce follicular necrosis of the single cell type, resulting in alopecia. Hair follicle dystrophy can be classified as a form of necrosis, as follicular keratinocytes undergo uncoordinated vacuolar degeneration or apoptosis. In the diffuse form of adnexal necrosis, adnexal epithelium demonstrates complete loss of cellular detail due to the diffuse necrosis of adnexal keratinocytes.

Synonym(s): **Hair follicle dystrophy**.



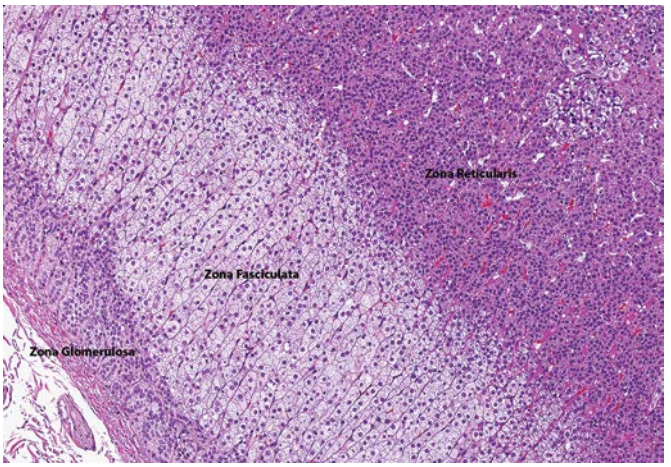
A hair follicle from a Lewis rat given a kinase inhibitor with multifocal single cell necrosis as illustrated by the arrows, H&E. (Figure used with permission from Diegel, K.L. et al. 2013.)

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A

ADR is an acronym for adverse drug reaction. See **Adverse Drug Reaction** for further information.

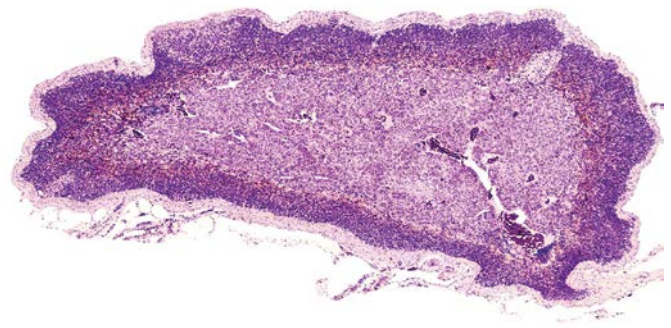
Adrenal cortex represents the outer layer of the adrenal gland, which is typically divided into three main layers or "zones": the outermost zona glomerulosa, the middle zona fasciculata, and the innermost zona reticularis. Cortical cells originate from the embryonic mesodermal mesenchyme and function in regulating metabolism, secondary sex characteristics, stress responses, blood pressure, and electrolyte balance through secretion of hormones (mineralocorticoid, glucocorticoid, and gonadocorticoid hormones). Mice do not have a visible zona reticularis, but instead have an X zone, the function of which is uncertain but may produce an enzyme involved in progesterone inactivation. See Appendix 3 for more information.



Adrenal cortex, cynomolgus monkey, H&E.

Adrenal cortical adenoma, benign is a tumor composed of neoplastic adrenal cortical cells originating from the adrenal cortex. Refer to **Endocrine Glands** in Appendix 2 for more information.

Adrenal cortical atrophy is characterized by a reduction in thickness of the adrenal cortex due to a decrease in individual cortical cell size and/or number. It may be unilateral or bilateral, and most often affects the zona fasciculata and zona reticularis in most animals. Atrophy of the adrenal cortex may be due to inflammation (e.g., autoimmune adrenocortical adenitis), administration of exogenous steroids, or may be idiopathic, and if extensive can result in adrenocortical insufficiency (i.e., Addison disease).



Adrenal gland cortical atrophy, Sprague Dawley rat, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Adrenal cortical carcinoma, malignant is a tumor composed of neoplastic adrenal cortical cells. These tumors usually contain bizarre, rapidly dividing cells and can grow quickly with significant local invasion. Refer to **Endocrine Glands** in Appendix 2 for more information.

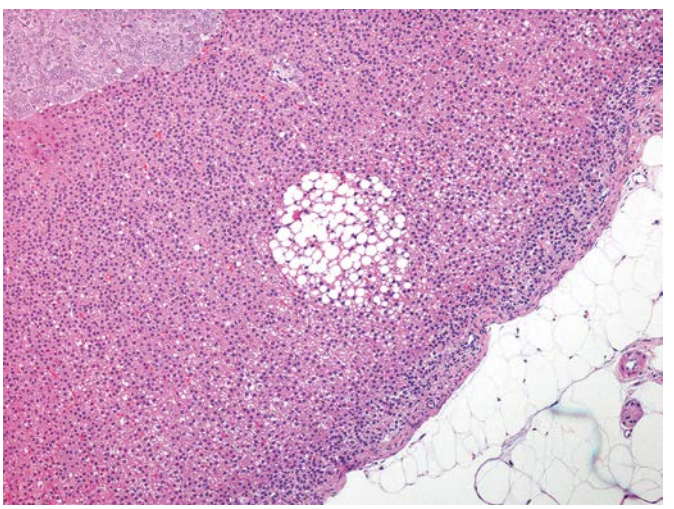
Adrenal cortical hyperplasia refers to the increase in the number of cells involving any of the three zones of the cortex (zona fasciculata, zona reticularis, zona glomerulosa) resulting in the enlargement of adrenal cortex. Refer to **Endocrine Glands** in Appendix 2 for more information.

Adrenal cortical hypertrophy is an increase in size of the adrenal cortex, which may be focal or diffuse, resulting from individual cell enlargement.

Adrenal cortical myelolipoma is a benign neoplasm composed of adipose tissue and hematopoietic cells and is thought to develop from metaplastic transformation of cells in the adrenal cortex. Refer to **Endocrine Glands** in Appendix 2 for more information.

Adrenal cortical tumor, see the preferred terms **Adrenal cortical adenoma, benign**; **Adrenal cortical carcinoma, malignant**.

Adrenal cortical vacuolation is characterized by increased numbers of round, clear spaces (vacuoles) in the cytoplasm of adrenal cortical cells. Cytoplasmic vacuoles may be small and numerous, or single and large. This change usually involves



Adrenal gland cortical vacuolation, Sprague Dawley rat, H&E.

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the zona fasciculata, and may be focal or diffuse, unilateral or bilateral. Focal cortical vacuolation is commonly seen as a spontaneous finding in aged rats but is rarely noted in other species. Diffuse cortical vacuolation is often a physiologic response to a drug or stress.

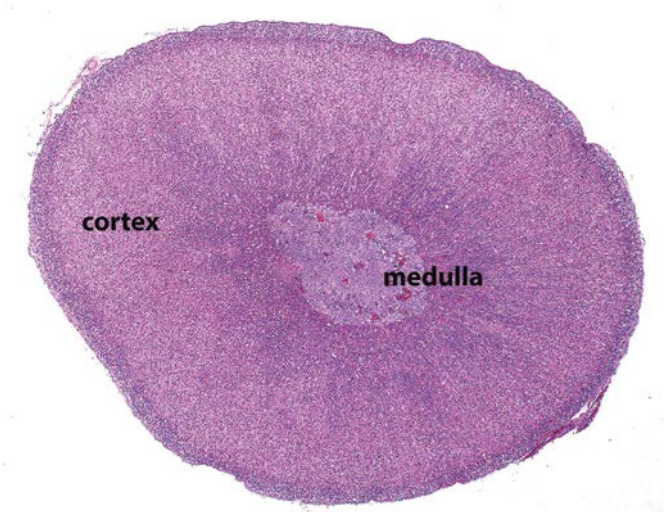
Synonym(s): **Adrenal fatty change**.

Adrenal extracortical nodule, see the preferred term **Accessory adrenal cortical tissue**.

Adrenal fatty change, see the preferred term **Adrenal cortical vacuolation**.

Adrenal gland is a paired, encapsulated endocrine gland of mammals located in the perirenal adipose tissue cranial to the kidneys, and is organized into a central medulla and an outer cortex. The adrenal cortex is divided into three zones: the zona glomerulosa, zona fasciculate, and zona reticularis (see adrenal cortex image). Each zone contains cells that have specific roles in the production and secretion of hormones in response to complex feedback mechanisms from the renin-angiotensin-aldosterone system (RAAS) and the hypothalamic pituitary adrenal axis (HPA). Abnormal function in the adrenal cortex results in either hyperadrenocorticism (Cushing's disease) or hypoadrenocorticism (Addison disease). Comparatively, the medulla originates from the neural crest and has sympathomimetic functions that play a role in the "fight-or-flight" response through secretion of catecholamines (epinephrine/adrenaline, norepinephrine/noradrenalin, and dopamine) from chromaffin cells reacting to nerve impulses from preganglionic sympathetic neurons of the spinal cord. Catecholamine hormones from the adrenal medulla also serve to regulate blood pressure. The most common cause of medullary dysfunction is the neoplasm pheochromocytoma. See Appendix 3 for more information.

Synonym(s): **Suprarenal gland**.



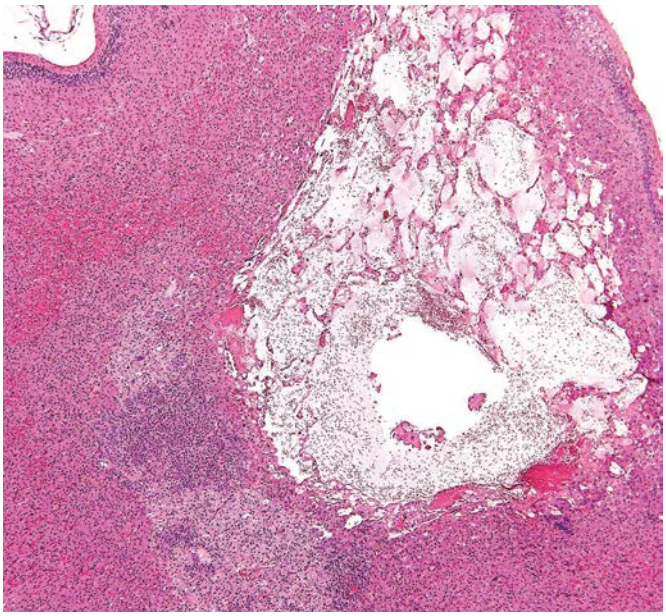
Adrenal gland, Sprague Dawley rat, H&E.

Adrenal gland cortical peliosis, see the preferred term **Adrenal gland cystic degeneration**.

Adrenal gland cystic change, see the preferred term **Adrenal gland cystic degeneration**.

Adrenal gland cystic degeneration is best described in the rat, and is characterized by dilated, fluid- and blood-filled vascular channels. This finding is most commonly located in the adrenal cortex and can range from mildly dilated sinusoids to markedly expanded cystic spaces that significantly alter the cortical architecture. Cystic degeneration is occasionally associated with other cortical abnormalities, such as tumors, hypertrophy, or hyperplasia.

Synonym(s): **Adrenal gland cystic change**; **adrenal gland cortical peliosis**.



Adrenal gland, cortex, cystic degeneration, F344/N rat, H&E. (Images provided courtesy of National the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

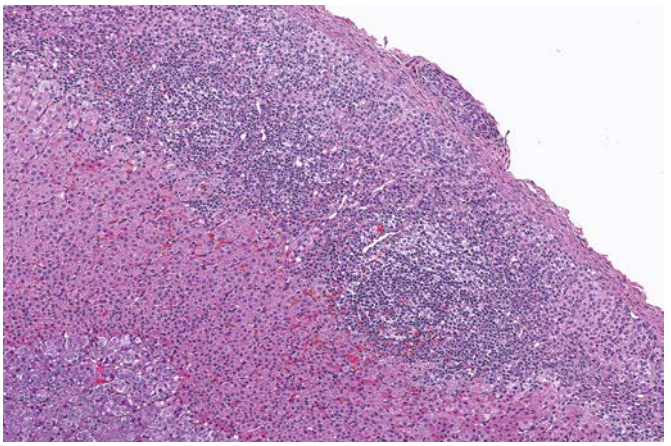
Adrenal gland, ectopic, see the preferred term **Accessory adrenal cortical tissue.**

Adrenal gland inflammation is a term used for inflammation of one or both of the adrenal glands, and can be secondary to infectious (e.g., bacterial or viral) or noninfectious (e.g., autoimmune or idiopathic) causes. Inflammation occurs in association with a generalized inflammatory condition or by extension of inflammation into the adjacent organs. In acute cases, neutrophils predominate. In chronic conditions, lymphocytes, macrophages, and plasma cells are more common. Degeneration, necrosis, and/or loss of adrenal epithelial cells (atrophy), and edema and hemorrhage are frequently present. Adrenal gland inflammation can have significant sequelae leading to failure to produce and secrete important bioactive hormones through a temporary

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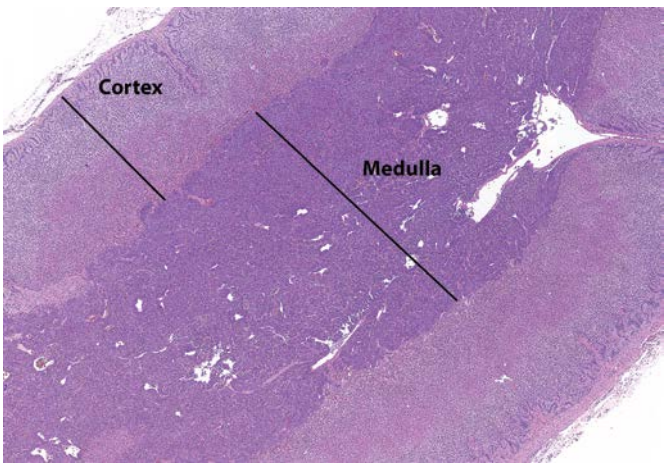
or permanent disruption of the adrenal glandular cells, resulting in Addison disease.

Synonym(s): **Adrenalitis**.



Adrenal gland, cortex, mononuclear cell inflammation with multifocal cortical atrophy and hyperplasia, cynomolgus monkey, H&E.

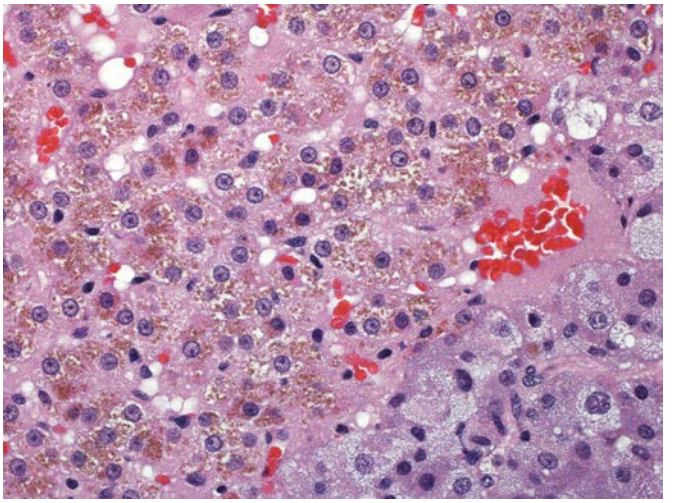
Adrenal gland medulla is the central region of the adrenal gland, subtending the adrenal cortical zona reticularis. The neuroendocrine cells of the adrenal medulla, the chromaffin cells, secrete catecholamines (epinephrine/adrenaline, norepinephrine/noradrenaline) and dopamine. The adrenal medulla responds to neurological stimulation it receives from the sympathetic nervous system (spinal cord sympathetic ganglia). See Appendix 3 for more information.



Adrenal gland, medulla (with cortex), beagle dog, H&E.

Adrenal gland pigmentation is characterized by the deposition of pigment, usually granular, yellow-brown lipofuscin pigment, often in the cells of the zona reticularis. Small amounts of lipofuscin pigment are commonly present as a normal feature in older rats and nonhuman primates. In large amounts or in younger animals, lipofuscin pigmentation suggests there is altered cell metabolism or increased organelle turnover, as can be seen with hormone-induced atrophy or pathological production of storage disease.

Synonym(s): **Lipofuscin pigment**; **lipofuscinosis**; **ceroid pigment**; **brown degeneration**.



Adrenal gland, cortex, pigmentation, cynomolgus monkey, H&E.

Adrenal gland subcapsular cell adenoma, see the preferred term **Adrenal gland subcapsular cell tumor, benign**.

Adrenal gland subcapsular cell carcinoma, see the preferred term **Adrenal gland subcapsular cell tumor, malignant.**

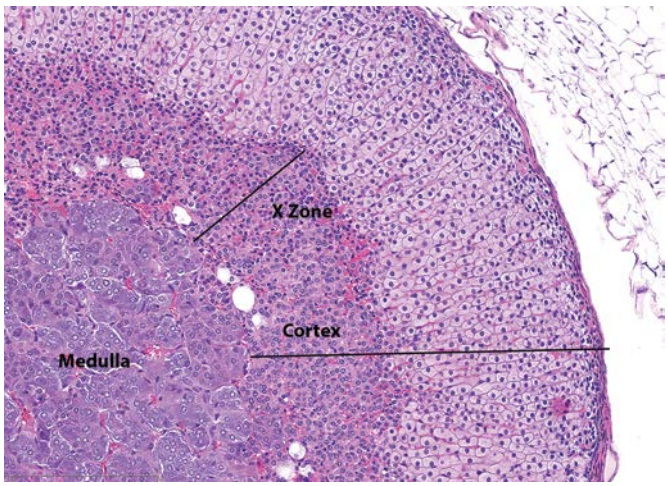
Adrenal gland subcapsular cell hyperplasia is characterized by a subcapsular focus of small, basophilic cells that extend into the zona fasciculata. Refer to **Endocrine Glands** in Appendix 2 for more information.

Adrenal gland subcapsular cell tumor, benign is a well-demarcated, nodular neoplasm in mice that is composed of transformed subcapsular progenitor cells (type A—densely cellular, small, oval-spindle, with scant basophilic cytoplasm; type B—large, polygonal cells with clear cytoplasm and small lipid vacuoles; or mixed type A/B cells) within the subcapsular space of the adrenal gland. Refer to **Endocrine Glands** in Appendix 2 for more information.

Adrenal gland subcapsular cell tumor, malignant is a neoplasm only observed in mice that arises from undifferentiated progenitor cells in the subcapsular space of the adrenal cortex and that have cytological atypia, are organized in nests, ribbons, or cords, and invade into the adjacent tissue and out of the capsule. Refer to **Endocrine Glands** in Appendix 2 for more information.

Adrenal gland X zone is a unique adrenal cortical zone in young mice, consisting of small, eosinophilic cells located at the junction of the cortex and medulla. This zone appears a few days after birth in mice of both sexes, is fully developed at weaning, and regresses after sexual maturity (X zone involution). It has been suggested that these cells produce an enzyme involved in progesterone inactivation.

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Adrenal x-zone of a young mouse with annotation of of the cortex and medulla annotated, H&E.

Adrenal gland X zone involution represents the normal physiologic process of regression of the adrenal X zone in young mice. The X zone cells undergo degeneration and necrosis, and ultimately disappear causing collapse, condensation, and eventual loss of the X zone. Pigment-laden cells may accumulate in this area. In females, regressing X zone cells have prominent vacuolation. In males, the X-zone regresses at sexual maturity (approximately 5 weeks of age). In females, the X-zone disappears rapidly at first pregnancy, but in virgin mice regresses more gradually. This process is controlled by sex and thyroid hormones.

Adrenal gland X zone persistence occurs in the mouse adrenal beyond the normal period of involution after puberty (i.e., adrenal gland X zone involution), most commonly due to perturbations in sex hormones. Castration or administration of pituitary gonadotropin in young mice prolongs the persistence of the X zone in females and prepubertal males and can cause the reappearance of X zone cells in postpubertal males.

Adrenaline, see the preferred term **Catecholamine**.

Adrenalitis, see the preferred term **Adrenal gland inflammation**.

Adrenal medullary ganglioneuroma, benign is a rare tumor comprised of neoplastic ganglion cells and neurofibrillary matrix and supporting cells, such as stellate and Schwann cells that have been reported as spontaneous lesions in a variety of animals. Refer to **Endocrine Glands** in Appendix 2 for more information.

Adrenal medullary neuroblastoma, malignant is a neoplasm originating from sympathetic neural crest cells and uncommonly occurring as spontaneous lesions in rodents and certain transgenic mouse models. Refer to **Endocrine Glands** in Appendix 2 for more information.

Adrenal medulla tumor, see the preferred terms **Pheochromocytoma, Adrenal medullary ganglioneuroma**, or **Adrenal medullary neuroblastoma**.

Adrenal rest, see the preferred term **Accessory adrenal cortical tissue**.

Adrenocortical choristoma, see the preferred term **Accessory adrenal cortical tissue**.

Adrenocortical hypertrophy, see the preferred term **Endocrine glands** in **Adrenal cortical hypertrophy**.

Adrenocortical rest, see the preferred term **Accessory adrenocortical tissue**.

Adrenocortical tissue, ectopic, see the preferred term **Accessory adrenal cortical tissue**.

Adrenocorticotropic hormone (ACTH) is a peptide hormone containing 39 amino acids which is synthesized and secreted by the pituitary gland in response to corticotropic-releasing hormone (CRH) as part of the hypothalamic-pituitary-adrenal axis (HPA). Corticotropes in the anterior lobe of the pituitary gland produce proopiomelanocortin (POMC), which is further processed by enzymes within the cell to produce ACTH and other bioactive molecules. The primary effect of ACTH is in the zona fasciculata and zona reticularis of the adrenal cortex, including stimulation of steroid production such as glucocorticoids and gonadocorticoids, both important for metabolism and immune function. The production of these products in the adrenal cortex acts as a negative feedback mechanism in the HPA axis regulating production of CRH by the hypothalamus, and ACTH by the pituitary gland.

Adverse drug reaction (ADR; i.e., adverse drug event) is a response to a medicinal product which is noxious and unintended and that occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease or for the restoration, correction, or modification of physiological function. Adverse events have been divided into at least two different types: type A interaction is generally dose dependent and is a consequence of either the desired or the undesired pharmacology of the drug, and type B interactions are not related to the pharmacology and not always clearly dose dependent. The latter type B interactions are often termed idiosyncratic wherein the mechanisms are poorly understood.

Adverse effect is an undesirable, harmful effect resulting from medication or surgery, or exposure to chemicals.

Adverse effects (in toxicology studies) are any changes related to treatment with a test substance that are considered

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as potentially harmful to the well-being of the test species, resulting in dysfunction, or negatively impacting the ability of an animal to thrive or develop normally. Often the assessment of a finding as "adverse" is subjective, based on the direction of a change, its incidence, magnitude, or severity compared to control or background findings, and whether functional impairment is a measured or a projected negative outcome. Treatment-related changes of low severity or of questionable negative impact on normal function and development may be less likely to be adverse if demonstrated to ameliorate or reverse to control or background levels with cessation of treatment, thereby allowing an animal or organ system to recover. Similarly, findings considered clearly adverse at higher doses or exposure levels may not be deemed adverse at lower dose levels if of lower incidence and severity than at higher dose levels. Effects related to the pharmacodynamics of a test substance may result in adverse on-target or off-target effects at high-dose or exposure levels, or in highly sensitive species. Adverse effects of a test substance should be defined or characterized only within the confines of the conditions of a given toxicology study and for the species tested, and not generalized across species unless determined to be a class-effect or similar results have been obtained in other toxicology species. In studies conducted in support of human safety, an adverse effect may be discussed in context of human relevance; however, the finding is nonetheless adverse in the test species.

Aerobic is a process requiring oxygen and taking place in the presence of oxygen.

Aerosol is a suspension of liquid droplets in air, which may be used as a dosing formulation for toxicity studies by the inhalation route.

Age-dependent physeal closure, see the preferred term **Growth plate closed**.

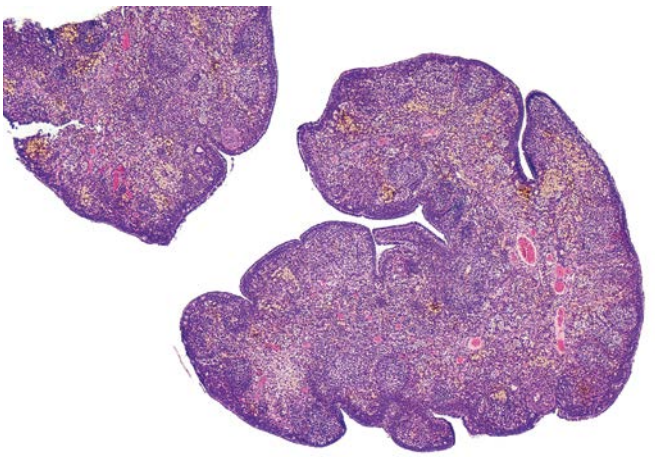
Agency for Toxic Substance and Disease Registry (ATSDR) is an agency of the U.S. Department of Health and Human Services dealing with hazardous substances in the environment.

Agenesis refers to the absence of or total failure to develop any part of a tissue or organ due to lack of its primordium (anlagen). Agenesis can be fatal if it occurs in an unpaired organ; few examples exist, as most cases are fatal in utero. Interestingly, agenesis of the corpus callosum of the brain in some strains of mice (BALB/c, 129) is not fatal, and these animals do not exhibit neurologic abnormalities. In paired organs (such as the kidneys), unilateral agenesis is typically not fatal, but can lead to premature organ failure.

Age-related involution, see the preferred term **Thymic involution, age-related**.

Age-related ovarian atrophy is characterized by nonspecific changes of decreased growing follicles, decreased/absent corpora lutea, and prominent interstitium. Primordial follicles are also reduced or absent. This constellation of changes occurs naturally with reproductive senescence in most laboratory species, but the physiologic mechanisms differ. (See **Anestrus** and **Ovarian atrophy** for further information.) Other reproductive tract organs will commonly show atrophic changes related to or secondary to the ovarian atrophy. This condition is difficult to discern from xenobiotic-induced atrophy.

Differential diagnoses: **Anestrus**; **Ovarian atrophy**.
Synonym(s): **Ovarian senescence**.



Atrophy characterized by decreased follicles, no corpora lutea, ovary, F344/N rat, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

Agonist is an agent that produces a stimulatory effect on a receptor or set of receptors (system). The stimulatory effect is generally defined by the biological systems affected. Alpha adrenergic agonists stimulate the receptors for epinephrine and are used to treat a variety of conditions (e.g., systemically for low blood pressure and topically for increased pressure in the eye [glaucoma]).

Ah receptor (Aryl hydrocarbon receptor, AhR, TCDD-binding protein) is a ligand-activated transcription factor which regulates the biological responses to planar aromatic hydrocarbons. The cytosolic receptor is normally in an inactive state bound to chaperone molecules. Upon interaction with a ligand, the receptor ligand complex, assisted by the AhR nuclear translocator protein, moves into the nucleus where it induces the transcription of a variety of genes in a pleiotropic response. The receptor was first identified in studies to explain differences in the response of mouse strains to the polycyclic hydrocarbon 3-methylcholanthrene, particularly with respect to the induction of cytochrome P448 (Cyp1A1, Cyp1A2); however, several other genes are induced as part of the pleiotropic response, including Cyp1B1, aldehyde dehydrogenase 3, glucuronyl transferase 1A1 (UGT1A1), Ya subunit of glutathione transferase(GST), NAD(P)H quinone oxidoreductase,

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δ-aminolevulinic acid synthetase, prostaglandin endoperoxidase H synthase 2, p-glycoprotein (MDR1), and BCRP and the AhR itself. See **Enzyme induction** for further information.

Alanine aminotransferase (ALT), formerly known as serum glutamic pyruvic transaminase (SGPT), is an enzyme responsible for the transfer of an amino group from alanine to α-ketoglutarate. ALT is found mainly in the liver, but also in kidney, skeletal muscle, and myocardium. The serum activity is monitored as part of the routine clinical chemistry panel. Elevated plasma activity can be an indication of liver toxicity. See **Liver enzymes**, **Liver damage**, and **Liver function test** for further information.

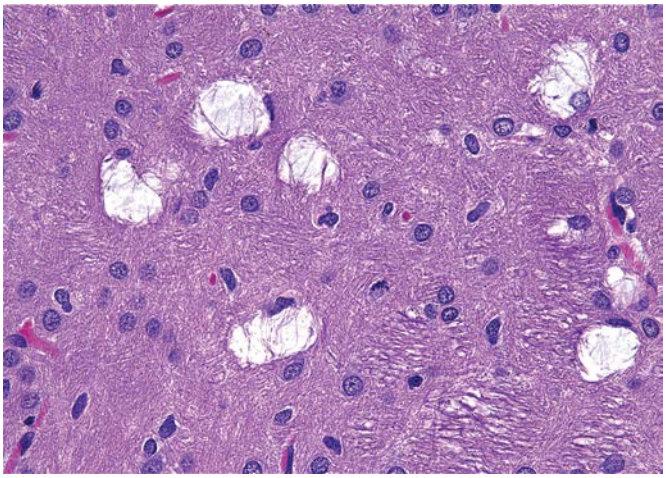
Albumin is a protein produced by the liver. It is the most abundant protein in plasma, accounting for almost 50% of the total protein content with a nominal concentration range of 2–3 g/dL in rodents, 3.0–3.5 g/dL in beagle dogs, 3.0–5.0 g/dL in mini-pigs, 4.0–5.0 g/dL in cynomolgus monkeys, and 3.0–5.0 g/dL in humans. Circulating albumin is important in the plasma protein binding of many drugs as well as endogenous ligands such as fatty acids, hormones, and calcium; therefore, alterations in normal albumin concentrations in the blood may result in secondary effects on total and free drug or substrate concentrations. These changes may indirectly affect the potential for toxicity. Albumin concentration in the blood will often decrease in acute-phase inflammatory reactions, as liver catabolism of albumin is often cited as the primary source for amino acids required in the synthesis of acute-phase inflammatory proteins.

Albumin binding is the non-covalent interaction of a drug with plasma albumin. See **Plasma protein binding** for further information.

Albuminuria is the secretion of significant levels of albumin in the urine, usually as a sign of kidney damage or toxicity.

Synonym(s): **Proteinuria**.

Alcohol artifact is caused by holding immersion-fixed central nervous system (CNS) tissues in >70% ethanol for prolonged periods. Methanol added as a stabilizing agent to standard buffered formalin preparations can also contribute to alcohol artifact. The artifact has the potential to mask a pathologic lesion, especially intramyelinic edema. Alcohol artifact is usually bilaterally symmetric, affects white matter more than gray matter, and tends to be more pronounced in superficial areas of the brain, along the cut edge of tissue blocks, and in the optic nerve. Alcohol artifact often occurs in laboratories where many tissues (not just brain) are processed in bulk. Steps can be taken to prevent this artifact but often requires processing of neural tissues separately from other tissues, which may not be practical, especially where brain is not the focus of a study, or where histologic processes are optimized to prepare other tissues such as retina. Transferring tissues to 70% ethanol after fixation may also be necessary to optimize immunohistochemistry on formalin-fixed tissues for some antigens/antibodies. See **White matter vacuolation** and **Intramyelinic edema** for further information.



Alcohol artifact. Irregularly shaped but generally round clear spaces often traversed by fine pink strands are an artifact commonly encountered in formalin-fixed CNS tissues, particularly within white matter following prolonged exposure to alcohol. Rat. H&E.

Alcohol dehydrogenase (EC 1.1.1.1) is a family of enzymes responsible for the formation of aldehydes from alcohols using nicotinamide adenine dinucleotide (NAD) as a cosubstrate:

$$\text{R-CH}_2\text{OH} + \text{NAD}^+ \rightarrow \text{R-CHO} + \text{NADH} + \text{H}^+$$

Several different forms of human liver alcohol dehydrogenase (which is a zinc-containing dimer of 2-polypeptides) exist. The aldehyde products may be more toxic than the alcohols from which they are formed and can be further metabolized by aldehyde dehydrogenases. See **Aldehyde dehydrogenase** for further information.

Alcohol-related birth defects in humans manifest as intrauterine growth retardation (IUGR), mental retardation, small head, and facial defects (eye, nose). See **Fetal Alcohol Syndrome (FAS)**.

Aldehyde dehydrogenase (EC 1.2.1.3) is a family of enzymes responsible for the conversion of aldehydes into the corresponding carboxylic acid, using either NAD or NADP and water as cosubstrates:

$$\text{R-CHO} + \text{NAD}^+ \text{H}_2\text{O} \rightarrow \text{R-COOH} + \text{NADH} + \text{H}^+$$

In this reaction, the aldehyde reacts with a cysteine moiety at the active site of the enzyme forming an acyl cysteine and donating the hydrogen to the NAD. The acyl cysteine is then hydrolyzed by water, releasing the carboxylic acid.

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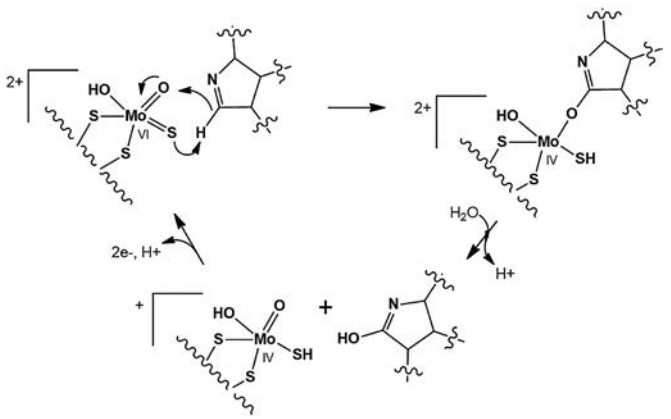
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Aldehyde dehydrogenase activity has a polymorphic distribution within the human population, whereas people who are deficient in aldehyde dehydrogenase activity have a lower tolerance for alcohol, since the unpleasant effects of excess alcohol consumption are caused by the buildup of acetaldehyde. This fact is used in the treatment of alcoholism by the drug disufiram, which is an aldehyde dehydrogenase inhibitor.

Aldehyde oxidase (EC 1.2.3.1) is a molybdenum-containing flavoprotein which catalyzes the conversion of aldehydes to carboxylic acids and the hydroxylation of some heterocyclic drugs.

$$\text{R-CHO} + \text{H}_2\text{O} + \text{O}_2 \rightarrow \text{R-COOH} + \text{H}_2\text{O}_2$$

This enzyme reduces oxygen during the reaction, but the oxygen atom incorporated into the aldehyde originates from water. The scheme below shows the mechanism of heterocyclic hydroxylation by aldehyde oxidase:



Aldehyde oxidase activity is generally higher in the liver of primates than rodents and dogs. Thus, rodent ADME studies may underestimate the contribution of aldehyde oxidase to the overall metabolism of a drug in humans that can cause unexpectedly rapid clearance of drugs that are substrates, resulting in unexpected toxicities or a lack of efficacy.

Aldosterone is a mineralocorticoid steroid hormone produced in the zona glomerulosa of the adrenal gland. See **Mineralocorticoid** for further information.

Aliesterases, see **Carboxylesterase** for further information.

Alkaline phosphatase (ALP) is an enzyme whose activity is often measured as part of a clinical chemistry panel in general toxicology studies. Increased plasma activity of ALP may result from hepatobiliary, bone, or kidney toxicity. In cases where there is no correlative tissue histopathology, isoenzyme characterization may be used to determine the tissue of origin. Serum ALP normally declines with age, and the differences between younger and older animals can be pronounced, especially in rodents.

Alkalosis is an increase of alkali or basic substances in the body resulting in a plasma >pH 7.45. Alkalosis may be respiratory in origin resulting from hyperventilation and excess loss of carbon dioxide, or metabolic in nature associated with prolonged vomiting, hypovolemia, diuretic use, and hypokalemia (i.e., an increase in bicarbonate (HCO_3^-), with or without a compensatory increase in carbon dioxide partial pressure (P_{CO2}), where pH may be high or nearly normal).

Allele is a gene variant, normally a mutant.

Allergen is an agent that may induce a vigorous immune response resulting in an allergic reaction. The ability of drugs to induce immune responses is assessed in sensitization tests, such as the local lymph node assay. See **Skin sensitization tests** and **Local lymph node assay** for further information.

Allergy is a hypersensitivity reaction caused by an immune response to an allergen.

Allometric scaling is the relationship between body mass and other body functions (e.g., metabolic rate) or body structures (e.g., bone length). In drug development, allometric scaling is used to predict the pharmacokinetic properties of a drug in humans based on the pharmacokinetic behavior in animal species. In combination with efficacy data from in vitro experiments and animal models, this data can predict the human therapeutic dose. Although elaborate physiologically based pharmacokinetic (PBPK) models are available, the guidance for determining the safe starting dose for a Phase 1 clinical trial uses scaling based on body surface area. The table in the next page is taken from the FDA guidance (Guidance for Industry Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers, July 2005).

Allowable human daily intake (AHDI) is an estimate of the amount of food additive or food component that may be consumed daily over a lifetime without appreciable risk to health. ADHI is also known as acceptable daily intake (ADI).

Alopecia is the complete loss of hair and is a common cutaneous toxicity secondary to systemically administered drugs, particularly to chemotherapeutic agents that have an effect on disrupting the cell cycle in actively dividing cells, such as those in the hair matrix during hair shaft generation in the anagen phase of the hair cycle. Numerous chemotherapeutic agents can induce alopecia, with four major classes of agents that are classified based on their mechanism of inducing alopecia. Microtubule inhibitors, such as paclitaxel, induce the highest incidence of alopecia at >80%, followed by topoisomerase inhibitors such as doxorubicin at 60–100%, nucleic acid alkylators such as cyclophosphamide at 60%, and 10–50% for antimetabolites that only damage cells during S phase, when

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Conversion of Animal Doses to Human Equivalent Doses Based on Body Surface Area

Species	To Convert Animal Dose in mg/kg to Dose in mg/m², Multiply by k_m	To Convert Animal Dose in mg/kg to in HED[a] in mg/kg, Either:	
		Divide Animal Dose by	Multiply Animal Dose by
Human	37	–	–
Child (20 kg)[b]	25	–	–
Mouse	3	12.3	0.08
Hamster	5	7.4	0.13
Rat	6	6.2	0.16
Ferret	7	5.3	0.19
Guinea pig	8	4.6	0.22
Rabbit	12	3.1	0.32
Dog	20	1.8	0.54
Primates			
Monkeys[c]	12	3.1	0.32
Marmoset	6	6.2	0.16
Squirrel monkey	7	5.3	0.19
Baboon	20	1.8	0.54
Micro-pig	27	1.4	0.73
Mini-pig	35	1.1	0.95

[a] Assumes 60 kg human. For species not listed or for weights outside the standard ranges, HED can be calculated from the following formula:

HED = Animal does in mg/kg × (Animal weight in kg/Human weight in kg)$^{0.33}$

[b] This k_m value is provided for reference only since healthy children will rarely be volunteers for Phase 1 trials.

[c] For example, cynomolgus, rhesus, and stumptail.

they are actively synthesizing DNA, such as 5-fluorouracil plus leucovorin or methotrexate. Combinations of two or more chemotherapeutic agents usually induce a greater incidence and more severe alopecia than single-agent chemotherapy does. There are two commonly used animal models for modeling chemotherapy-induced alopecia. The first is neonatal rats that have follicles synchronized in anagen shortly after birth, and the second is depilation of adult mice in order to synchronize the hair follicles in anagen. These models have allowed investigation of mechanisms underlying the development of chemotherapy-induced alopecia, as well as evaluation of agents for the potential prevention and/or therapy of alopecia. A number of agents have been tested for their ability to prevent alopecia in these models, including cyclosporin A, minoxidil, antioxidants, apoptosis inhibitors, and a variety of cytokines and growth factors, all with variable degrees of effectiveness. Regardless of the specific agent that induces the alopecia, the histopathologic appearance of lesions is similar, with single cell necrosis or apoptosis of follicular keratinocytes, particularly those in the hair bulb and/or hair matrix epithelium. Sebaceous gland toxicity has also been described following administration of chemotherapeutic agents and may be associated with or be a contributing cause of alopecia, since sebum is an essential component for normal hair growth.

α1-acid glycoprotein is an acute-phase protein produced by the liver and found in the plasma, where it may bind basic drugs. As an acute-phase protein, the plasma levels may increase as a consequence of inflammation, which may result in increased binding of basic drugs to plasma proteins. See **Plasma protein binding** for further information.

Alpha 2u-globulin (α-2u-g) hyaline droplet nephropathy, see the preferred term **Hyaline droplet nephropathy**.

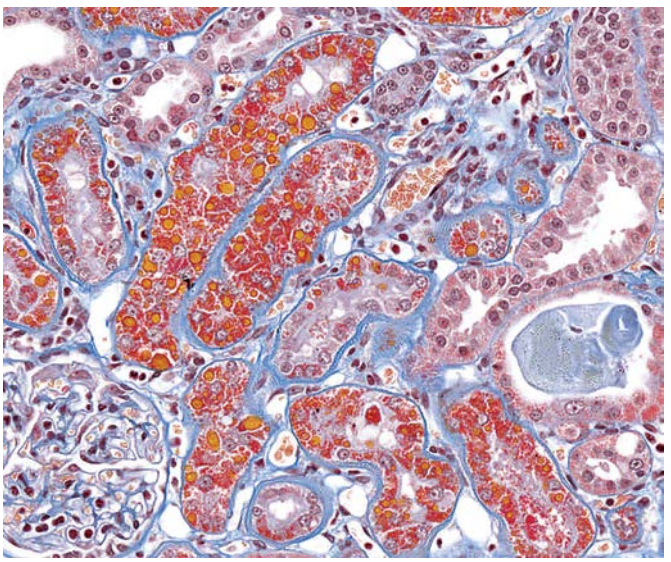
Alpha 2u-globulin (α-2u-g) nephropathy is a specific form of chemically induced rat nephropathy that can be associated with the development of renal tubule tumors, and which is considered to be species- and gender-specific. Alpha 2u-g is a circulating, low-molecular-weight protein synthesized in large amounts in the liver of the mature male rat but not in female rats and is not abundantly produced in any other species. Female rats do synthesize α-2u-g but only in small amounts in glands such as the perianal and Meibomian glands and in the salivary glands of both sexes. In the male rat, the protein is freely filtered through the glomerulus, and is reabsorbed by the proximal convoluted tubule (PCT) cells, where it is degraded within lysosomes. The PCT cytoplasmic hyaline droplets in the normal mature male rat consist of α-2u-g. Compared to other circulating low-molecular-weight proteins, α-2u-g has a lengthy half-life measured in hours rather than minutes. Some xenobiotic hydrocarbons with properties of lipophilicity and small steric volume bind to circulating α-2u-g and make the protein more difficult to catabolize in the phagolysosome,

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leading to a chronic form of cell loss. The intracytoplasmic accumulation of the protein is seen as bright, eosinophilic hyaline droplets within a few days of chemical exposure when stained by hematoxylin and eosin (H&E), and the droplets often have a crystalloid appearance denoting pure protein. The droplets are better visualized with Mallory Heidenhain stain or by fluorescence microscopy. After a few weeks, chronic cell loss results in formation of granular casts at the junction of the outer and inner stripes of the outer medulla, where the P3 segment of the proximal tubule narrows into the thin descending limb of Henle. After a few months of exposure to the inciting substance, linear mineralized deposits form in the descending limb of Henle loops, proximal to the sharp hairpin turn, and the granular casts tend to disappear. Exacerbated hyaline droplets in the PCT, granular casts, and linear papillary mineralization are almost pathognomonic for α-2u-g nephropathy. Chronically, when a majority of a treatment group is noticeably affected, exacerbation of the lesions of chronic progressive nephropathy and renal tumors occurs. It is presumed that chronic cell loss is the mode of action underlying tumor formation, but as this is a species-specific phenomenon, the tumors are not considered relevant for species extrapolation in hazard or risk assessment. The male mouse also synthesizes an abundant protein (mouse urinary protein [MUP] with pheromonal activity) that is excreted in urine, but has different biologic properties than α-2u-g.

Synonym(s): **Renal eosinophilic droplets**; **hyaline droplet nephropathy**.



Alpha 2u-globulin nephropathy, rat kidney, Mallory Heidenhain. (Reproduced with permission of Society of Toxicology from Frazier et al. 2012.)

Alpha helix is a right-handed spiral and a common secondary structure motif in proteins.

Alpha 2u-globulin is a small protein (MW 18,700 Daltons) produced by the liver of the male rat and whose levels are controlled by androgenic hormones. It readily filters through the glomerulus with about 50% of the protein in the filtrate being reabsorbed in the proximal tubules of the nephron. A number of agents (e.g., d-limonene, unleaded gasoline, 1,4-dichlorobenzene, etc.) bind to α-2u-globulin in the male rat and increase its production. Excessive production and reabsorption in the proximal tubules can result in increased α-2u-globulin concentrations that may become toxic to the proximal tubular cells, resulting in an α-2u-globulin nephropathy. Chronic treatment with agents that cause this nephropathy may result in kidney tumor formation in the male rat, but not in female rats.

Alteration in iris color, see the preferred terms **Iris increased pigmentation** or **Iris decreased pigmentation**.

Alternate splicing is a process needed to generate different gene products (proteins) from the same gene, by different processing of the same transcript to produce different mRNAs.

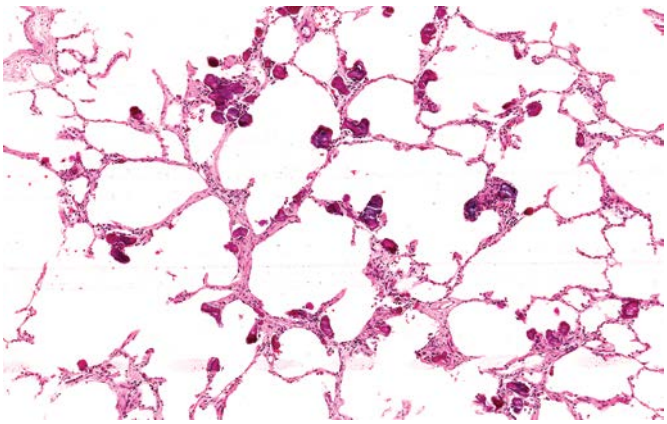
Alveolar clearance is the process of removal of agents deposited in the lung. Such clearance occurs by several different processes depending on the solubility of the agents. Insoluble particles may be transported on the mucociliary escalator or be subject to phagocytosis by pulmonary macrophages, whereas soluble agents and proteins may be subject to endocytosis by alveolar epithelial cells (transcytosis), or to paracellular diffusion across the epithelial barrier. Some proteins, such as albumin, may also be cleared by receptor-mediated processes.

Alveolar lipoproteinosis, see the preferred term **Pulmonary alveolar proteinosis**.

Alveolar macrophages play an important role in innate immunity in the lung, and act as antigen-presenting cells. This second function, when combined with their mobility (via transepithelial migration to the lymphatic system) means they are an important link between innate and adaptive immunity. In sections taken from lungs fixed by formalin instillation, alveolar macrophages appear rounded and often "free-floating" in the alveolar airspace. This is an artifact of the fixation technique, and in healthy lungs fixed with formalin vapor, they appear flattened, and typically concentrate at alveolar septal junctions. Ultrastructurally, they are characterized by the presence of numerous mitochondria and secondary lysosomes. Activated macrophages have been subdivided into classically activated (M1), which have largely antiproliferative, inflammatory, and cytotoxic activity, and alternatively activated (M2), which have a generally anti-inflammatory impact and are involved in initiation of wound healing and tissue remodeling. The activation state is dynamic, and an individual macrophage may switch between states depending on its environment. There is also evidence of regulation of the alveolar macrophage inflammatory response by direct interaction with the airway epithelium. Markers of an activated state include inducible nitric oxide synthase for M1 macrophages and arginase 1, Fizz1, and Ym1/2 for M2 macrophages. CD68 IHC is commonly used as a general marker for alveolar macrophages.

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Alveolar microlithiasis refers to the presence of rounded, basophilic bodies with a characteristic "onion skin" appearance within alveolar spaces. Their cellular origin is often difficult to determine, sometimes appearing apparently free in the alveoli, but sometimes seeming to overlie alveolar epithelial type II cells. The microliths may become ossified (mineralized). The mineralization does not usually elicit an inflammatory reaction but may be associated with interstitial fibrosis.



Alveolar microlithiasis, lung, dog, H&E.

Alzheimer Type II astrocytes, see the preferred term **Type II astrocytes**.

Ameloblast degeneration/necrosis may be caused by pharmaceutical agents that affect signaling pathways in development and differentiation of ameloblasts, resulting in atrophic or malformed teeth and shrinkage or disappearance of ameloblasts and other elements of tooth formation. This is evident especially in rodent incisors, which are constantly growing. Rabbits, guinea pigs, and any animal with constantly growing teeth might be similarly affected. Other agents that interfere with normal ameloblast function include tetracycline, colchicine, and an above optimal intake of fluoride. Pitted, discolored, and irregular enamel formation may occur when exposure occurs during tooth development. Disruption of enamel production may take place when there are high fevers, viral infections (such as canine distemper), or imbalance of minerals such as fluoride.

Differential diagnosis: **Autolysis**.

Ameloblastic fibro-odontoma, see the preferred term **Ameloblastic odontoma**.

Ameloblastic odontoma is a benign, mixed tumor of odontogenic (dental) origin that contains a variety of dental components (e.g., enamel, dentin, osteodentin, pulp) with the hard tissue (odontoma component) centrally located and neoplastic ameloblasts (soft tissue/ameloblastic component) at the tumor edges. Refer to **Bone, Muscle, and Tooth** in Appendix 2 for further information.

Ameloblastoma is a benign, expansile to infiltrative neoplasm of dental epithelial cells arranged in a variety of patterns (e.g., follicular, plexiform) surrounding stellate cells. No dental hard tissues are present. Refer to **Bone, Muscle, and Tooth** in Appendix 2 for further information.

Ameloblastoma, acanthomatous is locally invasive, often aggressive oral tumor in dogs composed of nonkeratinizing, polygonal, odontogenic epithelium arranged in wide sheets and cords bordered by a row of tall columnar cells, and central acantholytic cells with intercellular bridges. Refer to **Bone, Muscle, and Tooth** in Appendix 2 for further information.

Ameloblastoma, peripheral, see the preferred term **Ameloblastoma, acanthomatous**.

Ameloblasts are tall columnar cells with basal nuclei that produce enamel, the outer tooth layer, which is the hardest substance in the body, and these cells are present only during tooth formation. Animals such as rodents, with constantly growing incisors, have ameloblasts present in the incisor roots throughout their life, whereas animals such as dogs will no longer have ameloblasts once the permanent teeth have formed. Ameloblasts are derived from ectoderm and first secrete the pre-enamel, a collagenous matrix, which later mineralizes. The space occupied by enamel usually appears as a space in decalcified tissue sections as enamel dissolves during processing.

American Association of Poison Control Centers is a voluntary organization that supports poison centers in America. It maintains the Poison Data System, a national poison database.

American Board of Medical Toxicology (ABMT) is an organization of physicians specializing in medical toxicology founded in 1974. The ABMT was replaced by the American College of Medical Toxicology (ACMT) in 1993.

American Board of Toxicology (ABT) is a board that has been established globally to assess and confer accepted credentials for competency in toxicology.

American Board of Veterinary Toxicology is a group of specially trained veterinarians whose goals are to inform and educate the public, and whose principle membership includes private practice veterinarians, and veterinary students whose goals are to evaluate toxicological hazards to pets, livestock, and wildlife.

American College of Toxicology is a professional organization of toxicologists whose goals are to educate, lead, and serve toxicology and other safety science fields by exchanging information and views on applied toxicology and safety assessment.

Ames test is a bacterial assay to test for reverse gene mutations, using histidine-dependent *Salmonella typhimurium*

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strains developed in the 1970s by Bruce Ames, Professor of Biochemistry at UC-Berkeley, which can detect both frame shift and base substitution mutations. The properties of the major tester strains are shown in the table below.

Bacterial Strain	Target gene	Plasmids	Type of Mutation
S. typhimurium TA100	hisD	pKM101	Frame shift
S. typhimurium TA98	hisG	pKM101	Base-pair substitution
S. typhimurium TA102	hisG	pKM101, pAQ1	Base-pair substitution
S. typhimurium TA1537	hisG		Base-pair substitution
S. typhimurium TA1537	hisC		Frame shift
Escherichia coli WP2 uvrA	trp		Base-pair substitution

When developed by Ames, the system was novel in that it used a metabolic activating system with rat liver subcellular fractions to generate mutagenic metabolites from promutagenic compounds. It is the widest used genotoxicity test and a very good predictor of genotoxic carcinogens.

Amine oxidases (EC 1.4.3.21 and 1.4.3.22) is a family of copper-containing enzymes that catalyze the oxidative deamination of aliphatic amines thereby converting the amine into the corresponding aldehyde:

$$\text{R-CH}_2\text{NH}_2 + \text{O}_2 + \text{H}_2\text{O} \rightarrow \text{R-CHO} + \text{H}_2\text{O}_2 + \text{NH}_3$$

Amino acid conjugation is a Phase 2 reaction in which xenobiotic carboxylic acids are conjugated with an amino acid such a glycine, glutamine, or taurine. Amino acid conjugation occurs in the mitochondria. In a first step, the carboxylic acid reacts with coenzyme A to form a thioester in an ATP-dependent reaction catalyzed by acyl CoA synthetases. The drug thioester then reacts with the amine group of the amino acid in a reaction catalyzed by acyl CoA amino acid *N*-acyltransferase.

$$\text{R-COOH} + \text{ATP} \rightarrow \text{R-CO} \sim \text{AMP} + \text{PPi} + \text{H}_2\text{O}$$

$$\text{R-CO} \sim \text{AMP} + \text{CoA-SH} \rightarrow \text{R-CO} \sim \text{S-CoA} + \text{AMP}$$

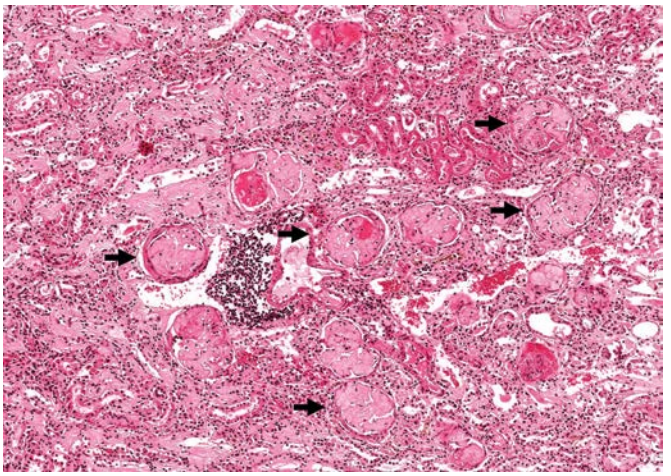
$$\text{R-CO} \sim \text{S-CoA} + \text{NH}_2\text{CH}_2\text{COOH} \rightarrow \text{R-CO-NHCH}_2\text{COOH} + \text{CoA-SH}$$

Several different acyl CoA synthetases, or ATP-dependent acid:CoA ligases, are known, including short-chain/acetyl CoA synthetase (acetate: CoA ligase [AMP], EC 6.2.1.1); medium-chain/butyryl CoA synthetase (medium-chain fatty acid: CoA ligase [AMP], EC 6.2.1.2), long-chain fatty acyl CoA synthetase (acyl CoA synthetase, long-chain fatty acid: CoA ligase EC 6.2.1.3) and a GTP dependent medium-chain fatty acid: CoA ligase [GDP], EC 6.2.1.10). Of these, the medium- and long-chain fatty acid synthetases appear to be the most involved in forming coenzyme A esters of carboxylic acid drugs. The acyl CoA amino acid *N*-acyl transferases are specific for the amino acid conjugated but will accept a variety of acyl CoA substrates.

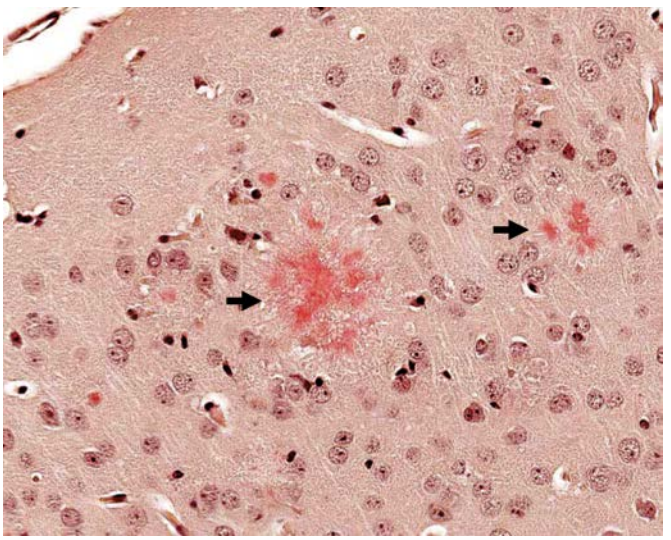
Amphophilic-vacuolar (A-V) tumor is a morphologically distinct benign or malignant neoplasm of the rat kidney composed of lobules of eosinophilic- or amphophilic-staining tubular cells containing vacuolated cytoplasm. A-V tumors are suspected of being familial (genetic) in origin. These neoplasms do not metastasize and are not chemically induced. Refer to **Urinary System** in Appendix 2 for further information.

Ampullary glands are branched tubular glands lined by simple columnar epithelium formed as an enlargement of the ductus deferens in its terminal portion and are present in rodents and dogs.

Amyloid is extracellular material associated with a number of inherited and inflammatory disorders in which



Amyloid in the renal glomeruli of a mouse, H&E. Glomeruli (as indicated by arrows) are expanded by accumulation of amorphous eosinophilic substance interpreted as amyloid. (Reproduced with the permission of Germann, P. and Morawietz, G. (eds.) *Toxicopathology Case Collection CD-ROM*. European Society of Toxicologic Pathology.)



Amyloid in the brain of a transgenic mouse, Congo red stain. Multiple foci (as indicated by arrows) of irregular eosinophilic positive staining material are noted between neurons. (Reproduced with the permission of Germann, P. and Morawietz, G. (eds.) *Toxicopathology Case Collection CD-ROM*. European Society of Toxicologic Pathology.)

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deposits of fibrillary (beta-pleated) proteins are responsible for tissue damage and functional compromise. Amyloid deposits can be observed by microscopic examination revealing an amorphous, eosinophilic substance that stains pink to orange-red following Congo red staining and displays characteristic apple-green birefringence by polarized microscopy.

Analgesic nephropathy, see the preferred term **Renal papillary necrosis**.

Analgesics are agents that produce loss of sensory perception (analgesia or numbness). Analgesics are generally given to relieve pain sensations. They may act on peripheral or central nervous systems and include opioids and nonsteroidal anti-inflammatory drugs (NSAIDs).

Anaphylaxis is a serious, rapid allergic reaction triggered by the release of inflammatory modulators and cytokines from mast cells and basophils. It is usually an immunologic reaction triggered by an antigen; however, some substances such as macrolide antibiotics or some formulation excipients may directly cause mast cell degranulation in laboratory animals in toxicity studies.

Androblastoma, see the preferred terms **Sertoli-Leydig cell mixed tumor, benign** and **Sertoli-Leydig cell tumor, benign**.

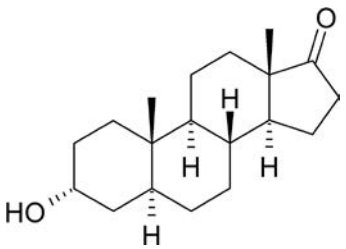
Androblastoma, malignant, see the preferred term **Sertoli cell tumor, malignant**.

Androgen is a hormone produced from the precursor substance, cholesterol, primarily by the gonads and/or the adrenal glands. Androgens direct embryological sex organ development and adult secondary male sexual characteristics in mammals by binding organ-specific androgen receptors. Androgenic hormones include dihydrotestosterone (DHT), androstenedione, testosterone, dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEA-S), androstenedione (A4), and androstanediol (A5). Testosterone is the primary male sex hormone of the postnatal period and beyond and is intimately involved in the development of muscle and bone mass, body hair growth and distribution, and other sex-specific characteristics for both males and females. In addition, testosterone plays a role in thromboxane A_2 receptor function, and thus regulates platelet aggregation in humans and nonhuman primates.

Androgen-binding protein (ABP) is a glycoprotein produced by the Sertoli cells in the testes and secreted into the luminal fluid where it binds testosterone, enabling its transport in the seminiferous tubule fluid to the epididymis. It is similar in structure to the sex hormone–binding protein produced in the liver and binds testosterone in the plasma.

Androgens are hormones that stimulate the development of male characteristics through interaction with an androgen receptor. The main androgens are testosterone, dihydrotestosterone, and androstenedione. See **Male sex hormones** for further information.

Androsterone is a metabolite of testosterone which is a relatively weak androgen. See **Male sex hormones** for further information.



Anemia is a condition caused by a decrease in red blood cell parameters (red blood cell count, hematocrit, hemoglobin) in the blood, which may be caused by a toxicity to the bone marrow, by blood loss, or by destruction of red blood cells. The term *anemia* should be used judiciously in toxicology studies (if at all), as it is a diagnostic clinical term and hence more appropriate only when the reduction in red blood cell mass would be expected to result in a true deficiency of the oxygen-carrying capacity of the blood.

Anemic hypoxia is a condition caused by decreased blood oxygen levels as a result of anemia and the accompanying reduction in hemoglobin levels.

Anesthetic is an agent that produces lack of sensory perception in either a specific area (local or regional), or an overall (general) effect via systemic administration. In the systemic administration, a loss of both sensation and consciousness is produced. This is sometimes referred to as "painless sleep." Local anesthetics act by preventing nerve transmission via blocking sodium channels.

Anestrus is the cessation of the estrous cycle characterized morphologically by atrophy of the female reproductive tract (i.e., ovary, uterus, and vagina/cervix) and vaginal/cervical mucification (See **Increased vaginal mucinification** for further information). In all laboratory species, anestrus can be associated spontaneously with age-related senescence. Xenobiotics that markedly decrease body weight gain or block the hypothalamic-pituitary-ovarian (HPO) axis directly and inhibit ovarian production of steroid hormones may also lead to anestrus. Anestrus is part of the normal cycle for the dog and is of long duration (80–240 days). In a retrospective review of 102 control laboratory beagles used in toxicology studies, over 50% were anestrus.

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Aneuploidy is a numerical aberration of chromosomes—either duplication or loss of individual chromosomes of a chromosome set.

Aneurysm is a localized dilation of a vessel wall. This can affect blood vessels of all types and also lymphatics, but the term is most often applied to large elastic arteries and the aorta. Dilation occurs due to localized mural weakness that allows blood pressure to distend the vessel focally, usually causing thinning of the vessel wall. Morphologically, aneurysms can be classified as dilated or dissecting. Dilated aneurysms appear as distensions of the vessel wall, which may be concentric or along one side of the vessel. The vessel wall is thinner at the site of distension, with the media primarily affected. Dissecting aneurysms usually occur following tearing of the intima, with blood entering the vessel wall and pooling within it. The affected wall then expands externally due to formation of a mural cystic space. Weakening can be due to a variety of causes that result in injury or remodeling, including accumulation of exogenous and endogenous materials, dietary deficiencies, and localized stress. Copper deficiency and copper chelators, such as β-aminopropionitrile and penicillamine, cause aneurysms by impairing the function of lysyl oxidase, a copper-containing enzyme essential for the cross-linking of collagen and elastin. Pharmaceuticals that cause segmental vasodilation or vasoconstriction can cause weakness of vessel walls. Aneurysms are rare in common laboratory species but can occur in genetically predisposed strains and experimental animal models. Aneurysmal rupture of large elastic arteries or the aorta can result in death.

Differential diagnoses: **Hematoma**; **Angiectasis**.

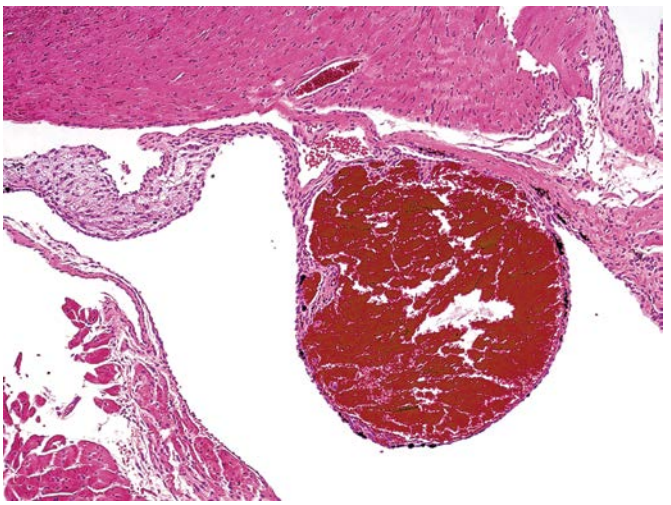


Aneurysm, aorta, rat, H&E.

Angiectasis refers to a focal collection of dilated blood vessels. This phenomenon may occur due to congestion, weakening of vessel walls, or increases in hemodynamic pressure. Morphologically, small blood vessels or clear spaces lined by a single layer of flattened endothelial cells are seen. Areas of angiectasis are not usually circumscribed. Varying numbers of erythrocytes are present within the spaces or lumens, depending on the exsanguination status of the animal. Angiectasis can occur in any organ and should be differentiated from agonal or postmortem artifacts.

Differential diagnosis: **Hemangioma**.

Synonym(s): **Telangiectasis (in liver)**; **vessel dilatation**; **sinus/vessel dilation**.



Angiectasis, valve, Rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology.)

Angiolipoma, infiltrative, see the preferred term **Angioma, intramuscular**.

Angiolipoma, intramuscular, see the preferred term **Angioma, intramuscular**.

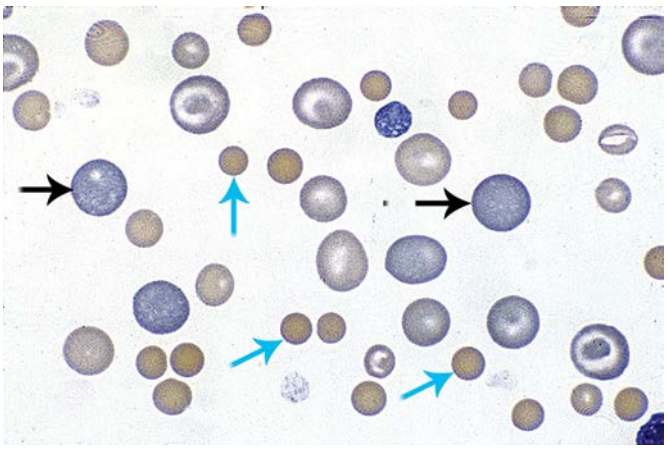
Angioma, intramuscular is a mass of variable size that develops within skeletal muscles. These masses are composed of numerous profiles of small capillaries or cavernous blood vessels filled with red blood cells and separated by collagenous stroma. In the majority of cases, these vascular proliferations are associated with the accumulation of mature white adipose cells and are referred to as infiltrative angiolipomas. Refer to **Bone, Muscle, and Tooth** in Appendix 2 for further information.

Angiomatous hyperplasia is a focal, well-demarcated lesion consisting of increased numbers of capillaries and other vascular structures lined by normal-appearing, flattened endothelium. The lesion is most frequently seen in the subcutaneous adipose tissue. Refer to **Cardiovascular System** in Appendix 2 for further information.

Anisocytosis means variation in the size of red blood cells. Anisocytosis may be due to the presence of cells that are larger and/or smaller when compared to normally sized erythrocytes. Healthy individuals will have a low level of anisocytosis due to the presence of low numbers of polychromatophilic

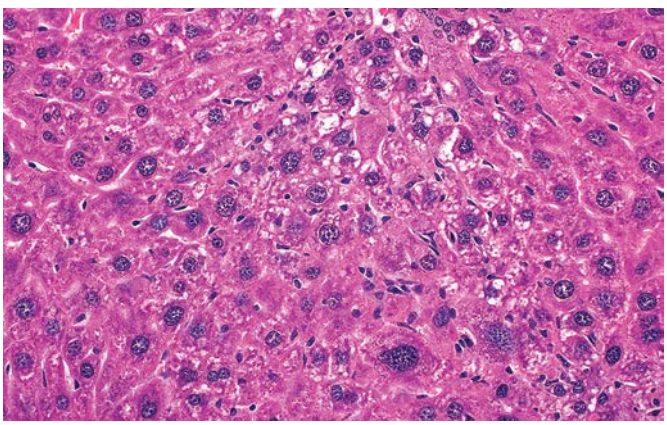
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erythrocytes, which are larger than mature red blood cells. Macrocytosis, or large red blood cells, can occur due to either congenital or acquired conditions, with B_{12} or folate deficiency being the most common. Microcytosis can also occur through either congenital or acquired conditions, with iron deficiency being the most prevalent cause. High levels of anisocytosis in animals are often observed as a regenerative response to hemolytic anemia. The red cell distribution width is a quantitative assessment of variation in red blood cell size.



Marked anisocytosis, hemolytic anemia, cynomolgus monkey. Red cells range in size from very small microspherocytes (blue arrows) to large, blue-gray polychromatophilic erythrocytes (black arrows).

Anisokaryosis is an increased variation in nuclear size greater than that expected in a particular tissue. Normal nuclear size and shape varies by both tissue and species. Increased anisokaryosis is seen in cases of increases in the metabolic demands of a tissue in response to damage or following neoplastic transformation. See **Nuclear atypia** for further information.



Anisokaryosis and anisocytosis of hepatocytes with *N*-nitrosodiethylamine (DEN)- and carbon tetrachloride (CCl4)-induced liver injury in a mouse, H&E.

Anitschkow cell sarcoma, see the preferred terms **Intramural schwannoma** or **Endocardial schwannoma**.

Anophthalmia is a rare unilateral or bilateral developmental absence of the globe in the orbit, frequently associated with histologic abnormalities of the brain and extraocular tissues. In laboratory animals, anophthalmia is most frequently identified as a sporadic spontaneous finding in certain strains of rodents (e.g., C57BL/10 mice), in genetically engineered mice with mutations in SOX2, OTX2, STRA6, BCOR, HCCS, BMP4, and SMOC1, and in teratogenic studies in rodents and rabbits. This finding must be differentiated from an extreme variant of microphthalmia.

Differential diagnosis: **Microphthalmia**.

Anovulatory cycle is a nonproductive estrous cycle in which ovulation does not occur. In nonhuman primate (NHP) toxicology studies, an anovulatory cycle may be observed in aged NHPs, in monkeys recently attaining puberty, in subordinate monkeys, and in mature cycling NHPs, the latter in group housing situations. The uterus will be quiescent in a monkey after an anovulatory cycle.

Differential diagnosis: **Anestrus**.

Anoxia is a severe form of hypoxia, with complete absence of oxygen supply to the dependent organs and tissues.

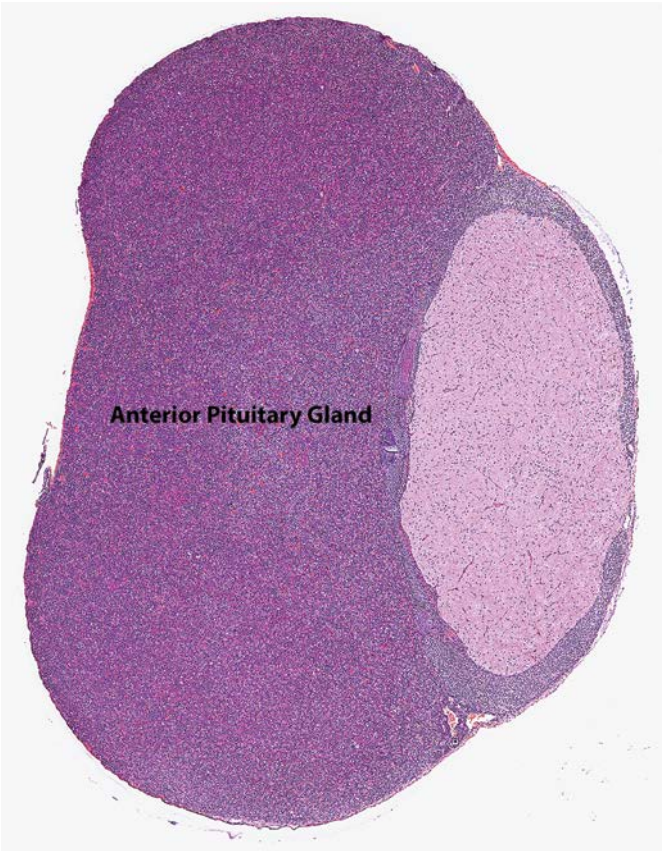
Antagonism (antagonist) is an agent that blocks or modifies stimulation of a receptor or set of receptors (system) from causing the normally expected response to the agonist or another agent. Beta adrenergic blockers are agonists that block the effects of epinephrine. They are used to treat a variety of conditions (e.g., high blood pressure, migraines). Antagonism may be pharmacological—that is, caused by an administered antagonist acting at the same site as the agonist.

Anterior pituitary gland is composed of the pars distalis, pars tuberalis, and pars intermedia subcompartments that are derived embryologically from Rathke's pouch. The anterior pituitary gland is one of the two lobes of the pituitary gland and is responsible for producing six essential hormones from five cell types: somatotropes, lactotropes, corticotropes, gonadotropes, and thyrotropes. Acidophils are named for their deeply eosinophilic cytoplasm when stained with hematoxylin and eosin (H&E) and include the somatotropes and lactotropes that secrete growth hormone (GH) and prolactin, respectively. Basophils that stain blue to pale pink with H&E stain are corticotropes and secrete adrenocorticotropic hormone (ACTH). Follicle-stimulating hormone (FSH), luteinizing hormone (LH), and thyroid-stimulating hormone (TSH) are produced by gonadotropes and thyrotropes, also known as chromophobes due to their poorly staining or clear cytoplasm. Hormones produced by the hypothalamus serve to regulate those produced by the anterior pituitary gland. Hormones from the hypothalamic nuclei travel along the tuberoinfundibular tract, releasing into a capillary plexus that leads to the anterior pituitary gland. At the anterior pituitary gland, hypothalamic hormones signal up- or down-regulation of anterior pituitary gland hormone production, and release into the circulation. See Appendix 3 for more information.

Synonym(s): **Adenohypophysis, pars anterior**.

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A



Pituitary gland, cynomolgus monkey, H&E.

Anterior prostate, see the preferred term **Coagulating gland**.

Anterior synechia (cornea) is a clinical term for adhesions; see the preferred term **Iris adhesion**.

Antibody-dependent cellular cytotoxicity (ADCC) is an immune-mediated cytotoxicity triggered by the binding of the Fc region on IgG1 or binding of IgG3 to the Fc receptor of effector cells, such as natural killer cells, neutrophils, or monocytes. Once activated through this receptor interaction, the effector cells secrete cytotoxic proteins resulting in the lysis of the target cells (cells with the epitope binding the antibody).

Anticodon is a codon or base triplet of the tRNA molecule that is complementary to the respective mRNA.

Antidiuretic hormone (ADH) is a peptide hormone secreted from the posterior pituitary. Its primary function is to retain water in the body by increasing water reabsorption in the collecting ducts of the kidneys. Higher concentrations of ADH can cause constriction of arterioles, thereby leading to increased arterial blood pressure. ADH secretion is regulated by plasma osmolarity. Decreases in blood pressure and volume, nausea, and vomiting can stimulate secretion of ADH. Deficiency in the secretion of ADH from the posterior pituitary can result in diabetes insipidus, and thus excessive urine production.

Synonym(s): **Arginine vasopressin**.

Antidote is a chemical or drug which is generally given to counteract the undesirable effects of a poison, drug or toxin in the system. An example of an antidote would be giving ethanol or fomepizole to counteract Ethylene glycol poisoning due to the ingestion of automobile antifreeze.

Anuria is the result of the failure of the kidneys to produce urine.

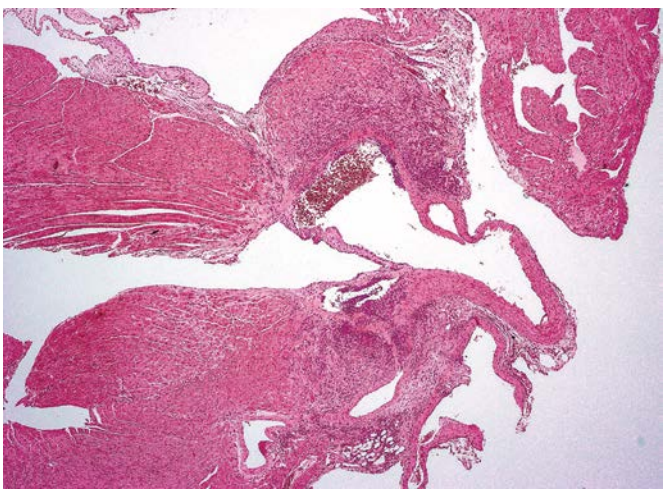
Aortic arteritis, see the preferred term **Aortic inflammation**.

Aortic body tumor, see the preferred term **Paraganglioma**.

Aortic inflammation is most commonly observed at the base or root of the aorta in most species. It may develop as part of a generalized vasculitis or myocardial inflammatory syndrome or appear in isolation. Inflammation can result in narrowing of the vessel due to mural thickening or cause mural weakness that results in aneurysmal dilation, both of which can lead to cardiac malfunction. Aortic inflammation is seen as a spontaneous change in older rodents, usually as part of a generalized vascular or cardiac pathological syndrome such as panarteritis or myocardial degeneration. This finding has been induced by a variety of test items and nutritional regimes. Vitamin A deficiency, high fat diets, and administration of ethanol have all been found to induce localized oxidative stress, leading to aortic inflammation in various rodent strains. Although more often due to noninfectious causes, aortic inflammation can develop due to infectious agents.

In man, aortic inflammation occurs in association with a number of autoimmune syndromes including rheumatoid arthritis, Takayasu arteritis, and systemic lupus erythematosus.

Synonym(s): **Aortic arteritis**; **aortitis**.



Aortic inflammation, rat, H&E.

Aortitis, see the preferred term **Aortic inflammation**.

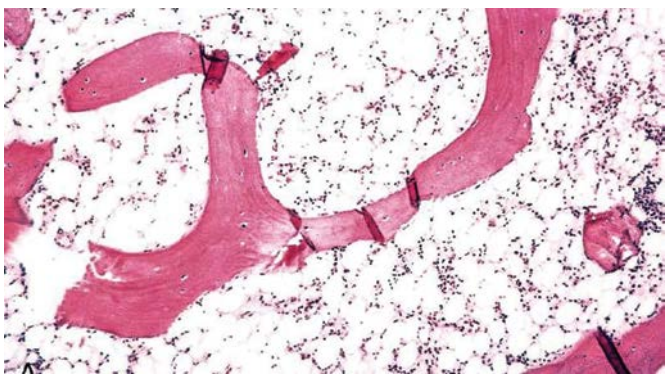
API (active pharmaceutical ingredient) is any substance or mixture of substances intended to be used in the manufacture

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of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product.

Aplasia refers to the lack of tissue or organ due to a failure to develop from an existing primordium or anlage. Partial failure to develop is referred to as hypoplasia. This can be acquired in tissues with rapidly cycling cells, such as the hematopoietic system, where aplastic anemia is an acquired (transient or permanent) failure of red blood cell (RBC) development. Aplasia of hematopoietic cells (aplastic pancytopenia) can result from exposure to antimicrobials, chemotherapeutic agents, and aflatoxin B1, to name a few. See **Agenesis** and **Hypoplasia** for further information.

Aplastic anemia is a rare disease that results in peripheral pancytopenia and severe bone marrow hypoplasia. Damage to bone marrow stem cells results in failure to produce erythrocytes, leukocytes, and platelets. About half the cases of aplastic anemia have an unknown etiology, but others have been linked to chemicals, drugs, radiation, infection, immune disorders, and hereditary defects. Benzene is one of the most common toxicants associated with aplastic anemia. The condition is suspected in individuals with combined anemia, neutropenia, and thrombocytopenia in peripheral blood, but diagnosis needs to be confirmed by bone marrow evaluation to rule out other possibilities such as neoplastic infiltrates or myelofibrosis. Subjects with aplastic anemia are typically treated with immunosuppressive drugs in an effort to achieve remission and bone marrow repopulation.



Severely hypoplastic bone marrow, aplastic anemia, rat (H&E).

Apoptosis is a highly regulated, delicately orchestrated, energy-dependent form of cell death. Through a series of biochemical signals, a cell undergoes self-degradation. Microscopic characteristics include cell shrinkage, nuclear chromatin fragmentation, and the formation of membrane-bound degraded cell components (the "apoptotic body"), which are removed through phagocytosis by neighboring cells or resident macrophages. Because there is internal cellular degradation without the release of cytoplasmic materials into the surrounding substrate, apoptosis does not incite inflammation. Apoptosis is the functional means of cell deletion in embryogenesis central to the morphogenesis of organs, thymic T-cell deletion for programming and self-tolerance, and other organ-specific changes of normal growth and homeostasis. Under pathological conditions such as cell injury or abnormal cell signaling, apoptosis may be induced, resulting in premature or increased cell loss. In general, stimuli that induce apoptosis, and that fail to resolve or escalate in intensity, will shift the signaling cascade away from apoptosis toward cellular necrosis. A recent publication by Elmore et al. (see **General Pathology** in **For Further Reading**) provides guidance to the toxicologic pathologist on the mechanisms, features, and nomenclature of necrosis and apoptosis. Although the terms *single cell necrosis* (i.e., oncotic necrosis) and *apoptosis* have been used interchangeably, the necrotic and apoptotic pathways differ significantly, and the terms should be applied separately where possible.

Apudoma is a tumor originating from cells derived from the embryological neural crest with amine precursor uptake and decarboxylation (APUD) properties when evaluated cytochemically. Refer to **Endocrine Glands** in Appendix 2 for more information.

05APUDoma (APUD = amine precursor uptake and decarboxylase), see the preferred term **Stomach neuroendocrine cell tumor, benign/malignant**.

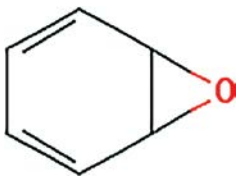
Arachnoid mater is the layer of meninges that holds and forms a barrier between the cerebrospinal fluid (CSF) and external structures. Meninges are composed of three major layers. The pia mater on the surface of the brain follows all the contours. The arachnoid mater holds and forms a barrier between the CSF and external structures. Together, the pia and arachnoid mater are called the leptomeninges. The third and outermost layer of the meninges, the dura mater, forms a thick fibrous covering around the CNS. Refer to Appendix 3 for further information.

Area of basophilic cellular alteration, see the preferred term **Basophilic focus of cellular alteration**.

Area of clear cellular alteration, see the preferred term **Clear cell focus of cellular alteration**.

Area of eosinophilic cellular alteration, see the preferred term **Eosinophilic focus of cellular alteration**.

Arene oxides are epoxides formed in a double bond of an aromatic ring (e.g., benzene oxide). Metabolically, such epoxides are a consequence of cytochrome P450 oxidation. See **Cytochrome P450** for further information.



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Arginine vasopressin, see the preferred term **Antidiuretic hormone**.

Aromatic hydroxylation is the formation of phenols from aromatic compounds, often catalyzed by cytochromes P450 hydroxylation. Hydroxylations may result from the direct insertion of hydroxyl groups or from epoxidation with subsequent rearrangement. See **Cytochrome P450** for further information.

Arrhenoblastoma, see the preferred terms **Sertoli-Leydig cell mixed tumor, benign** and **Sertoli-Leydig cell tumor, benign**.

Arrhythmia is any change in the normal electrocardiogram (ECG) or rhythm of the heart. These occur when the coordinated electrical impulses are disrupted. In dogs, a normal sinus arrhythmia occurs when the vagal nerve is stimulated during inspiration causing the heart to slow. Hormone or ion imbalance can also result in arrhythmias. Arrhythmias can also be caused by a weak or damaged heart.

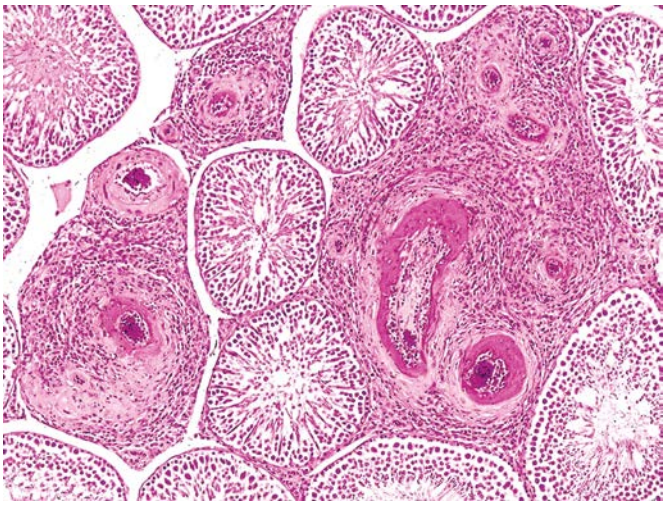
Arterial calcification, see the preferred term **Arterial medial mineralization**.

Arterial calcinosis, see the preferred term **Arterial medial mineralization**.

Arterial dystrophic calcification, see the preferred term **Arterial medial mineralization**.

Arterial inflammation is comprised of a spectrum of changes that includes hemorrhage, fibrosis, edema, and mixed inflammatory cell infiltrates. This change involves the medial layer of the arterial wall, such that perivascular inflammatory cell cuffing without mural involvement should not be included under this term. Inflammation appears as medial expansion or disruption of the mural architecture, with mixed inflammatory cell infiltration, which can be primarily lymphoplasmacytic or granulocytic, or a combination of both. The change can manifest on its own or accompany medial degeneration. Severe lesions may extend into the perivascular fascia or arterial lumen, completely obliterating the normal vascular components. There are published cases in beagle dogs with what is known as beagle pain syndrome, which typically involves multiple arteries and often severe arterial inflammation of the meningeal arteries that can manifest clinically as pain and pyrexia. Arterial inflammation may occur spontaneously or be induced by a range of compound classes. Mechanisms of induction include increased stress due to vasoconstriction or vasodilation, direct toxicity to a component of the vessel, or altered localized regulation of cytokines and chemokines.

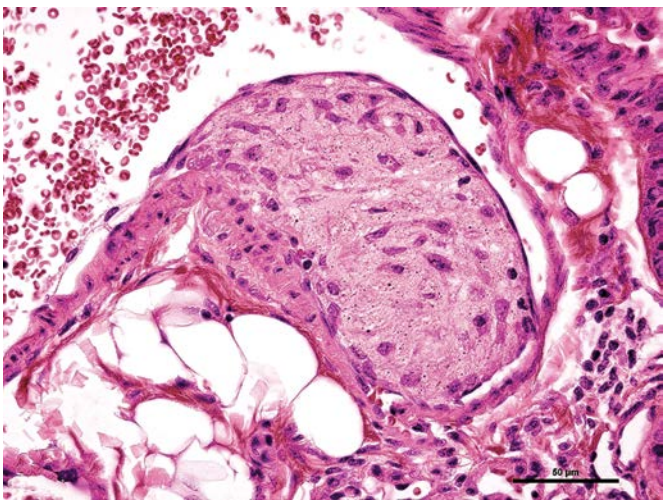
Differential diagnosis: **Arterial medial degeneration**.
Synonym(s): **Arteritis**; **vasculitis**, **artery**; **panarteritis**.



Arterial inflammation, testis, rat, H&E.

Arterial intimal hyperplasia, see the preferred term **Arterial intimal proliferation**.

Arterial intramural plaque is formed when there is deposition of cholesterol-based lipids within the arterial wall. When advanced, arterial plaque often contains foci of mineralization, necrosis, hemorrhage, fibrosis, and/or local inflammation. Arterial plaque in humans is a major contributor to cardiovascular disease–related morbidity and mortality, but rarely occurs as a spontaneous finding in the laboratory animal species used in safety assessment. Dietary models have been developed in nonhuman primates (e.g., rhesus and cynomolgus macaques), mini-pigs, and dogs, and plaque may be seen in the aorta and coronary vessels of older animals. Animal models of plaque in



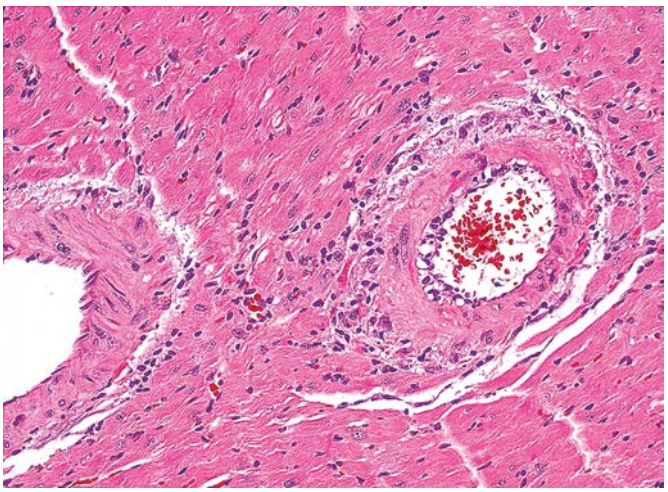
Arterial intramural plaque, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology.)

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rats and rabbits typically have a contributing genetic component to promote sustained hypercholesterolemia. Most plaque in animal models is primarily lipid with or without mineralization and is distributed in larger arteries such as the aorta, while involvement of the coronary and carotid arteries carries a worse prognosis in humans. The vulnerable plaque of greatest concern in humans is characterized by a thin, fibrous cap over a necrotic, mineralized core, and is thus prone to rupture and local thrombus formation.

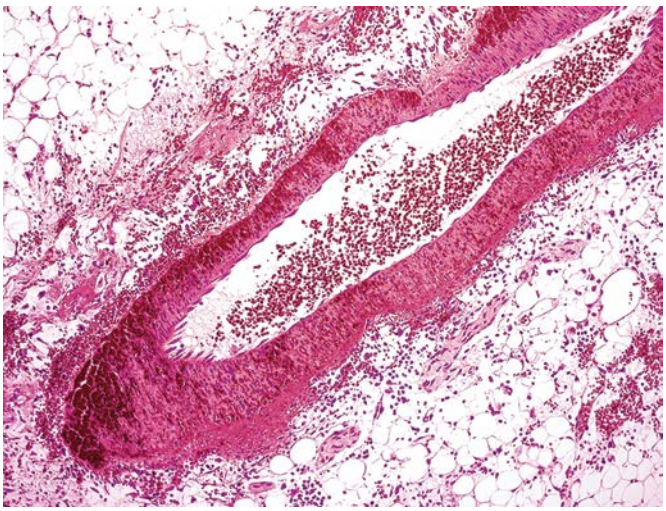
Synonym(s): **Arteriosclerosis**; **atheroma**; **atherosclerosis**.

Arterial medial degeneration affects the smooth muscle and possibly the associated elastin fibers, which make up the middle (medial) layer of arteries. It is characterized by fragmentation or vacuolation of smooth muscle cells, loss or fragmentation of smooth muscle nuclei, and possibly expansion of the media by hyaline eosinophilic material (fibrinoid change) and/or hemorrhage or edema. The artery may undergo necrosis and become occluded. In larger vessels this may result in bulging of the wall and can lead to an aneurysm. This may be caused by alteration in blood pressure or perfusion, or it may occur in an area of damaged tissue.



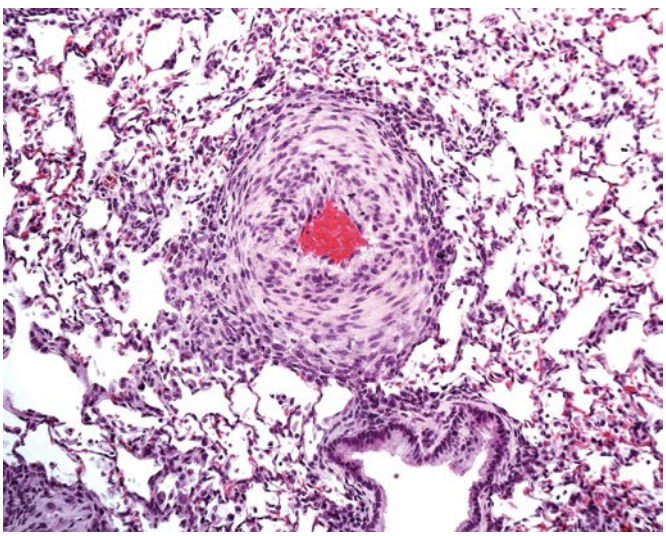
Arterial medial degeneration; characterized by loss of nuclear detail, nuclear pyknosis, and medial fragmentation and vacuolation of smooth muscle cells and in this lesion accompanied by perivascular edema, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology.)

Arterial medial hemorrhage is the extravasation of red blood cells into the tunica media of an artery in the absence of medial necrosis and/or medial inflammation (morphologic diagnoses should indicate the initiating event or the most prominent finding). This acute change may be segmental or circumferential, and typically affects small- to medium-sized arteries. This finding is typically drug induced and is often caused by biomechanical damage due to potent vasodilator (e.g., fenoldopam) or vasoconstrictor drugs, but direct cellular toxicity to the medial smooth muscle can also occur.



Arterial medial hemorrhage, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology.)

Arterial medial hypertrophy is thickening of the middle layer of the arteries with hypertrophy/hyperplasia of the smooth muscle cells. This is a response to hypertension, and can be seen in the spontaneously hypertensive rat, as well as a response to disease or administration of vasopressive agents causing a rise in blood pressure.



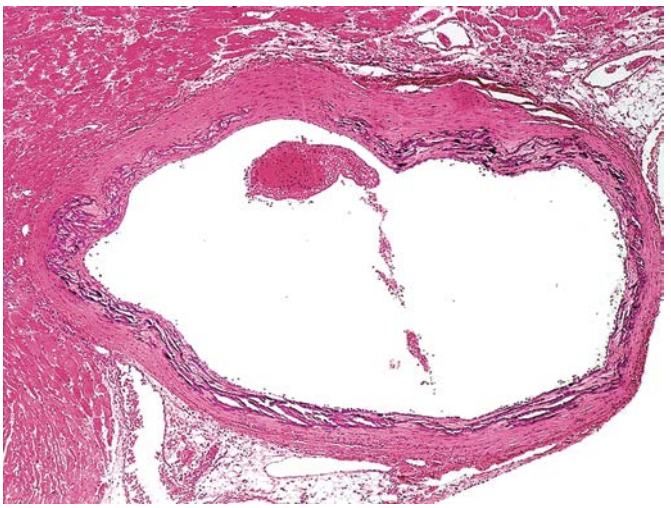
Arterial medial hypertrophy, rat, H&E.

Arterial medial mineralization manifests as basophilic granular calcium rich material within the vessel wall and can be localized or diffuse. Localized deposition often occurs as a sequel to injury and tissue damage (dystrophic mineralization). Hypercalcemic syndromes caused by calcium phosphorus imbalances due to renal disease or administration of vitamin D analogues can result in mineralization of several organs (metastatic mineralization), which typically includes vasculature.

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Synonym(s): **Arterial calcinosis**; **arterial calcification**; **arterial mural mineralization**; **arterial dystrophic mineralization**.



Arterial medial mineralization, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology.)

Arterial mural mineralization, see the preferred term **Arterial medial mineralization**.

Arteriosclerosis, see the preferred term **Arterial intramural plaque**.

Arteritis, see the preferred term **Arterial inflammation**.

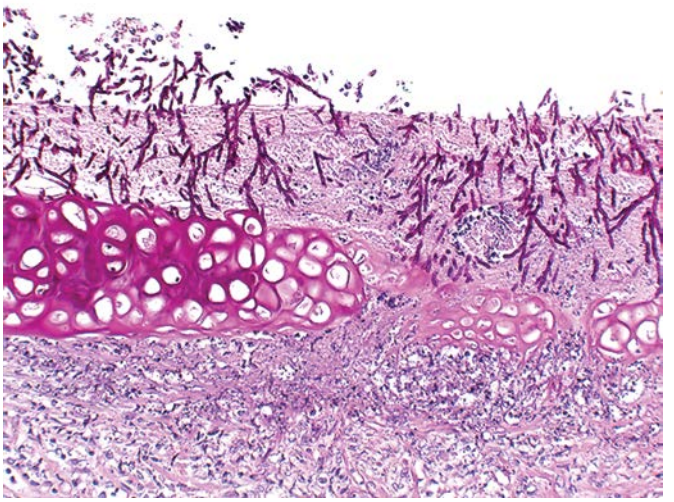
Arylesterases, see **Carboxylesterase** for further information.

Aryl hydrocarbon hydroxylase (AHH) is a cytochrome P450–dependent monooxygenase activity which catalyzes the oxidation of polycyclic aromatic compounds such as benzo(a)pyrene. The activity, which is dependent on Cyp1A1, is induced by treatment with polycyclic hydrocarbons and other Ah receptor ligands and is responsible for the metabolic activation of carcinogens, such as benzo(a)pyrene, via the formation of reactive electrophilic epoxides. See **Cytochrome P450** for further information.

Ascending pyelonephritis, see the preferred term **Pyelonephritis**.

Aspartate aminotransferase (AST), also known as serum glutamic oxaloacetic transaminase (SGOT), catalyzes the reversible transfer of an α-amino group between aspartate and glutamate. AST activity is found in liver, kidney, skeletal muscle, and brain and is routinely measured in the clinical chemistry panel of repeat-dose toxicity studies. Elevated AST activity is used as an indication of liver damage. See **Liver enzymes**, **Liver damage**, and **Liver function test** for further information.

Aspergillosis is a fungal infection caused by *Aspergillus* sp. These fungi are ubiquitous saprophytes found in the environment, and in immunocompromised animals inhaled conidia can germinate and colonize all levels of the respiratory tract. Chronic infection is characterized by tissue destruction, thought to be due to secretion of proteolytic enzymes such as elastase, with consequent invasive hyphal growth that can be clearly demonstrated by periodic acid-Schiff (PAS) and Grocott stains. One should try to differentiate this condition from other causes of necrosis or inflammation in the respiratory system.



Aspergillosis, nasal cavity, dog, H&E.

Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC) is an international nonprofit organization that promotes the humane treatment of animals in science. Participation by institutions in the AAALAC program is voluntary.

Astrocytes are the most numerous glial (support) cells within the central nervous system (CNS). Astrocytes have numerous cell processes, giving them a star-shaped appearance, that often end in expansions called end feet. These astrocytic end feet surround brain capillaries and completely line the interface of the CNS with blood vessels (where they are a critical part of the blood-brain barrier), the ependymal lining of the ventricular system, and the leptomeninges. Astrocytes process neuronal metabolic waste and metabolize certain toxins in order to protect the neurons. They also recycle electrolytes released by neurons during transmission of a nerve impulse and metabolize and recycle many neurotransmitters. Astrocytes are involved in cell-cell communication and monitor the extracellular matrix of the CNS. Astrocytes are involved in repairing damage within the CNS and become larger (astrocyte hypertrophy) or proliferate in response to noxious stimuli, a phenomenon known as astrocytosis.

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Astrocytes, Type II, see the preferred term **Type II astrocytes**.

Astrocyte swelling/vacuolation is expansion of the astrocyte cytoplasm and/or organelles due to accumulation of fluid and/or metabolic byproducts, likely due to impaired energy utilization. Astrocyte swelling will result in bilaterally symmetrical vacuolation of the neuropil, predominantly within gray matter, and may result in compression of neurons. Since astrocyte end feet surround capillaries, swelling of the astrocytic end feet may cause secondary compression of capillaries. See **Intramyelinic edema** for further information.

Synonym(s): **Gliopathy, acute**; **glia syndrome**; **gliovascular lesion**.

Astrocytoma is a glial tumor of astrocytic origin originating from the neuroepithelial/ectoderm and generally noted as malignant, low-grade or malignant, high-grade in toxicologic pathology. Refer to **Nervous System** in Appendix 2 for further information.

Astrocytoma, malignant (high grade) is a glial neoplasm of neoplastic astrocytes originating from the neuroectoderm that is highly infiltrative, poorly demarcated, densely cellular, and often multicentric within the brain. As a notable difference from most other species, neoplastic cells in rat astrocytomas lack glial fibrillary acidic protein (GFAP) immunoreactivity. Refer to **Nervous System** in Appendix 2 for further information.

Astrocytoma, malignant (low grade) is a glial tumor originating from the neuroectoderm that is poorly demarcated, with low to moderate cellularity, and is usually focal within the brain. As a notable difference from most other species, neoplastic cells in rat astrocytomas lack glial fibrillary acidic protein (GFAP) immunoreactivity. Refer to **Nervous System** in Appendix 2 for further information.

Astrocytosis is proliferation of astrocytes in response to injury and tissue defects in the CNS. Scar formation in the CNS occurs via astrocyte proliferation rather than by fibrosis/collagen deposition. Astrocytosis is a subtype of the broader term *gliosis*. Refer to **Nervous System** in Appendix 2 for further information.

Ataxia is a condition in which the individual is unable to control the voluntary muscles. This can be due to a loss in central nervous system function (brain and spinal column) by cancer, infection, or can be chemically induced (e.g., alcohol, antiepileptic drugs), or it can be due to a lack of proprioception (joint position sense). The external signs are incoordination, especially involving the extremities.

Atheroma, see the preferred term **Arterial intramural plaque**.

Atherosclerosis, see the preferred term **Arterial intramural plaque**.

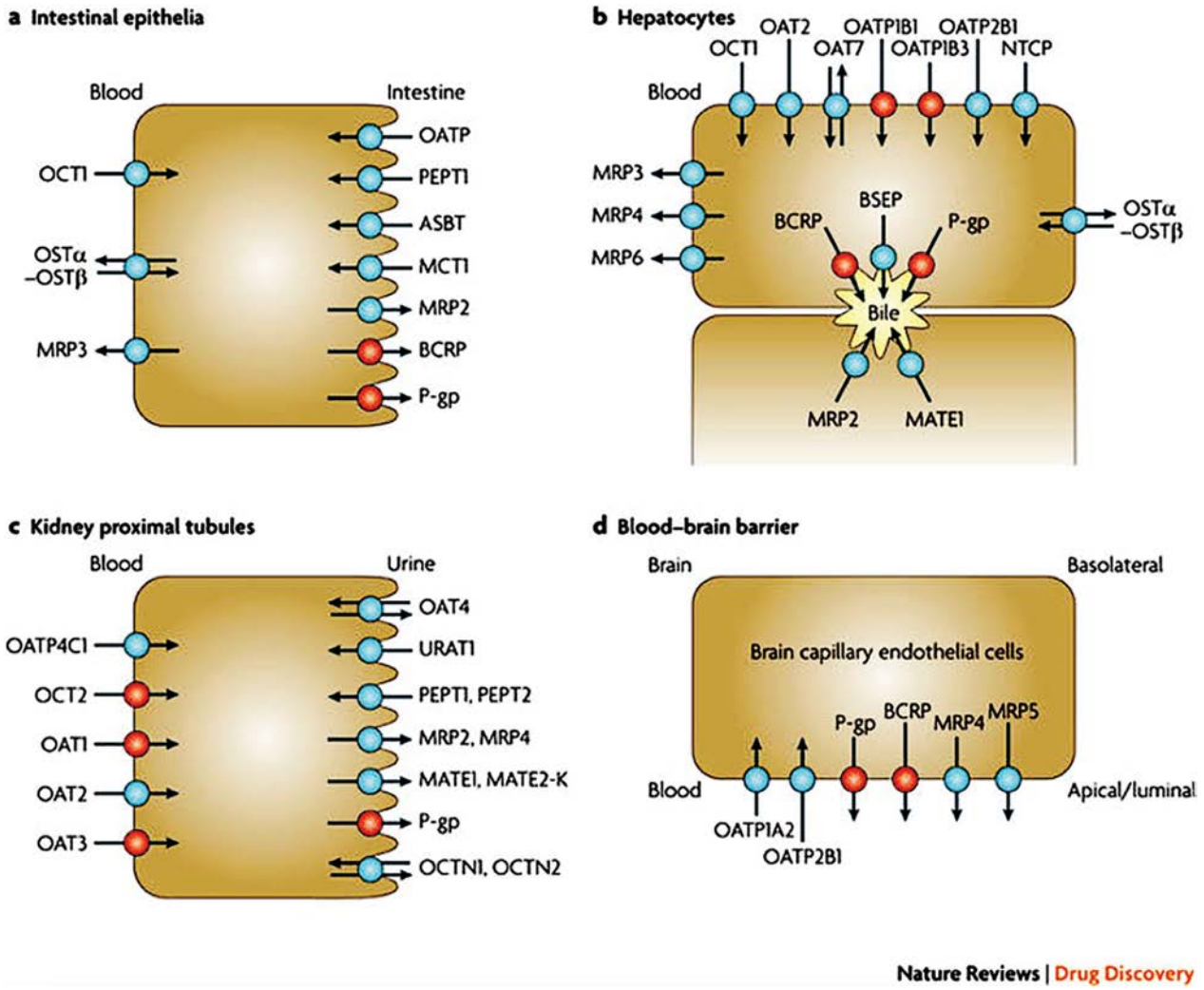
Atopic dermatitis (atopy) is a form of type I hypersensitivity that is the cutaneous manifestation of a systemic inflammatory process. In humans, it is also referred to as eczema, though eczema can encompass a wide range of cutaneous inflammatory conditions. The specific causes are unknown, but in humans it is felt to have a genetic basis and is often seen in association with asthma. Atopic dermatitis is also frequently seen in domestic animals, including cats, horses, and particularly in dogs. The clinical manifestations are similar to those in humans, and as in humans, a genetic basis is suspected. For dogs and cats, house dust mite hypersensitivity has been implicated. Atopic dermatitis manifests clinically as pruritic erythematous and edematous plaques. There is no definitive histologic appearance, although perivascular dermal inflammatory infiltrates consisting of lymphocytes, neutrophils, and sometimes eosinophils are commonly present. As a type I hypersensitivity reaction, the pathogenesis of atopic dermatitis involves the development of IgE antibodies to the sensitizing allergen(s), mast cell degranulation, and a Th2 polarized inflammatory response driven by cytokines such as IL-4, IL-5, and IL-13.

ATP-binding cassette transporters are transporters with an ATP-binding site which functions as a primary active transport pump using the energy from ATP hydrolysis to drive the process, in which a conformational change in the transmembrane protein allows the substrate bound on one side of a membrane to be released on the other side of the membrane. The typical location of major drug transporter proteins is shown in the figure (see next page top).

Atretic preovulatory follicle is a late-stage follicle lined by apoptotic granulosa cells. In the appropriate plane of section, there will be a degenerate oocyte visible.

Atrial thrombosis manifests as a fibrinoid mass with enmeshed red blood cells, adhering to the atrial endothelium. The affected atrium is often enlarged and pale, and the thrombus may have been incorporated into the atrial wall in some cases. This change occurs as a background finding in rats and mice on long-term studies, where it can be secondary to severe cardiomyopathy. In general, in all species the left atrium is most often affected. Thrombus formation in mice is sometimes associated with renal disease or systemic amyloidosis. Chronic lesions can display recanalization, fibrous organization, and cartilaginous metaplasia. Several classes of xenobiotics induce atrial thrombi. These can act through a variety of mechanisms, including myocardial or endothelial injury, circulatory stasis, or impaired atrial contractile function. Genetic mouse models with impaired cardiac contractility and hypercoagulability are susceptible to

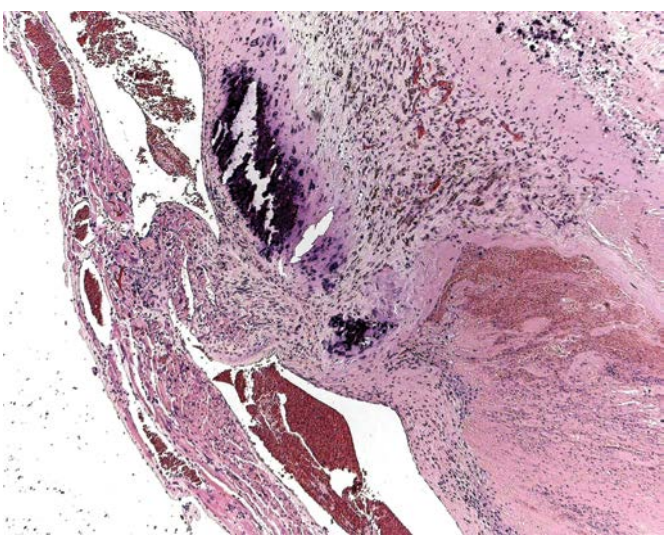
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(*Nature Reviews Drug Discovery*. 2010; 9:215–236.)

developing atrial thrombi. Osborne Mendel rats fed a high-fat diet are similarly prone.

Synonym(s): **Atrial thrombus**.



Atrial thrombosis, rat, H&E.

Atrial thrombus, see the preferred term **Atrial thrombosis**.

Atriocaval mesothelioma is a proliferation of cells originating from the atriocaval node, which is located at the junction of the right atrium with the vena cava. These spontaneous neoplasms are generally rare and occur more often in rats than in mice. Refer to **Cardiovascular System** in Appendix 2 for further information.

Atriocaval node tumor, see the preferred term **Atriocaval mesothelioma**.

Atrophy is a decrease in organ or tissue volume. This reduction can be through cellular loss via apoptosis, decreased cell proliferation, or shrinkage of cells. Atrophy occurs in normal embryonic development and physiological function, as a result of disease, disuse, or from loss of trophic support (i.e., hormonal alterations, impeded blood flow, reduced nutrition).

Atypical gastric hyperplasia is an intraepithelial small focus with cytological characteristics seen in adenomas and should not be diagnosed as an adenoma but as atypical gastric

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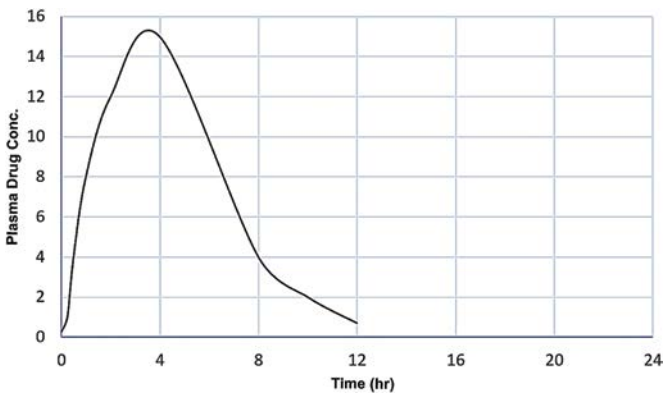
hyperplasia. Refer to **Gastrointestinal Tract** in Appendix 2 for further information.

Atypical renal tubule cell hyperplasia (ATH) represents the precursor to renal tubular adenoma. ATH is confined to a single tubule and is mostly a solid proliferation composed of eosinophilic to slightly basophilic cells with a "glassy" cytoplasmic sheen. The cells generally have well-defined cell margins. The expansive nature of ATH is confirmed by the presence of attenuated fibroblasts encircling the lesion but lack capillary ingrowth. Refer to **Urinary System** in Appendix 2 for further information.

Atypical urothelial cell hyperplasia is a focal lesion consisting of disordered, pleomorphic urothelial cells, and is regarded as the precursor of urothelial neoplasia. Refer to **Urinary System** in Appendix 2 for further information.

AUC (area under curve), as used in pharmacokinetics, is a measure of the integral systemic exposure, usually to the pharmacologically active drug component, and defines the plasma (or tissue) concentration as a function of time after dose. More precisely, the term should be area under the plasma (tissue) concentration-time curve. It is derived from the measured concentrations of parent drug and can also represent main metabolites or total drug-derived products in blood, plasma, or tissues. The diagram below shows a typical plasma drug concentration-versus-time profile following oral administration of a drug. The AUC is derived by using the trapezoidal rule and is a measure of the overall (integral) systemic exposure.

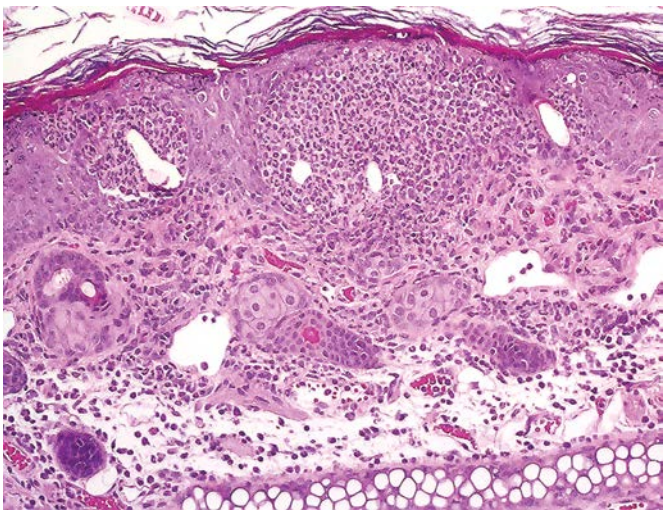
The term may be affixed with the actual time over which the measurements were taken. For example, $AUC_{0\text{-}24}$ or $AUC_{0\text{-}T}$ for samples taken over a 24-hour period, in a single-dosing interval for repeat dosing or may be extrapolated to infinity $AUC_{0\text{-}T}$. The difference between the measured values and the value extrapolated to infinity will depend upon the rate of clearance of the compound. It has become common practice to express safety margins from the NOAEL (no observed adverse effect levels) in toxicology studies to doses used in human therapy by assessing the comparative AUC values, so that the safety margin is based on integral systemic exposure rather than administered dose. In this manner, differences in the disposition of the drug between animals and humans are compensated.



Auricular cartilage inflammation involves the cartilage and adjacent tissues of the outer ear (pinna). These lesions occur spontaneously as round, raised lesions on the pinnae of usually older mice and rats, and occasionally dogs. Inflammation is usually granulomatous and associated with cartilage degeneration (chondrolysis), fibrosis, and regenerative hyperplasia of the cartilage sometimes with bone formation within the cartilage. Experimentally, intradermal injection of type II collagen induces an autoimmune-like disease of cartilage, and corrosive agents applied to the ear may induce inflammation with extension into the cartilage. Metal and plastic identifier ear tag implantation that damages the cartilage will also induce this change.

Differential diagnosis: **Chondroma**; **Osteoma**; **External ear canal inflammation (otitis externa)**.

Synonym(s): **Auricular chondritis**; **auricular chondrolysis**; **auricular chondropathy**.



Auricular cartilage inflammation, outer ear (pinna), C57BL/6 mouse, H&E.

Auricular chondritis, see the preferred term **Auricular cartilage inflammation**.

Auricular chondrolysis, see **Auricular chondritis**.

Auricular chondropathy, see **Auricular chondritis**.

Autoagglutination, see the preferred term **Red blood cell (RBC) agglutination**.

Autofluorescence means "self" fluorescence and is a characteristic of degenerating or necrotic neurons, where it is particularly helpful to identify neuronal necrosis. When light of a particular wavelength excites a fluorophore, this is seen as fluorescence. When the fluorescent molecule is endogenous to the cell or tissue, this is called autofluorescence, in contrast to use of a fluorescent reporter molecule that is applied exogenously to locate a structure. Autofluorescent structures within cells include mitochondria and lysosomes, and in the extracellular matrix, collagen and elastin can autofluoresce. Changes to these

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structures during pathologic conditions can aid in identifying the pathology. See **Neuronal necrosis** for further information.

Autoimmunity is a condition in which the body produces an immune response against its own healthy cells and tissues.

Autolysis is the process of tissue breakdown through the action of cellular enzyme following death (postmortem). Features include reduced cellular detail and staining in tissues without an inflammatory cell response. Care should be taken to distinguish autolysis from necrosis and to ensure tissues are properly collected and preserved at necropsy.

Autonomic nervous system has components in both the central nervous system (CNS) and peripheral nervous system (PNS), interacts closely with the hormonal (or endocrine) systems, and innervates smooth muscle, cardiac muscle, or glands that make up the visceral system. The enteric nervous system is a fairly autonomous subdivision of the autonomic nervous system that controls the gastrointestinal tract. Refer to Appendix 3 for further information.

Synonym(s): **Visceromotor nervous system**.

Autophagic vacuole is an intracytoplasmic globule surrounded by a thin, clear halo and a membrane. The vacuole can range in color from hypereosinophilic to basophilic on hematoxylin and eosin (H&E) staining. Autophagy occurs in all tissues as it is a necessary homeostatic mechanism whereby intracellular organelles and cytosol are first sequestered away from the remaining cytoplasm and then degraded within organelles; however, acinar cells of the exocrine pancreas are particularly sensitive to the formation of autophagic vacuoles following exposure to compounds such as vinblastine and cycloheximide.

Autophagy is the process of lysosomal digestion of a cell's own contents. It begins with the formation of an autophagic vacuole, which contains intracellular structures bound for digestion. The vacuole fuses with a lysosome containing digestive enzymes to form an autophagolysosome. Autophagy is necessary for the removal of damaged organelles and can appear prominent in cells undergoing atrophy from nutrient deprivation or hormonal involution.

Avoidance conditioning is a learned behavior where the organism avoids a situation or behavior that is associated with unpleasant circumstances or sensations. The negative stimuli (e.g., electric shock) can be delivered through any sensory input (sight, sound, smell, taste, touch, etc.). Avoidance is generally accomplished by consistently associating a negative reinforcement to an activity (active or passive avoidance). To be most effective, the unpleasant or negative stimulus needs to be applied consistently with every occurrence of the behavior.

Axonal atrophy is characterized by decreased average axonal diameter with increased interaxonal space that may be accompanied by axonal swelling. In experiments where a constrictor is placed around an axon, this will result in swelling of the axon proximal to the constriction and axonal atrophy distal to the constriction, which will recover if the constriction is removed. Axonal atrophy indicates disturbed anterograde (central to peripheral; somatofugal) transport of structural molecules essential for the maintenance of the axons and is an adaptive change that can be transient or progressive. Long axons of the peripheral nervous system are therefore most vulnerable to this change. See **Axonal transport** for further information.

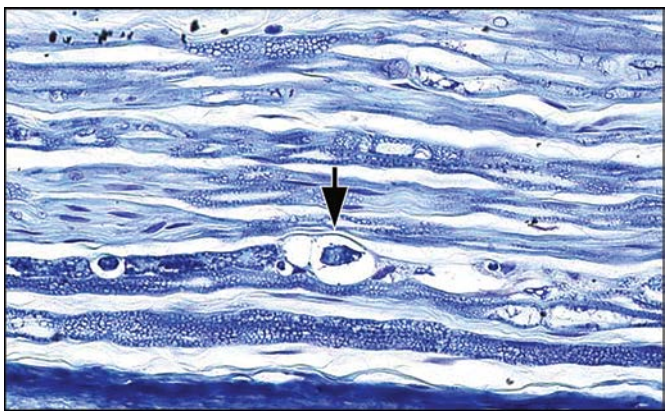
Synonym(s): **Somatofugal atrophy**.

Axonal degeneration is a breakdown of axonal structure, and generally indicates primary axonal injury but may also be secondary to primary myelin damage. Early axonal degeneration is characterized by multiple swollen, eosinophilic axons. Later axonal degeneration is characterized by fragmentation of the axons with formation of "digestion chambers" containing phagocytic macrophages (Gitter cells) and axonal fragments. In the peripheral nervous system, this may be accompanied by axonal regeneration and proliferation of Schwann cells that produce the myelin around peripheral axons. Myelin is formed from many concentric layers of Schwann cell membrane wrapping around an axon, with one Schwann cell forming the myelin for one axon segment between the nodes of Ranvier, which are the divisions between adjacent rolls of myelin along the length of the axon. Myelin insulates and protects the axon and enables faster transmission of nerve impulses. With primary axonal injury, myelin is initially unaffected, but then begins to retract from the nodes of Ranvier, forming an undulating profile. In lesions that are more chronic, the retracted myelin may form ovoids of degenerate myelin. Schwann cells break down the myelin debris and become vacuolated. A low level of axonal degeneration is commonly observed in aged rats of all strains, especially in the spinal cord, with a lower incidence occurring in aged mice. The Zitter rat strain has an inherited degeneration of axons in the pons and thalamus. Intramuscular injections for restraint (i.e., ketamine) or husbandry (i.e., antiparasitics) are commonly administered to the thigh region, especially in nonhuman primates. If the nerve (most commonly sciatic nerve) is inadvertently injected, this can result in significant axonal degeneration that is usually unilateral. To help distinguish iatrogenic injury–related sciatic nerve axonal degeneration (usually unilateral) from treatment-related sciatic nerve degeneration (frequently bilateral) it is recommended to evaluate nerves bilaterally in those species where intramuscular injections are used. See **Axonal spheroids** and **Gitter cells** for further information.

Synonym(s): **Axonopathy, dying-back axonopathy**; **Nerve fiber degeneration**; **Wallerian-type degeneration**. *NOTE:* These synonyms must be used with caution as they can imply a specific pathogenesis of the axonal degeneration. Axonopathy implies a primary axonal injury with loss of the distal axon but no damage to the nerve cell body.

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Dying back axonopathy implies that the nerve cell body has been damaged and axonal degeneration subsequently begins at the axonal terminus (synapse) and progresses toward the injured nerve cell body. Wallerian degeneration is the acute axonal degeneration seen following surgical transection of the axon(s), and so Wallerian-type degeneration implies a chemical or traumatic transection of the axons causing acute degeneration distal to the transection. See **Wallerian degeneration/Wallerian-type degeneration** for further information.

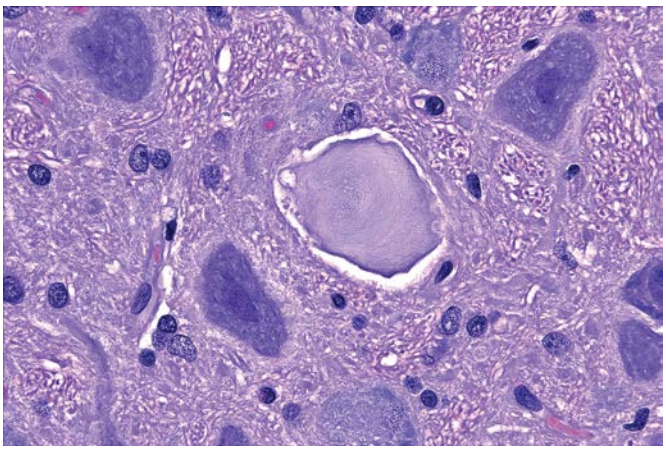


Axonal degeneration characterized by dilated spaces (digestion chambers) that contain a swollen axon and/or fragments of degenerating myelin. Sciatic nerve, dog, Luxol fast blue. (Copyright 2018 Pfizer.)

Axonal dystrophy is characterized by large, eosinophilic, fusiform structures within axons called axonal spheroids that are intra-axonal accumulations of cytoskeletal constituents. These structures are best visualized on longitudinal section. On cross-section, the affected axons will have larger diameter than nearby unaffected axons. The mechanism is not always clear but is often associated with an impairment of retrograde axonal transport so that organelles and neurofilaments accumulate at sites of axonal constriction. These spheroids tend to persist for long periods and usually do not elicit an inflammatory reaction or undergo dissolution. Axonal dystrophy can arise as a spontaneous lesion in the caudal brainstem relay nuclei (cuneate, gracile nuclei, or dorsal funiculus of spinal cord) of aged rats. Axonal dystrophy can also be seen with many neuronal storage diseases, vitamin E deficiency, diabetic rats, and some neurotoxicants including acrylamide, carbon disulfide, 3,30-iminodipropionitrile, and g-diketones. See **Axonal transport** for further information.

Synonym(s): **Axonal swelling**; **neuroaxonal dystrophy**.

Axonal spheroids are large, eosinophilic, oval or fusiform structures within axons undergoing degeneration. When present in the cerebellum, these are also called axonal torpedo, or torpedo cells. See **Axonal degeneration**, **Axonal dystrophy**, **Axonal torpedo**, and **Torpedo cells** for further information.



Axonal spheroids. Large and irregularly shaped hyaline eosinophilic spheroids occur commonly as spontaneous changes in normal dogs. Brain, dog. H&E.

Axonal swelling, see the preferred term **Axonal dystrophy**.

Axonal torpedo is a synonym for axonal spheroid when affected axons belong to the Purkinje cells in the cerebellum. See **Axonal spheroid**, **Axonal degeneration**, and **Axonal dystrophy** for further information.

Axonal transport is conveyance of material within axons (neuronal cell processes) between the neuronal cell body and the endplates of the axons. Anterograde axonal transport is central to peripheral transport of material, from the neuronal cell body to the endplates of the axons. Five groups of anterograde axonal transport mechanisms are recognized, each with different speeds of axonal transport. Proteins conveyed by each group share an affinity for that transport mechanism and carrier. The fast, anterograde transport groups are Group I (70–400 mm/day), Group II (20–70 mm/day), and Group III (4–20 mm/day), which primarily convey plasma membrane proteins such as Na+ and K+ ATPases, and membrane bound organelles such as mitochondria and secretory vesicles. Microtubules are the basis of fast anterograde transport; therefore, any compound that disrupts microtubules will arrest fast axonal transport. The slow anterograde transport groups are Group IV (1–4 mm/day) and Group V (0.2–1.2 mm/day) that primarily convey cytoskeletal proteins that provide the axon with structural support. These cytoskeletal proteins include neurofilaments, tubulins, actin, and glycolytic enzymes such as neuron-specific enolase. Retrograde axonal transport is peripheral to central transport of material, from the endplates of axons to the neuronal cell body. Retrograde transport is fast (60+ mm/day) and transports neuroactive molecules, neurotropic viruses (e.g., rabies, herpes, etc.) and neurotrophins such as nerve growth factor that enter the axon via receptors at axon terminals, as well as degraded axonal constituents that are returned to the cell body for recycling or destruction. These degraded axonal constituents may also provide feedback to the neuron to modulate its anabolic versus catabolic activities. Defects of retrograde transport are implicated in 2,5-hexandione and acrylamide toxicity, and the peripheral neuropathy of diabetes.

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Synonym(s): **Somatofugal transport (anterograde)**; **somatopetal transport (retrograde)**.

Axonopathy, see the preferred term **Axonal degeneration**.

Axonopathy, dying back, see the preferred term **Axonal degeneration**.

Axons are neuronal cell processes that transmit information between the neuronal cell body and serve as a conduit for movement of materials necessary for maintenance of the health of the neuron.

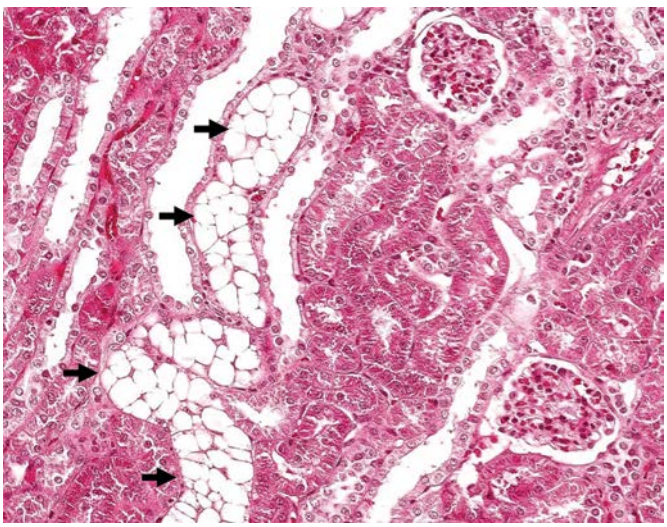
Azotemia refers to increased levels of nitrogen-containing compounds in the blood. This includes both blood urea nitrogen (BUN) and creatinine, which are normally removed by healthy kidneys. Azotemia may be due to pre-renal (i.e., hypoperfusion, compromised liver), renal (i.e., tubular necrosis, chronic renal disease) or post-renal (i.e., urethral obstruction, urolithiasis) causes.

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B

Bacterial mutagenesis is the ability of a compound to induce mutations in bacterial cells. A number of methods have been developed to detect mutations in bacterial cells as surrogate for a general mutagenesis also affecting mammalian cells. The most popular method is the Ames test (Salmonella reverse mutation test). See **Ames Test** for further information.

Ballooning degeneration describes intracellular edema, usually within keratinocytes of the non-basal layers of the epidermis. The cell size increases and there is cytoplasmic pallor or formation of vacuoles. The nucleus may be displaced. When keratinocytes of the basal cell layer are distended by edema, the change is described as hydropic degeneration or vacuolar degeneration. When it occurs in keratinocytes in other layers of the epidermis, it is described as ballooning degeneration. The term has also been applied to degenerating hepatocytes in human fatty liver and viral hepatitis.



Ballooning degeneration of renal tubular epithelial cells in a rabbit administered anthracycline, H&E. Tubules (as indicated by arrows) are lined by cells distended with large clear vacuoles. (Reproduced with the permission of Germann, P. and Morawietz, G. (eds.) *Toxicopathology Case Collection CD-ROM*. European Society of Toxicologic Pathology.)

Basal cell carcinoma is a malignant neoplasm derived from stem cells within hair follicles and/or the interfollicular epidermis. These tumors are poorly circumscribed, with some association with the epidermis and/or the adnexa and extensive local invasion into the dermis and/or subcutis. They are composed of lobules and cords of closely packed cells that are supported by variable amounts of fibrovascular stroma. Refer to **Skin** in Appendix 2 for further information.

Basal cell hyperplasia is an increase in the number of basal cells in the epidermis. It usually occurs with generalized hyperplasia of the epidermis (i.e., increased cell populations in all layers of the epidermis). Basal cell hyperplasia is not considered to be a separate diagnostic entity, only occurs in conjunction with epidermal hyperplasia, and is not considered a precursor of basal cell tumors. Refer to **Skin** in Appendix 2 for further information.

Basal cell tumor is a benign neoplasm derived from stem cells within hair follicles and/or the interfollicular epidermis and is classified into three distinct types: basosquamous type, trichoblastoma type, and granular type. All basal cell tumors are fairly well circumscribed and multilobulated with some association with the epidermis. Refer to **Skin** in Appendix 2 for further information.

Basal cell tumor, malignant, see the preferred term **Basal cell carcinoma**.

Base pair is the pairing of homologue DNA bases within the DNA double helix. Adenosine pairs with thymidine and guanosine pairs with cytosine.

Base pair substitution is a type of DNA point mutation that results in the replacement of one base pair by another; for example, replacement of an adenosine-thymidine pair with a guanosine-cytosine pair.

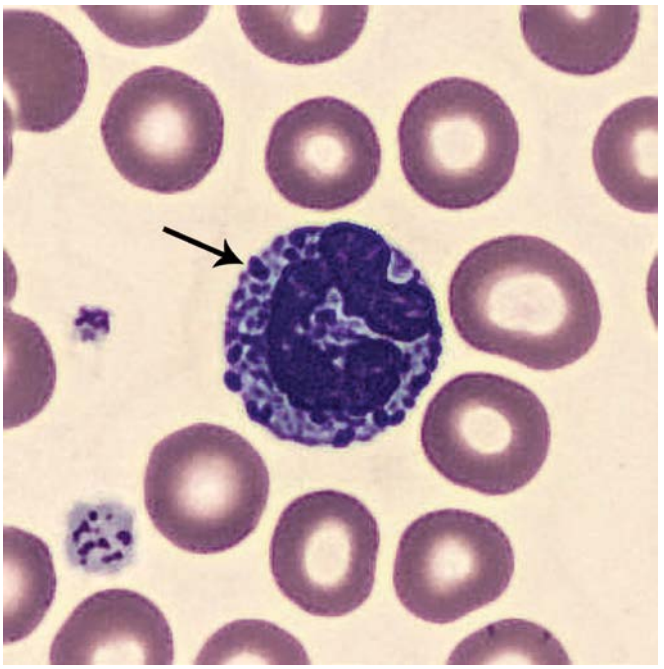
Base pair transition is a subtype of substitution mutation that results in the replacement of a purine (adenosine or guanosine) by a purine or another pyrimidine (cytosine or thymidine) by another pyrimidine.

Base pair transversion is a subtype of substitution mutation with replacement of a purine by a pyrimidine, or vice versa.

Basophil is a type of mature leukocyte (white blood cell) present in low numbers (<1%) in the peripheral blood. Basophils are about 10–15 μm in diameter and have pale blue cytoplasm with numerous large acidic granules with an affinity for blue dye, and a bilobed nucleus. Growth factors that promote basophil progenitor cell proliferation, terminal differentiation, and maturation include GM-CSF, IL-3, IL-5, SCF, and IL-4. Maturation in the bone marrow takes about 2.5 days, and the half-life in peripheral blood is only a few days. These cells are part of the innate immune system and play a role in the late stage of IgE-mediated hypersensitivity and IgE-mediated chronic allergic inflammation, where they help recruit neutrophils and eosinophils. They

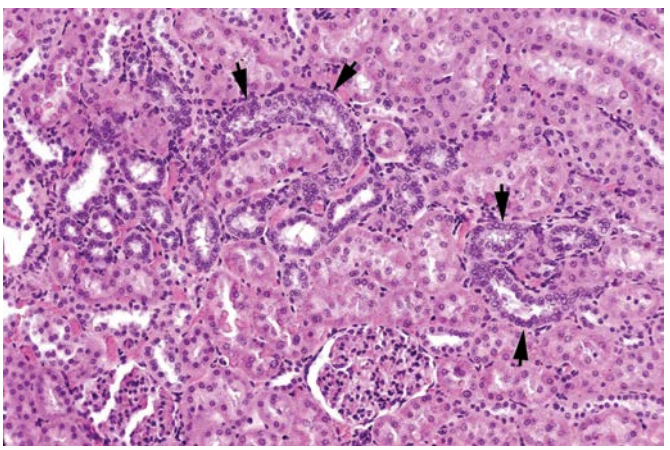
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are also involved in type 2 immune responses to helminth infections, and release large quantities of preformed IL-4, which amplifies the Th2 response. Basophil granules contain histamine, heparin, and tryptase, which are released following degranulation in response to the cross-linking of antigen and IgE bound to FcεRI. Basophilia (i.e., increased numbers of basophils) is uncommon and is most often associated with allergic disease or parasitism. Rare causes include basophilic leukemia or mast cell neoplasia. Basophils are the least numerous granulocyte in peripheral blood; therefore, low numbers are not biologically significant.



Basophil (arrow), blood smear, rabbit.

Basophilia refers to a normal-appearing cell containing basophilic cytoplasm in hematoxylin and eosin (H&E)-stained sections. There may be an increased nuclear:cytoplasmic ratio with increased numbers of mitoses. In the kidney, basophilia of tubular epithelium may be indicative of regeneration (increased numbers of ribosomes/RNA synthesis) following injury. When associated with a thickened basement membrane, basophilia may be an early sign of chronic progressive nephropathy. In other locations, such as mammary gland, Zymbal's gland, preputial gland, and others, basophilia often indicates regeneration.



Basophilia of the tubules of the kidney of a rat, H&E. Arrows highlight renal tubules with a more basophilic cytoplasm (and increased nuclei) compared to surrounding tubules. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

Basophilic focus, see the preferred term **Basophilic focus of cellular alteration**.

Basophilic focus of altered hepatocytes, see the preferred term **Basophilic focus of cellular alteration**.

Basophilic focus of cellular alteration is a focal accumulation of hepatocytes with increased cytoplasmic basophilia compared to the surrounding hepatocytes in the liver. Hepatocytes in a basophilic focus merge with the adjacent hepatocyte cords, with little or no compression of the adjacent parenchyma. Refer to **Liver, Gallbladder, and Exocrine Pancreas** in Appendix 2 for further information.

Basophilic granules refers to light blue, punctate, intracytoplasmic accumulations of material that are commonly seen in the renal proximal tubular epithelium of animals exposed to specific xenobiotics. These granules may also be seen in the renal distal tubules, macrophages in various locations, and in hepatocytes. The granules often represent accumulations of phosphorothioate oligonucleotides which tend to be trapped in lysosomes because of poor excretion and/or poor intracellular metabolism. With increasing accumulation, cells may become vacuolated and degenerate. Confirmation of oligonucleotides in these granules may be performed by Hoechst dyes or other nucleic acid staining agents. See **Eosinophilic globules** for further information.

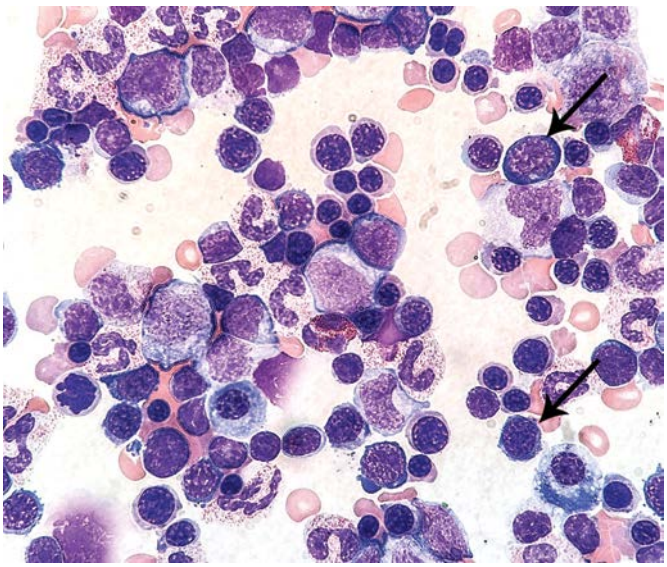
Basophilic neuron, see the preferred term **Dark neuron artifact**.

Basophilic preneoplastic focus, see the preferred term **Basophilic focus of cellular alteration**.

Basophilic rubricyte is the second of the four development stages in erythroid development within the bone marrow. Basophilic rubricytes are derived from prorubricytes through mitotic division. They are smaller than prorubricytes, with a size of approximately 10–17 μm in diameter. Cytoplasm is intensely basophilic and often darker in color than that observed in prorubricytes. Basophilia is due to the presence of high numbers of ribosomes required for hemoglobin synthesis. The nuclear to cytoplasmic ratio remains high. Nucleoli are barely visible in early stages of the basophilic rubricyte development and absent in later stages.

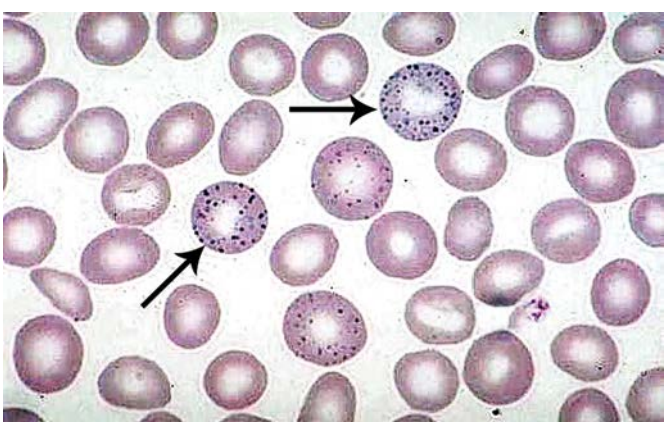
Synonym(s): **Basophilic normoblast**; **basophilic erythroblast**.

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Basophilic rubricyte (arrows), bone marrow, cynomolgus monkey.

Basophilic stippling is caused by the deposition of clumped ribosomes (i.e., containing RNA) in red blood cells. It can be seen in Wright-Giemsa–stained smears as a purple granulation within erythrocytes. It ranges from very fine stippling to coarse, punctate deposits. It is a hallmark finding for lead toxicity but can also be seen with other heavy metal toxicities, such as arsenic, bismuth, and copper, or chemical toxicity such as aniline or dinitrobenzene poisoning. Causes are numerous and diverse, including myelodysplastic syndromes, collagen disorders (rheumatoid arthritis, scleroderma, systemic lupus erythematosus), dyserythropoiesis (particularly megaloblastosis due to cobalamin or folic acid deficiency), lead and arsenic poisoning, prosthetic heart valves, and pyrimidine 5′-nucleotidase deficiency. Fine basophilic stippling is often associated with increased red cell production, and increased basophilic stippling correlates with increases in polychromasia. In contrast, coarse basophilic stippling is more frequently associated with impaired hemoglobin synthesis and instability of RNA. Therefore, coarse basophilic stippling occurs more frequently in megaloblastic anemia, lead poisoning, and thalassemias.



Basophilic stippling (arrows), blood smear, cynomolgus monkey.

Basosquamous cell carcinoma, see the preferred term **Basal cell carcinoma**.

Beagle pain syndrome, see the preferred term **Arterial inflammation**.

Behavior is characterized by any responses, actions, or expressions by an individual or organism that are directly or indirectly observable. In physiological testing these behaviors should be quantifiable, and observers need to be able to observe and quantify these behaviors consistently between sessions and between observers. Typical behaviors assessed in a toxicology study would be arousal, spontaneous activity, grooming, rearing, vocalization, sniffing, aggressiveness, scratching, or stereotypy.

Behavioral teratology is the study of behavioral impairment resulting from physiological birth defects caused by teratogens. This is also referred to as **Neurobehavioral teratology**.

Behavioral toxicity testing is the intentional exposure of organisms (the test system) to chemicals in order to study the behavioral modifications produced by the chemical. Some examples would be arousal, spontaneous activity, grooming, rearing, vocalization, sniffing, aggressiveness, scratching, or stereotypy. The exposure is generally well above levels in the environment or workplace in order to isolate the specific effects of the chemical. In acute or subchronic toxicology studies, behavioral testing can be performed after a single dose or after multiple daily doses for up to 3 months (90 days). The dosages used for such tests are generally at levels that are only limited by solubility or lethality. In most subchronic toxicity studies, behavioral tests are conducted at multiple regular intervals before, during, and after dosing several times during the study. In chronic toxicology testing of behavior, the organism can be exposed to the toxicant for up to 2 years. The dosage is generally above normal exposure but is low enough to ensure long-term survival of the organism. Behavioral tests are conducted before any treatment and at multiple times during the treatment period. If there is a treatment-free recovery period, testing will also take place during that time to assess reversibility of a potential effect. In the modified Irwin test, evaluations can occur multiple times at each testing period. Time points are selected in order to evaluate pretreatment response and several points to after dosing to detect changes in drug effect as the blood levels peak and decline. In pharmaceutical development, behavioral assessment is part of the safety pharmacology program and may be performed as either a standalone acute study or incorporated into the IND-enabling subchronic toxicity study by assessing behavior (often an Irwin test) on the first day of dosing.

Behavioral toxicology is the study of behavioral changes or neurological toxicities induced by either intentional or accidental chemical exposure. Typical behavioral endpoints in

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toxicity testing would be arousal, spontaneous activity, ataxia, grooming, rearing, vocalization, sniffing, aggressiveness, scratching, or stereotypy.

Benign, see **Tumor differentiation** for further information.

Benign cholangioma, see the preferred term **Cholangioma**.

Benign cystic cholangioma, see the preferred term **Cholangioma, cystic**.

Benign hemangioendothelioma, see the preferred term **Hepatic hemangioma.**

Benign hepatocellular tumor, see the preferred term **Hepatocellular adenoma**.

Benign hepatoma, see the preferred term **Hepatocellular adenoma**.

β-lipoprotein is a synonym for **Low-density lipoproteins**. See **Low-density lipoproteins** for further information.

Bile accumulation is characterized by accumulation of brown bile pigment between adjacent hepatocytes. Location is consistent with its presence in the canaliculi formed by a specialized region of the plasma membrane belonging to adjacent hepatocytes. Normally, neither the bile pigment nor the canaliculi are observed by light microscopy. However, in situations where there is inhibition of bile flow (also known as "cholestasis"), the canalicular accumulation of bile pigment may be detected. Bile pigment may be stained green using Hall's stain. Canalicular accumulation of bile may be associated with physical obstruction of the biliary duct system downstream. It also may result from inhibition of bile salt excretion by hepatocytes, usually as the result of dysfunction of canalicular membrane transporter pumps.

Bile acids are often derivatives of cholic acid; a good example is taurocholic acid, which is produced in the liver and secreted into the bile as an amino acid conjugate. Bile acids act as emulsifying agents to aid in the absorption of fats. If bile flow is inhibited, slowed, or blocked, bile components will accumulate in the liver as a result of cholestasis. Excretion of bile salts from the hepatocyte into the bile is facilitated by the bile salt export pump (BSEP), also called ABCB11. Drugs that inhibit this transport protein can also cause bile salt retention in the liver and consequent hepatotoxicity. See **Drug transporters** for further information.

Bile duct adenocarcinoma, see the preferred term **Cholangiocarcinoma**.

Bile duct adenoma, see the preferred term **Cholangioma**.

Bile duct adenomatosis, see the preferred term **Cholangiofibrosis**.

Bile duct carcinoma, see the preferred term **Cholangiocarcinoma**.

Bile duct hyperplasia is a lesion characterized by increased numbers of bile ducts within variable numbers of portal areas in the liver. The bile duct epithelium is well differentiated but may appear atrophic and sometimes even manifest necrosis. Refer to **Liver, Gallbladder, and Exocrine Pancreas** in Appendix 2 for further information.

Bile duct necrosis is characterized by cell death of bile duct epithelial cells. Nuclear and cytoplasmic changes are typical for necrosis of epithelial cells, and necrotic bile duct epithelium may slough into the lumens of bile ducts. The lesion is typically observed following drug or chemical treatments that are selective for the biliary epithelium, often sparing hepatocytes. The underlying mechanisms include pH-dependent deconjugation of toxic substances (parent compounds or metabolites) as well as preferential accumulation of toxic substances within the bile ducts. With some toxic substances, relative susceptibility of biliary epithelium to injury may vary between small ducts, larger intralobular ducts, and extrahepatic ducts.

Bile ductule cell hyperplasia, see the preferred term **Oval cell hyperplasia**.

Bile pigments are the colored heme breakdown products from the catabolism of hemoglobin and cytochromes that are excreted in the bile, the main ones being bilirubin (yellow-orange) and biliverdin (green). Bilirubin levels are often measured in toxicity studies as part of the clinical pathology panel to monitor liver function, although plasma bilirubin levels may increase as a result of hemolysis.

Bile secretion is the physiological process whereby hepatocytes produce bile that flows from the canaliculi (channels formed by adjacent hepatocytes) through the cholangioles (so-called canals of Hering) at the ductal plate, and then into the bile ducts. The bile ducts carry the bile out of the liver. At the canalicular membrane, bile secretion is dependent on the activity of membrane transporter pumps that export bile salts out of the hepatocyte. The transport of bile salts from the hepatocytes into the bile canaliculus provides the major osmotic driving force for bile salt–dependent flow (BSDF). Other solutes are transported by hepatocytes, cholangiolar epithelial cells, and bile ducts, thereby providing additional osmotic driving force for bile salt–independent flow (BSIF). Under normal conditions, the relative contributions of BSDF and BSIF are considered to vary between species.

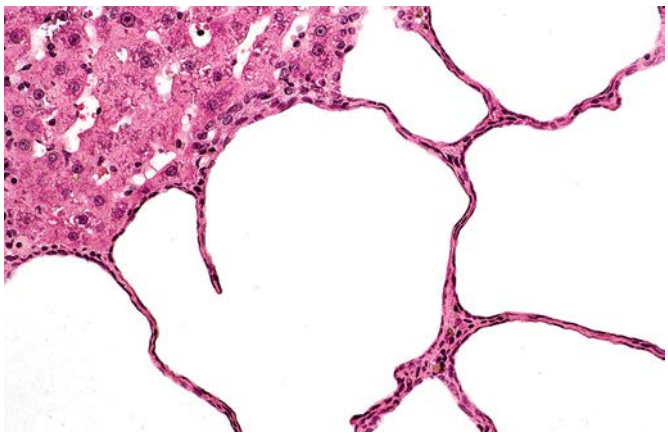
Biliary adenoma, see the preferred term **Cholangioma**.

Biliary cysts are single, mildly to markedly dilated bile ducts that form cysts within the liver parenchyma. The cysts are lined by attenuated biliary epithelium, may contain fluid, and slightly compress the adjacent liver parenchyma. They are relatively

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common in aging rats but must be differentiated from polycystic liver disease that has been reported in rats, mice, rabbits, and hamsters, a genetically based disease which is characterized by multiple, diffusely distributed cystic spaces throughout the liver, with reduction in hepatic parenchyma mass.

Synonym(s): **Hepatic cysts**.



Biliary cysts, rat, liver, H&E. (Reproduced with permission of the Society of Toxicologic Pathology from Thoolen et al. 2010.)

Biliary excretion is a major route of excretion of drugs, generally following metabolism in the liver, although some drugs may also be excreted unchanged in the bile. The compounds may diffuse into the bile ducts from the hepatocytes, or cellular extrusion may be facilitated by drug transporters such as BSEP, BCRP, MRD2, MATE 1, and pGp. Parent drug excreted in the bile may be reabsorbed from the intestinal tract, resulting in enterohepatic recirculation. Many drug conjugates such as direct glucuronides are also excreted in the bile, and these conjugates may then be hydrolyzed in the gut by bacterial enzymes resulting in release of the parent drug, which may also be reabsorbed. Enterohepatic recirculation is sometimes apparent from the plasma drug concentration time profiles, which show a second peak several hours after the initial administration.

Bilirubin, see **Bile pigments** for further information.

Bilirubinuric nephropathy is the accumulation of bilirubin pigment within the cytoplasm of renal tubular epithelial cells within any portion of the nephron or collecting duct.

Biliverdin, see **Bile pigments** for further information.

Binucleated hepatocytes, see the preferred term **Multinucleated hepatocytes**.

Binucleate neurons are neurons with two nuclei. Binucleate cells can be common in some tissues such as hepatocytes but are generally uncommon in neurons. Exceptions are the autonomic ganglia, where binucleate neurons may be seen more commonly, or in Purkinje cells of the cerebellum after inflammation. Binucleate cells in any organ can result from incomplete mitoses or from fusion of two cells. In the autonomic ganglia, binucleate neurons have been described in several rodent species and in humans. Investigations have shown a greater relative percentage of binucleate neurons in the autonomic ganglia of young growing animals than in adults, suggesting that these neurons are still dividing in these developing nervous systems, and that they may manifest a greater occurrence of incomplete cell division during mitosis. Binucleate Purkinje cells in the cerebellum are thought to result from fusion of hematopoietic cells with Purkinje cells under conditions of inflammation. In both cases, these may represent an attempt to replicate neurons. Binucleate neurons have also been described in the spinal cord of young and aged Sprague Dawley rats as an incidental finding.

Bioanalytics is a field of analytical chemistry that determines and measures the concentration of analytes (often drugs or their metabolites) in biological fluids or tissue extracts. In drug development, such analytics are mainly used for determination of the concentration of the parent drug and major metabolites in body fluids, such as blood or plasma, as part of the pharmacokinetic or toxicokinetic characterization. The most commonly used bioanalytic methods employ high-pressure liquid chromatography (HPLC) for separation, coupled with mass spectrometry (LC-MS) for detection, and enzyme linked immunosorbent assays (ELISA).

Bioavailability is the fraction (F) of the administered dose of a drug that reaches the systemic circulation. By definition, bioavailability following intravenous administration is 100%, but it may be less following other routes of administration, such as oral, intramuscular, inhalation, or subcutaneous due to factors including incomplete absorption from the site of administration or first-pass metabolism. See also **Absolute bioavailabilty** for further information.

Bioinformatics uses a combination of biology, computer science, mathematics, and statistics to develop software models to help in the interpretation of biological data (e.g., combining results from gene expression studies with the associated pathology to understand the molecular events underlying pathological changes).

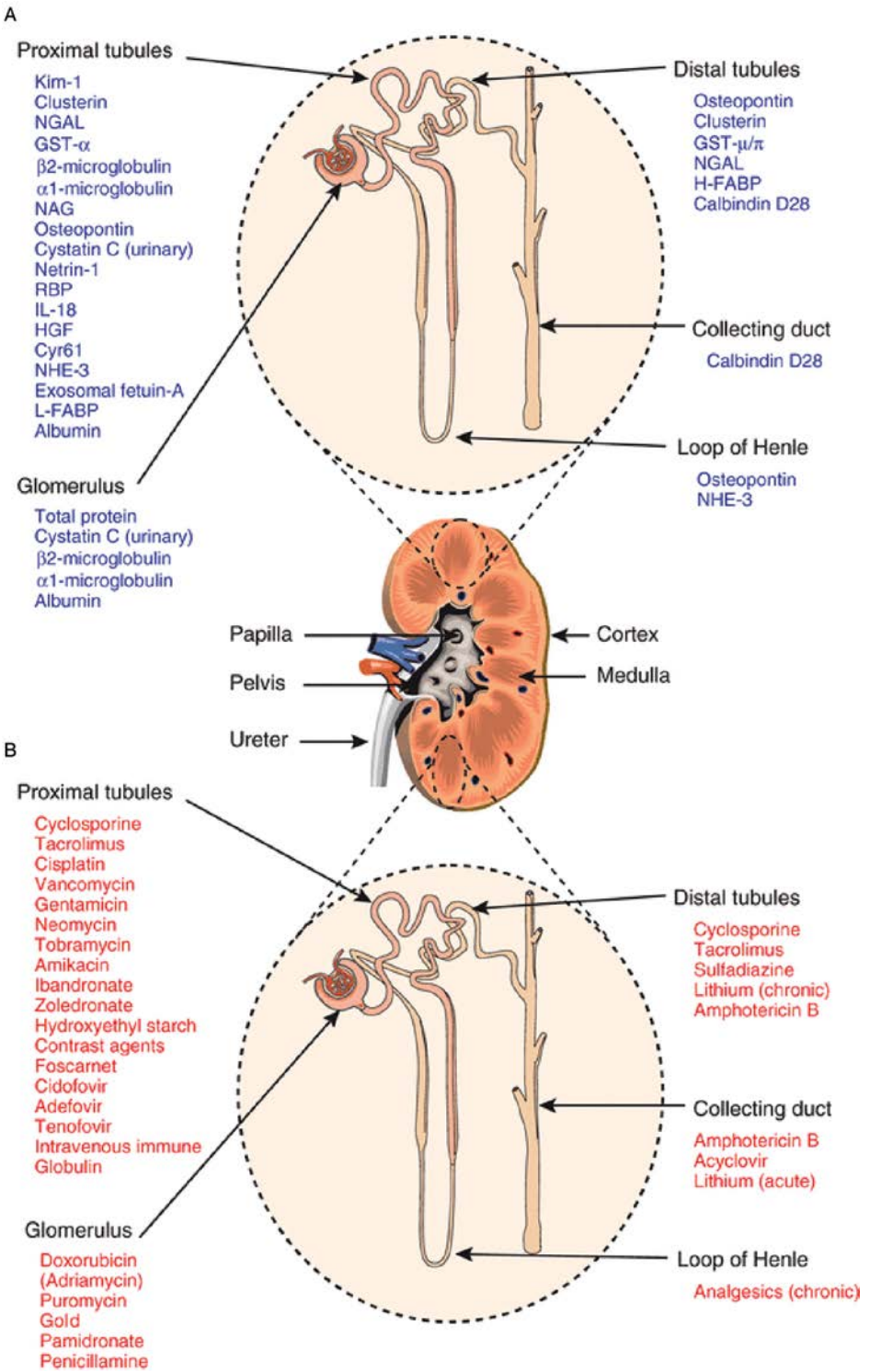
Biomarkers are predictive indicators of individual differences in an organism's response to experimental compound administration, either in a positive sense, showing the desired activity, or in a negative sense as an indicator of toxicity. They are often used as surrogates or prodromal indicators for endpoints which would require longer treatment. The clinical pathology panel assessed in routine toxicology studies is a well-established use of biomarkers; for example, increased plasma levels of the alanine aminotransferase (ALT) and aspartate aminotransferase (AST) as an indication of liver damage or toxicity, or elevations in plasma creatinine levels or blood urea nitrogen levels as an indication of renal function impairment as a consequence of renal toxicity. Use of

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biomarkers of either efficacy or toxicity can assist in decisions on the suitability of a drug candidate prior to conducting expensive clinical trials. Biomarkers may also be used to screen patient populations to preselect patients who would benefit from treatment, or to exclude those who would be susceptible to toxicity (see figure below).

BLAST is an acronym for basic local alignment search tool. BLAST is an algorithm for comparing primary biological sequence information, such as the amino acid sequences of proteins or the nucleotides of DNA sequences.

Blepharitis, see the preferred term **Eyelid inflammation**.



The utility of biomarkers to detect toxicity to different regions of the kidney. (A) Potential biomarkers of renal function, showing the specificity for toxicity in different regions of the nephron, and (B) Drugs known to cause toxicities in the different regions of the nephron. (From J.V. Bonventre et al. 2010. *Nat Biotechnol* 28:436–440.)

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Blepharoconjunctivitis, see the preferred terms **Eyelid inflammation** and **Conjunctiva inflammation**.

Blood is the suspension of cells derived from hematopoiesis in a fluid medium (plasma) present in the vascular system. Its volume is approximately 6% of the body weight in mammals, and main role is the transport of nutrients, cells, heat, and waste products. The red color is due to the hemoglobin in the erythrocytes, which are responsible for the oxygen transport. Arterial blood has a higher oxygen saturation and is brighter red than venous blood, which has a lower oxygen level. Approximately 45% of blood is made up of cellular or vesicular constituents such as erythrocytes, white blood cells, and platelets. The other 55% is made of plasma. This is mostly made up of water and approximately 8% proteins. Platelets and proteins are important for clotting of the blood. In toxicological pathology, blood is frequently collected for clinical pathology parameters, drug metabolism and pharmacokinetic (DMPK) measurements. The volumes taken can be critical, especially in small rodents.

Blood-brain barrier (BBB) is one of three major functional barriers in the central nervous system (CNS), all of which are discussed in more detail in Appendix 3. The first is the BBB between the blood and the brain parenchyma that occurs at the level of parenchymal capillaries. The second is the blood-CSF barrier between the blood and the cerebrospinal fluid that occurs in the choroid plexus and arachnoid. The third is the ependymal barrier, or CSF-brain barrier between the CSF and the brain parenchyma that occurs at the ependyma lining the ventricles. In the peripheral nervous system (PNS), there is a fourth barrier called the blood nerve barrier. The blood-CSF barrier, ependymal barrier, and blood-nerve barrier are discussed in more detail under those definitions and in Appendix 3. It is important to note that the BBB is functionally distinct from the blood-CSF barrier, and therefore measurement of a substance within the CSF does not equate to a measurement of that substance within the brain parenchyma. The BBB is the barrier between the lumen of capillaries within the brain parenchyma and the brain interstitial fluid. The primary constituents of the BBB are the tight junctions between capillary endothelial cells, with contribution from pericytes, and the basement membranes surrounding these capillaries, as well as astrocyte foot processes, and microglia surrounding parenchymal vessels. Within the ependymal lining of the third ventricle are specialized patches of ependyma (circumventricular organs) with fenestrated capillaries, where the BBB and blood-CSF barriers are incomplete. See **Ependymal barrier**, **Blood CFS-brain barrier**, **Blood nerve barrier, Circumventricular organs,** and Appendix 3 for further information.

Blood coagulation is examined as part of the clinical pathology assessment incorporated into specialized acute or repeat-dose toxicity studies by assessing the activated partial thromboplastin time (APTT), the fibrinogen concentration, and prothrombin time (PT).

Blood-CSF brain barrier is the barrier between the blood and the cerebrospinal fluid (CSF), which occurs at the choroid plexus and arachnoid. This is functionally different from the blood-brain barrier (BBB) and the ependymal barrier, which serve as barriers between brain parenchyma, and the blood or CSF, respectively. (See **Blood-brain barrier**, **Ependymal barrier**, and Appendix 3 for further information.) The choroid plexus is a highly vascularized villous structure derived from the ependyma and the pia mater and is found within the roof of the third and lateral ventricles. Villi of the choroid plexus have a core of fenestrated blood vessels that allows diffusion of molecules from the blood into the extracellular matrix of the choroid plexus following a concentration gradient. The villous surfaces are lined by choroid plexus epithelial cells that are joined by tight junctions (unlike ependymal cells), and thus are the primary constituents of the blood-CSF barrier. The choroid plexus epithelium produces the majority of the CSF by selective active transport of materials from the extracellular space, with passive diffusion of water. Compared to blood plasma, CSF has higher concentrations of sodium, chloride, and magnesium, and lower concentrations of potassium, calcium, glucose, and proteins. Normal CSF has very little protein ($\sim$14–45 mg/dL in humans) including immunoglobulins, and very few cells. There are specialized areas within the ependymal lining of the ventricles where the blood-CSF barrier is incomplete or there is transport of material between the CSF and blood. These areas are the circumventricular organs, and patches of tanycytes, respectively. See **ependymal barrier** and **choroid plexus** for further information.

Blood-nerve barrier is the barrier between blood and axons of the peripheral nerves. In the peripheral nervous system (PNS), Schwann cells form myelin around axons, and unmyelinated axons run in canals between Schwann cells and their basal lamina. External to the Schwann cells are three layers that contribute to the blood nerve barrier. The first layer is the **endoneurium**, which consists of type III collagen fibrils, and occasional fibroblasts, surrounding the Schwann cells and axons. Within the endoneurium are endoneurial capillaries with tight junctions, surrounded by pericytes, similar to the blood-brain barrier. The second layer is the **perineurium** surrounding each group (fascicle) of axons, formed of several concentric layers of specialized fibroblasts with a basal lamina, and tight junctions between fibroblasts. Together, the tight junctions of the endoneurial capillaries and the perineurium are the primary constituents of the blood-nerve barrier. The third layer is the **epineurium**, which is a dense connective tissue sheath with abundant type I collagen and typical fibroblasts that surrounds the nerve fiber. Refer to **Nervous System** in Appendix 3 for further information.

Blood-testis barrier (BTB) is an anatomical, physiological, and immunological barrier that creates a unique microenvironment in the testis for the completion of meiosis and the subsequent development of spermatids into spermatozoa via spermiogenesis. The barrier consists of the tight junctional

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complexes between Sertoli cells and controls the passage of molecules and cells from entering or exiting the seminiferous tubular lumen from the blood.

Blood urea nitrogen (BUN) is measured as an estimation of the urea concentration in the blood as part of the clinical pathology panel in toxicity studies to monitor kidney function. Although often elevated in renal toxicity, BUN may also increase as a result of altered fluid balance, or in dehydration. BUN, as a clinical chemistry analyte, is synonymous with the terms "plasma" or "serum" urea nitrogen.

B lymphocytes are one of the two major classes of lymphocytes. T lymphocytes are the other major class. B lymphocytes develop in the bursa of Fabricius in birds (and were named B lymphocytes after this organ), and in the bone marrow of mammals. B lymphocytes function in humoral adaptive immunity by recognizing antigen and, with (T cell–dependent) or without (T cell–independent) T lymphocyte help, differentiate into plasma cells that secrete antibodies, also termed immunoglobulins (Igs). B lymphocytes can also function as antigen-presenting cells (APCs; e.g., dendritic cells and macrophages). B lymphocyte development occurs in distinct stages, from the common lymphoid precursor (CLP), to pro-B cells to large, and then small pre-B cells, and finally to the immature translational B-cell stages of T1 and T2. During B lymphocyte development, Ig heavy-chain V, D, and J segments and light-chain B and J gene segments undergo recombination to generate extensive VDJ heavy-chain and VJ light-chain diversity. This Ig gene rearrangement leads to expression of Ig protein on the B lymphocyte surface to first form the pre-B-cell receptor (BCR) on pre-B lymphocytes, and then the mature BCR on immature B lymphocytes. Immature B lymphocytes, referred to as transitional B lymphocyte stages (T1 and T2), leave the bone marrow and acquire cell surface IgD as well as CD21 and CD22 expression. These immature B lymphocytes migrate to secondary lymphoid tissues, such as lymph node and spleen, to mature and form lymphoid follicles with active germinal centers following antigenic stimulation. During B lymphocyte activation, the Ig genes again undergo recombination to class switch from IgM and/or IgD to IgG, IgE, or IgA, and then clonally expand. Different B lymphocyte subsets with distinct functions and in some cases anatomic locations, such as B-1, B-2, marginal zone (MZ), and germinal center (GC) B cells, have been identified in mice. The B1, MZ, and GC B-cell subsets all contribute to antibody responses, including T cell–independent IgM responses, as well as adaptive immunity by terminal differentiation into plasma cells. Antigen activation of mature B cells leads first to GC formation and eventual maturation to plasma cells that exit the follicle and secrete antigen-specific antibodies. Memory B cells expressing mutated BCRs with enhanced affinities also develop in GCs. These memory B cells can rapidly expand and then differentiate into antibody-secreting plasma cells during secondary antigenic responses.

Body weight is assessed in toxicity studies as a very sensitive indictor of general toxicity and is often, but not always, associated with changes in food consumption. The maximum tolerated dose (MTD) in chronic toxicity and carcinogenicity studies is defined as the dose that causes a decrease in body weight gain by at least 10% without affecting mortality, although other endpoints of repeat-dose tolerability may be important in establishing the MTD.

Bone atrophy, see the preferred term **Bone decreased**.

Bone biomarkers are used to assess the activity of bone-forming and bone-resorbing cells (osteoblasts and osteoclasts, respectively) rather than cellular damage. Common bone formation markers include bone-specific alkaline phosphatase (BSAP) in many species (or total alkaline phosphatase [ALP] in the rat) for osteoblast activity and osteocalcin and procollagen type I amino (N) terminal propeptide (PINP) that are produced by osteoblasts which are forming bone matrix. Common bone resorption markers include tartrate-resistant acid phosphatase type 5b (TRAcP5b), which can be used as a rough indicator of osteoclast number and carboxy (C)-terminus telopeptide fragment of type I collagen (CTX or CTX1) that is a by-product of bone resorption.

Bone cysts can be either congenital or acquired and are most commonly found in the subchondral bone of the epiphyses of long bones. They are spherical structures. Acquired bone cysts are typically part of the bone changes in chronic degenerative joint disease (osteoarthritis).

Differential diagnosis: Insertions of tendons and ligaments sectioned tangentially.

Synonym(s): **Solitary bone cyst**; **unicameral bone cyst**.

Bone decreased (trabecular or cortical) can indicate thinner trabeculae (but a normal number), fewer trabeculae (of



Bone decreased in the tibia of a rat. There is a decreased amount of metaphyseal bone (primary and secondary spongiosa and trabeculae) beneath the growth plate with a concomitant increase in marrow space. Decalcified bone, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

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a normal thickness), or trabeculae that are both thinner and fewer than normal. Trabecular connectivity may be unchanged or may be decreased. Decreased cortical bone can indicate either a thinner cortical shell, a cortical shell with an increased porosity, or both. Bone mineral density (BMD) should be lower with significantly decreased bone.

Synonym(s): **Osteopenia**; **osteoporosis**; **bone atrophy**.

Bone density, see the preferred term **Bone mineral density**.

Bone fracture is a discontinuity in bone structure. Fractures can be complete or incomplete, simple or comminuted, displaced or nondisplaced, open or closed, and even microscopic (microfractures). Microfractures are probably the most common type, can occur in any trabecular or cortical bone, and are repaired by direct bone remodeling. Larger fractures are repaired by a complicated process of callus formation and intramembranous bone formation followed by bone remodeling. If the fracture healing process is compromised, a nonunion can occur.

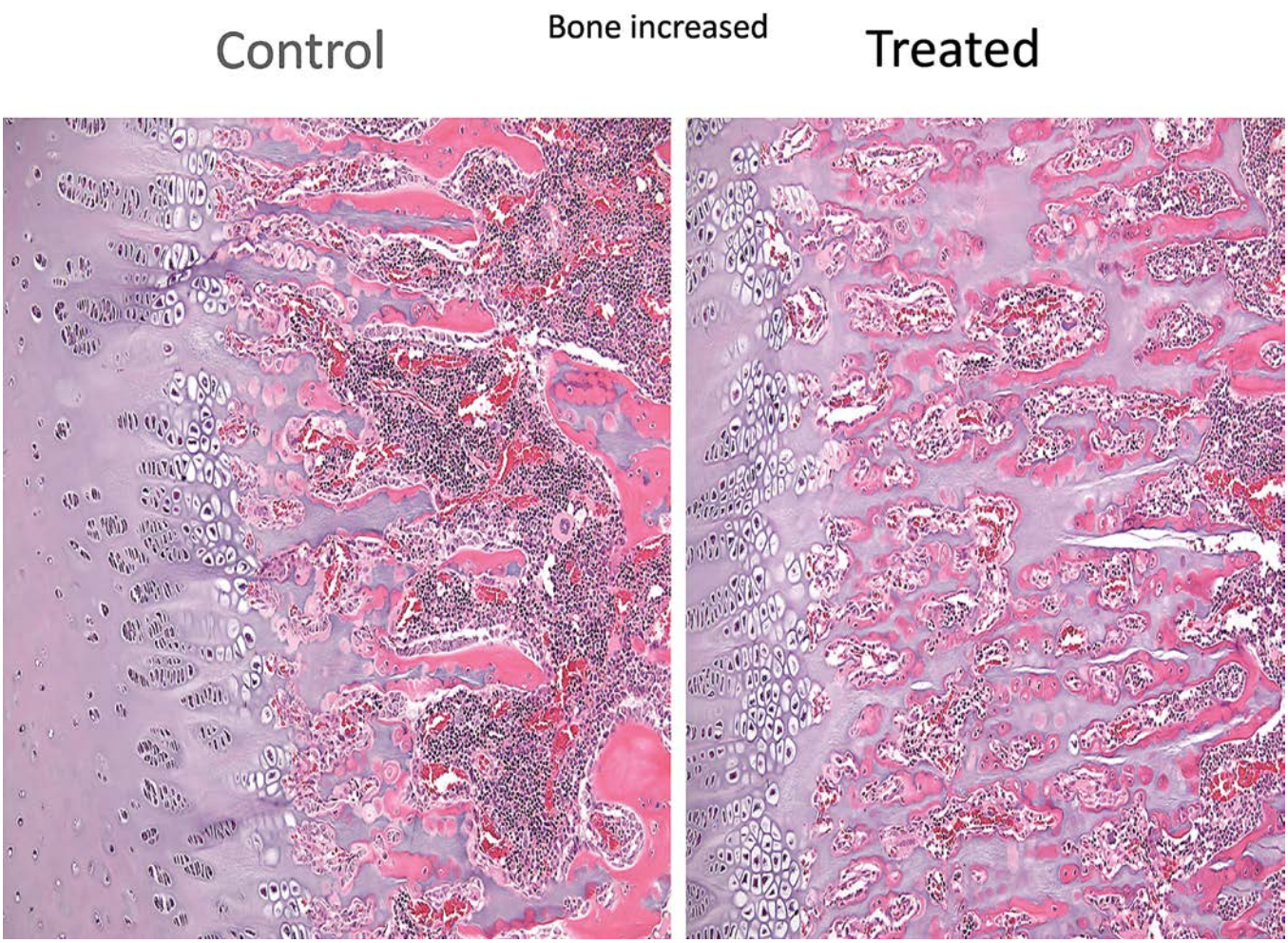
Differential diagnosis: **Osteosarcoma**.

Bone increased (trabecular or cortical) can refer to either increased trabecular thickness containing a normal number of trabeculae, an increased number of trabeculae (of normal thickness), or an increased number and thickness of trabeculae. Increased cortical bone may refer to a thicker cortical shell and/or decreased cortical porosity. Bone mineral density (BMD) should be increased. Processes that either decrease osteoclast function (e.g., bisphosphonate administration) and/or increased osteoblast function can lead to increased bone (i.e., augmentation of the secondary spongiosa [metaphyseal bone]) (see figure below).

Differential diagnoses: **Fibro-osseous lesion**; **Osteosarcoma**.

Synonym(s): **Osteopetrosis**; **hyperostosis (proliferative or non-proliferative)**; **osteosclerosis**; **trabecular hypertrophy**.

Bone increased eroded surface is a phenomenon in which osteoclast function has been altered. It is most noticeable in trabecular bone. The increased eroded surface is characterized by formation of erosion pits or an undulating



Bone increased in a dog administered a bisphosphonate. Compared to the control animal on the left, there is increased density of metaphyseal bone (primary and secondary spongiosa and trabeculae) with a concomitant decrease in marrow space. Cartilage cores persist in the trabeculae. Decalcified bone, H&E.

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surface; quiescent bone lining cells are absent from these surfaces. Examples of increased eroded surface can include prolonged continuous administration of parathyroid hormone (PTH) or PTH analogues that cause increased osteoclast recruitment and activity (increased erosion pits ["Howship's lacunae"] which may be sufficiently deep to split boney trabecula) or conversely, prolonged exposure to antiresorptive modalities, including bisphosphonates, which impair function of osteoclasts but not recruitment. Increased resorption surfaces in this case appear as long, shallow, undulating surfaces, representing failed attempts of osteoclastic resorption.

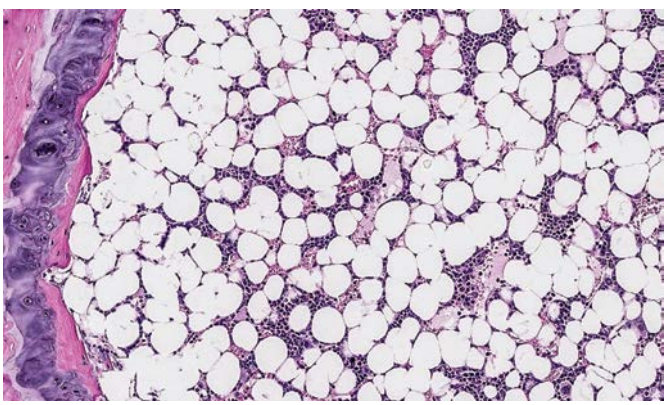
Synonym(s): **Dissecting osteoclasia**; **bone resorption**.

Bone marrow, adipocyte hypercellularity, see the preferred term **Bone marrow, increased adipocytes**.

Bone marrow, adipocyte hypocellularity, see the preferred term **Bone marrow, decreased adipocytes**.

Bone marrow adipocytes increased is characterized by an increased in number or density of adipocytes in either a focal or diffuse distribution. Relative decrease in hematopoietic cells may give the impression of increased adipocytes and should be differentiated.

Synonym(s): **Bone marrow**, **adipocyte hypercellularity**.



Adipocytes, increased, bone marrow, mouse (H&E).

Bone marrow aplasia usually refers to the absence of normal hematopoiesis due to failure of development.

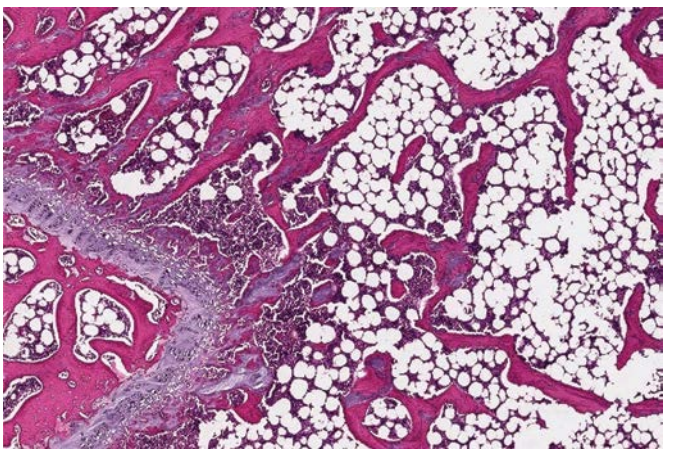
Bone marrow atrophy refers to decreased size or number of cells, usually hematopoietic, within the marrow cavity. The term may be used with a modifier and applied to specific cell populations within bone marrow. Femur/knee joint sections may be preferred for the general diagnosis over the sternum, although the term can be used in any bone marrow section. Bone marrow in sternum is generally more cellular than femur/knee joint sections.

Bone marrow congestion refers to dilated blood-filled blood vessels.

Bone marrow, decreased adipocytes refers to a reduction in number or density in either a focal or diffuse distribution. Relative increase in hematopoietic cells may give the impression of decreased adipocytes and should be differentiated.

Synonym(s): **Bone marrow**, **adipocyte hypocellularity**.

Bone marrow, decreased hematopoietic cells is characterized by fewer than normal numbers of hematopoietic cells within the medullary cavity. This is the preferred term for enhanced histopathology terminology as it is strictly descriptive and does not imply process or pathogenesis. Affected cell lineage (e.g., erythroid, myeloid, granulocytic, monocytic, megakaryocytic, lymphocytic, or NOS [not otherwise specified]) should be identified if possible.



Hematopoietic cells, decreased, bone marrow, mouse (H&E).

Bone marrow, decreased stromal cellularity is characterized by a decreased number or density of stromal cells. Changes in cellularity may occur in either a focal, multifocal, or diffuse distribution pattern. Identification of the specific cell type affected, e.g. fibroblasts/fibrocytes, adventitial reticular cells, or adipocytes, is encouraged. Decreased hematopoietic cellular components may result in the appearance of increased prominence of stromal elements that should be differentiated from true changes in stromal cell numbers or density. In practice, stromal changes are usually a component of other diagnoses and are infrequently identified as a standalone diagnosis. Comparison to control group animals is recommended.

Synonym(s): **Bone marrow stroma hypocellularity**.

Bone marrow depletion is the absence or decrease in number of cells. Bone marrow depletion implies that a pre-existing normal state with larger numbers of cells was present but now is decreased or absent. Generally applied, depletion implies a reduction in all hematopoietic cell types and generalized bone marrow suppression. Specific hematopoietic cell lineages may be specified by use of a modifier.

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Bone marrow dysplasia is an abnormal maturation of one or more lineages of blood cell and is often, but not always, considered a preneoplastic lesion. See **Hematopoietic dysplasia** for further information.

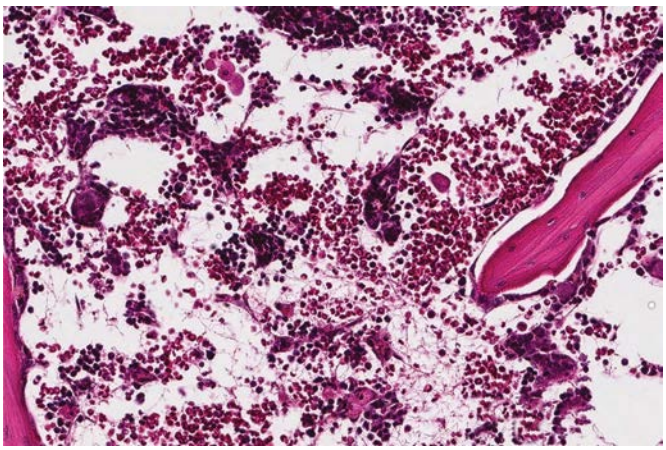
Bone marrow evaluation uses both a histologic section and cytologic bone marrow smear. The section gives an optimal assessment on the distribution and cellularity of the bone marrow and potential presence of tumors as well as a general overview of cell types. The smear allows more precise evaluation of cellular detail and maturation stages as well as relative proportions of myeloid and erythroid and other hematopoietic lineages. The evaluation also depends on a good quality bone marrow smear. The bone marrow smear should be made shortly after death of the animal, or alternatively, can be made in larger animals through bone marrow aspiration. Several techniques have been proposed; most commonly the smears are made like blood smears, or distributed on the examination slide with a small brush (wetted with e.g., fetal calf serum). It is important that both a monolayer for morphologic evaluation and a more condensed area for cellularity and relative arrangement are present. Bone marrow smears are often evaluated together with the bone section, which is not optimal for detailed cellularity evaluation due to decalcification processing of the section; however, it can provide information on the spatial arrangements of the different components. For a myelogram (i.e., differential cellular count of the bone marrow) at least 500–1000 cells must be identified and evaluated on the smear.

Bone marrow fibrosis occurs when fibrous connective tissue formed by fibroblasts as a result of a chronic inflammatory process involves the bone marrow cavity. This process may further be divided according to the predominant type of connective tissue (extracellular matrix proteins) present, either collagen or reticulin. Collagen versus reticulin cannot be easily distinguished in hematoxylin and eosin (H&E)-stained tissue sections. Special stains are needed for differentiation of the subtype. Refer to **Hematopoietic System** in Appendix 2 for further information.

Synonym(s): **Myelofibrosis**.

Bone marrow granulomatous inflammation is a chronic inflammatory response within the marrow cavity that is characterized by increased macrophages, epithelioid macrophages, and/or multinucleate giant cells. The added presence of necrosis and neutrophils represents pyogranulomatous inflammation. A granuloma is a focal, organized type of inflammatory lesion. Inflammation may be focal, multifocal, or diffuse.

Bone marrow hemorrhage refers to bleeding in the bone marrow with blood outside the vascular spaces.

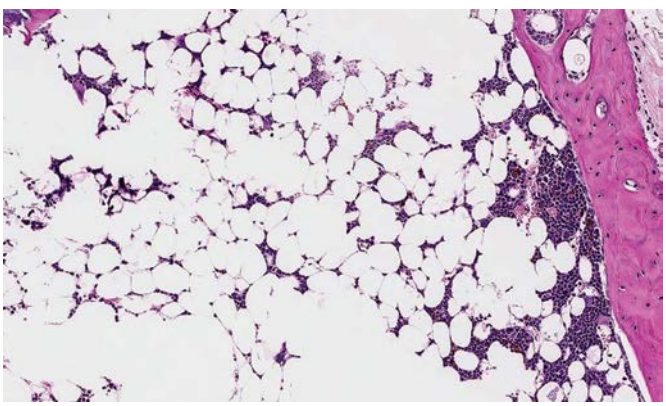


Hemorrhage, bone marrow, rat, H&E.

Bone marrow hyperplasia, see the preferred term **Hematopoietic cells, hypercellularity**.

Bone marrow hypocellularity of hematopoietic cells is characterized by fewer than normal numbers of hematopoietic cells in the medullary cavity. Pathogenesis may involve either decreased production or increased destruction of cells and may affect cells of one or more lineages. Hypocellularity is the preferred conventional term when a specific cell lineage is not being identified. Optimally, evaluation of bone marrow should separately assess differentiation of each hematopoietic cell lineage and specify which lineages are affected. "Hematopoietic cells, decreased" with identification of affected cell type is the preferred term for enhanced histopathology as it is strictly descriptive and does not imply a process.

Synonym(s): **Bone marrow hypoplasia**.



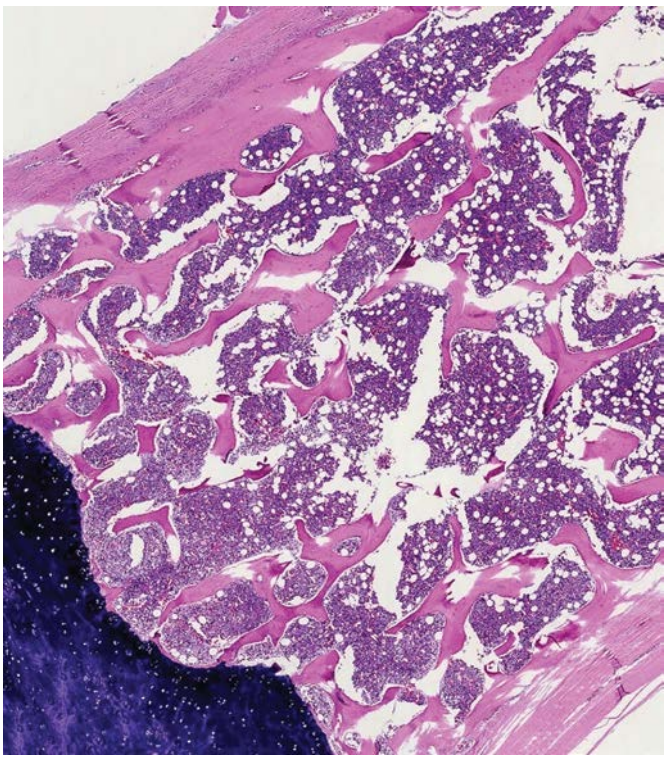
Hypocellularity, bone marrow, rat (H&E).

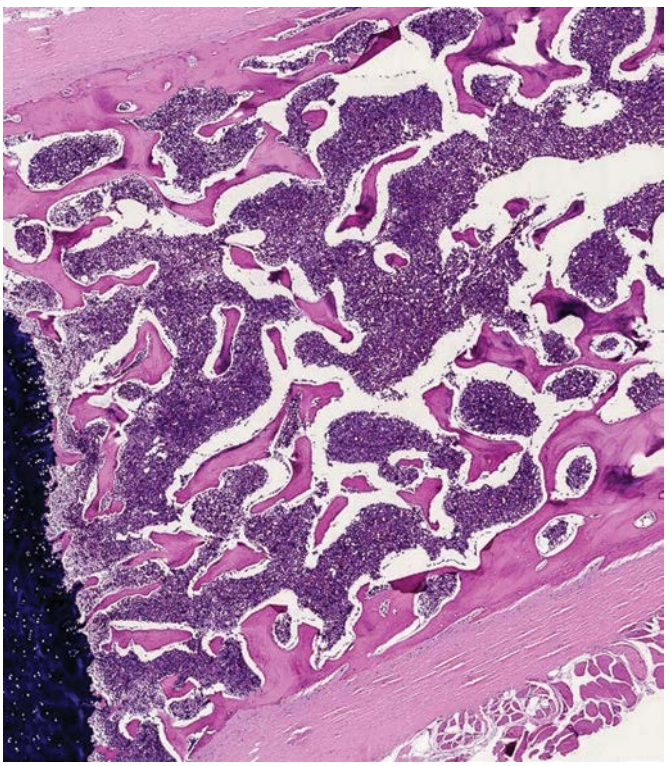
Bone marrow hypoplasia, see the preferred term **Bone marrow hypocellularity of hematopoietic cells**.

Bone marrow, increased hematopoietic cells is characterized by a greater than normal number of hematopoietic cells within the medullary cavity. This is the preferred term for

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enhanced histopathology terminology as it is strictly descriptive and does not imply process or pathogenesis. Affected cell lineage (e.g., erythroid, myeloid, granulocytic, monocytic, megakaryocytic, lymphocytic, or NOS [not otherwise specified]) should be identified if possible.

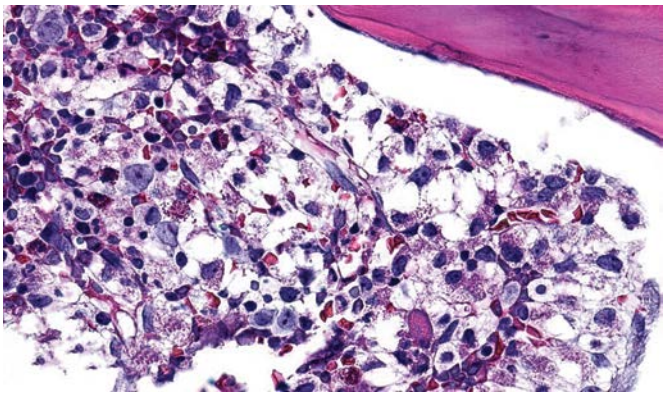




Bone marrow: normal (top); hematopoietic cells, increased/hypercellularity (bottom), cynomolgus monkey (H&E).

Bone marrow, increased macrophages is a condition characterized by an increased number of macrophages within the bone marrow cavity. An increase in macrophages alone must be differentiated from increased macrophages associated with granulomatous inflammation.

Synonym(s): **Bone marrow macrophage increased cellularity**; **bone marrow macrophage hyperplasia**.



Macrophages increased, bone marrow, cynomolgus monkey (H&E).

Bone marrow, increased mast cells may be multifocal or diffuse in distribution within the marrow cavity. The mechanism is undetermined. Mast cells may be increased due to a variety of conditions. Increased mast cells in other organs or systemically should be considered for proper interpretation of bone marrow changes.

Differential diagnoses: **Mast cell tumor**; **Mast cell leukemia**.

Synonym(s): **Bone marrow mast cell infiltrate**.

Bone marrow, increased stromal cellularity is characterized by an increased number or density of stromal cells. Changes in cellularity may occur in either a focal, multifocal, or diffuse pattern. Identification of the specific cell type affected, e.g. fibroblasts/fibrocytes, adventitial reticular cells, or adipocytes, is encouraged. In practice, stromal changes are usually a component of other diagnoses and are infrequently identified as a standalone diagnosis. Comparison to control group animals is recommended.

Synonym(s): **Bone marrow stroma hypercellularity**; **myelostromal proliferation**.

Bone marrow macrophage hyperplasia, see the preferred term **Bone marrow, increased macrophages**.

Bone marrow macrophage increased cellularity, see the preferred term **Bone marrow, increased macrophages**.

Bone marrow macrophages are normally present and are an important source of growth factors necessary for hematopoiesis. Macrophages (~11–20 μm in diameter) line the adventitial surface of vascular sinuses and form the center of erythropoietic islands. Macrophages phagocytize extruded nuclei of red blood cell precursors and defective red cells as well as play a role in iron metabolism. Phagocytized iron may be visualized by use of special stains. In addition, macrophages may be recruited as a component of an inflammatory response.

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Bone marrow mast cell infiltrate, see the preferred term **Bone marrow, increased mast cells**.

Bone marrow megakaryocyte depletion implies that numbers of this cell type are decreased due to destruction or loss. Megakaryocytes are identified in bone marrow as large cells with a multilobulated nucleus and produce platelets. Loss of megakaryocytes may or may not be a result of decreased platelet counts in blood, depending on chronicity and severity of the bone marrow change.

Synonym(s): **Bone marrow megakaryocytes decreased**.

Bone marrow megakaryocytes decreased, see the preferred term **Bone marrow megakaryocyte depletion**.

Bone marrow stroma is defined as the matrix or supporting tissue of an organ. Bone marrow is a hematopoietic organ, and therefore all nonhematopoietic cells may be classified as stromal.

Bone marrow stroma consists of a network of medullary vascular sinuses that originate from cortical capillaries and terminate in collecting vessels of systemic venous circulation. The wall of the medullary sinus is lined by endothelial cells supported by a thin basement membrane. Adventitial reticular cells (ARC) and macrophages line the adventitial surface. The reticulum of the marrow is composed of a meshwork of ARC cell bodies, their broad projecting cell processes, and their reticular fibers. ARCs are pluripotential cells with capability to differentiate into fibroblasts, contractile "barrier cells" with smooth muscle phenotype (myofibroblasts), and potentially adipocytes. Stromal elements produce extracellular matrix and a plethora of growth factors to support hematopoiesis.

Collagen and reticulin are extracellular substances and are distinguished from cellular elements. Increased collagen and reticulin often, but not always, occur concurrently with increased cellular elements. Reticulin or reticular fibers are an extracellular substance produced by adventitial reticular cells and consist of type I and type III collagen. Collagen is an extracellular substance produced by fibroblasts and is predominantly type I collagen.

Critical assessment of bone marrow stromal elements, with the notable exception of adipocytes, is difficult to evaluate in standard hematoxylin and eosin (H&E)-stained tissue sections. Definitive identification of non-adipose individual bone marrow stromal cells, reticulum fibers (e.g., Gomori silver stain) and collagen (e.g., trichrome stain) requires special stains. Decreases in hematopoietic cells may give the appearance of increased stromal elements.

The endosteal lining of marrow is formed by osteoblasts, osteoclasts, and elongated flat cells with a spindle-shaped nucleus. These cells contribute to the hematopoietic environment but are considered part of the skeletal system in toxicologic pathology.

Bone marrow stroma hypercellularity, see the preferred term **Bone marrow, increased stromal cellularity**.

Bone marrow stroma hypocellularity, see the preferred term **Bone marrow, decreased stromal cellularity**.

Bone marrow stroma, increased, see the preferred term **Bone marrow fibrosis**.

Bone mineral density (BMD) is a parameter measured clinically and nonclinically as an indicator of bone quality by quantifying the amount of minerals (primarily calcium, phosphorus, and magnesium) present within the mineralized bone matrix and is expressed as a mass per unit volume or area, depending on the technology used. It can be measured in cortical or trabecular bone. Nonclinically, the most common sites measured are the femoral diaphysis (cortical bone), distal femoral metaphysis (trabecular bone), and lumbar vertebrae. Clinically, the most commonly measured sites include vertebrae, wrist, and ankle. Technologies to acquire these measurements include dual energy x-ray absorptiometry (DXA) and peripheral quantitative computed tomography (pQCT).

Synonym(s): **Bone density**.

Bone, muscle, and tooth, Anatomy and Histology, see Appendix 3 for further information.

Bone necrosis occurs when bone marrow hematopoietic elements, adipocytes, and osteocytes in a defined region of bone have undergone coagulative necrosis. Osteocyte lacunae are empty and there is often a robust response by osteoclasts and osteoblasts to encapsulate the necrotic region. The most common site for bone necrosis is the femoral head due in part to its uniquely vulnerable blood supply (circumflex vessels). Femoral head necrosis has been observed in rats and dogs. In humans, corticosteroid use and excess alcohol consumption are risk factors as both can cause increased adiposity of the bone marrow at the femoral head, which can compromise the vascular supply to the region to such an extent (ischemia) that avascular bone necrosis (AVN) develops. Osteomyelitis also causes bone necrosis, as do some destructive primary and metastatic neoplasms. Osteonecrosis of the jaw (ONJ) has been reported in patients administered antiresorptive agents including bisphosphonates (particularly high doses intravenously) and RANKL (receptor activator of nuclear factor kappa-β ligand) inhibitors. The incidence of ONJ in patients administered low doses of antiresorptives is only slightly higher than the regular population. The putative mechanism of action includes interference of bone resorption combined with major invasive dental procedure(s) and concomitant inflammation.

Differential diagnosis: **Loss of osteocytes during routine processing (i.e., artifact)**.

Synonym(s): **Osteonecrosis**; **coxa plana**.

Bowman's capsular hyperplasia is an increase in the number of flattened lining cells of Bowman's capsule. Refer to **Urinary System** in Appendix 2 for further information.

Bowman's capsular metaplasia represents a change of the flattened lining cells of Bowman's capsule to cuboidal cells which are more numerous and appear hyperplastic. Male mice normally have cuboidal capsule cells. Refer to **Urinary System** in Appendix 2 for further information.

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Bowman's capsule is the single cell layer surrounding and enclosing the renal glomerular tuft, known as the parietal cell layer of the glomerulus. Bowman's cells are flattened and squamous-like in rats and dogs but are more cuboidal in male mice. The Bowman's capsule cells conjoin to form the commencement of the proximal convoluted tubule at the urinary pole of the glomerulus opposite to the vascular entry into the glomerulus.

Bowman's layer, is a subepithelial anterior limiting layer of collagen fibers that is present in the cornea of humans and nonhuman primates, but is microscopically absent in the corneal stroma of most other mammals. This term should not be confused with, or used to describe Bowman's capsule in the kidney.

Bowman's membrane, see the preferred term **Bowman's layer**.

Bowman's space is the area inside Bowman's capsule external to the glomerular tuft in the kidney. It represents the space for urine flow into the proximal tubule after glomerular filtration.

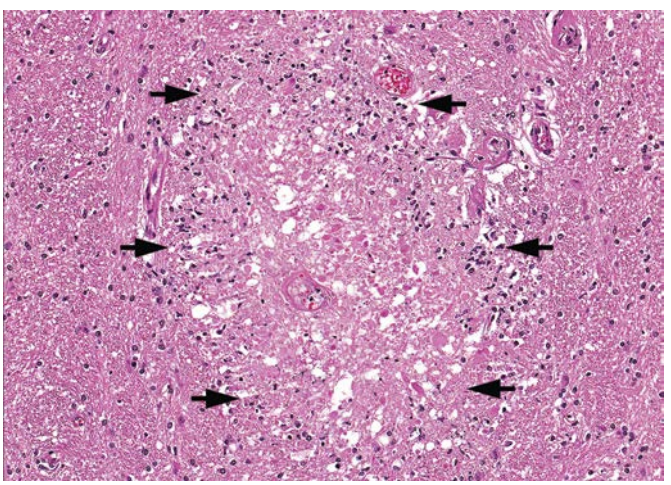
Bowman's space dilation is an expansion of the volume of the space between Bowman's capsule and the glomerular tuft in the kidney. This can occur in diseases involving urine reflux up the nephron and is usually associated with contraction of the glomerular tuft.

Synonym(s): **Bowman's space enlargement**.

Bowman's space enlargement, see the preferred term **Bowman's space dilation**.

Bradycardia is a decrease in heart rate. This can be the result of pathology involving the sinoatrial (SA) node (i.e., the heart's "natural pacemaker"), or natural feedback from blood pressure sensors.

Brain-CSF brain barrier, see **Blood-brain barrier** and **Ependymal barrier** for further information.



Acute brain infarct (outlined by arrows) is a focal region of necrosis caused by interrupted vascular supply. Dog, H&E.

Brain infarct is focal necrosis of brain tissue caused by interrupted blood supply, a process sometimes referred to as a stroke. Consequences of a brain infarct are variable and dependent upon the particular subanatomic region affected since brain domains are functionally heterogeneous. If the infarct does not result in death of the animal, the necrotic brain tissue will be removed by phagocytes, leaving a void sometimes large enough to form a cavitation. See **Cavitation** for further information.

Synonym(s): **Regional necrosis**.

Bronchi are the larger conducting airways of the respiratory system, with the first generation branching from the distal trachea and each subsequent generation becoming progressively narrower. The walls of bronchi are supported by cartilage, and interspecies differences in their arrangement and epithelial lining exist. In humans and nonhuman primates, branching is dichotomous, while in the rat and mouse, it is monopodial. In nonhuman primates, goblet cells and basal cells predominate in the bronchial epithelium, whereas the club cell is the principal nonciliated cell seen at this level in other laboratory animals. Club cells are also common throughout the respiratory tree in mice.

Bronchial adenoma, see the preferred term **Laryngeal, tracheal, bronchial, and bronchiolar papilloma**.

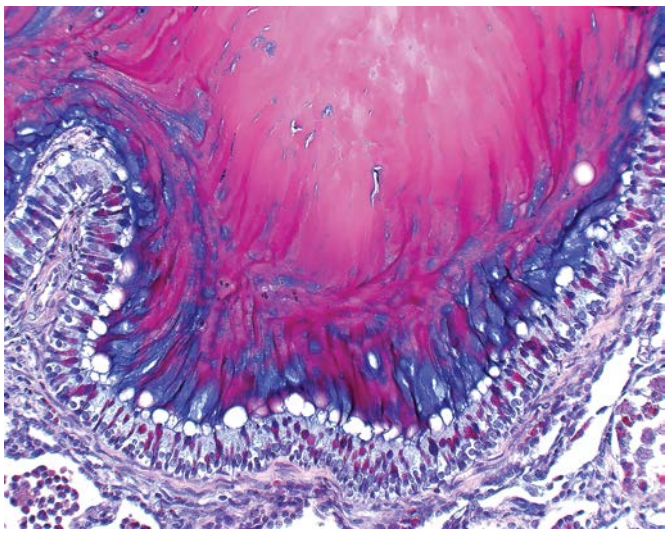
Bronchial goblet cell hyperplasia is characterized by increased numbers of large mucus-filled goblet cells lining airways. Refer to **Respiratory System** in Appendix 2 for further information.

Bronchial goblet cell metaplasia is characterized by large mucus-filled goblet cells lining terminal airways that are believed to represent club cells transdifferentiated to a secretory phenotype. Refer to **Respiratory System** in Appendix 2 for further information.

Bronchiectasis refers to dilation of the bronchial lumen, and the presence of mucopurulent exudates filling the luminal space. It is often accompanied by peribronchial fibrosis. Dilation is the result of pulmonary atelectasis distal to the airway blockage. Bronchiectasis should be differentiated from congenital abnormalities and foreign bodies.

Bronchiolar mucus plug is characterized by the obstruction of the bronchiolar lumen by inspissated mucus and is secondary to epithelial goblet cell hyperplasia in the bronchioles, or metaplasia in the terminal bronchioles. The luminal mucus usually stains strongly with Alcian blue in a periodic acid-Schiff/Alcian blue (PAS/AB) stain and may show continuity with mucus being secreted by goblet cells, suggesting continuous release. The plug develops due to overloading of the clearance mechanism, leading to mucus accumulation, stasis, and impaction. There may be "backflow" of this mucus into the alveolar ducts and adjacent alveoli, where it provokes a foamy macrophage reaction.

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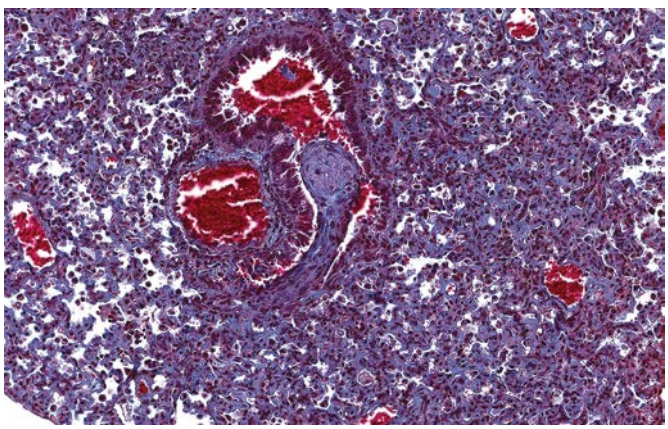


Bronchiolar mucus plug, lung, dog, PAS/AB.

Bronchioles are the most distal conducting airways and are characterized by thin walls, which in most laboratory species are devoid of cartilage. The bronchioles of rhesus monkeys, in addition to containing cartilage, also contain large bundles of smooth muscle that are not seen in other laboratory animals. The main secretory cell at this level is the club cell, and goblet cells are not normally present.

Bronchiolitis obliterans usually develops as a sequela of bronchiolar epithelial necrosis, ulceration, and exudation. The latter initially undergoes organization, followed by fibrosis and growth of polypoid projections into the lumina. These projections undergo re-epithelialization, which may lead to bronchiolar luminal recanalization. Thus the histological appearance of this condition is variable, correlating with the chronicity of the lesion.

Differential diagnoses: **Bronchioloalveolar adenoma**; **Bronchioloalveolar carcinoma**.



Bronchiolitis obliterans, lung, rat, Masson's trichrome.

Bronchiolization, see the preferred term **Bronchioloalveolar hyperplasia**.

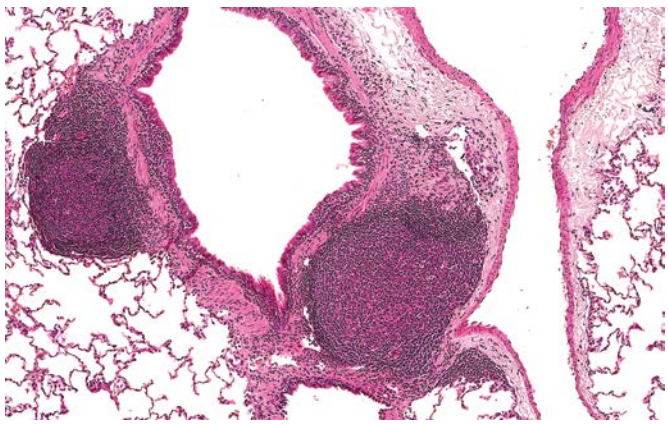
Bronchioloalveolar adenoma is a benign neoplasm that frequently arises from type II pneumocytes, and forms discrete nodules with some compression of the adjacent alveoli. Tumors may be alveolar, solid, or papillary, with little atypia. Refer to **Respiratory System** in Appendix 2 for further information.

Bronchioloalveolar carcinoma is a malignant neoplasm that arises in the same manner as does an adenoma but is typically larger, manifests increased mitoses and nuclear pleomorphism, and is invasive. Particularly in mice, multiple foci of carcinoma may be observed, and determining whether these represent two distinct neoplasms that arise independently or an extension of one existing intrapulmonary neoplasm is extremely challenging. Refer to **Respiratory System** in Appendix 2 for further information.

Bronchioloalveolar hyperplasia is characterized by the replacement of alveolar epithelium by the peripheral extension of the bronchiolar epithelium into the alveolar ducts and adjacent alveoli. Refer to **Respiratory System** in Appendix 2 for further information.

Bronchus-associated lymphoid tissue (BALT) is induced or acquired mucosa-associated lymphoid tissue (MALT) in the submucosa of the bronchi and bronchioles, which is consistently located at the bifurcations of the bronchi and bronchioles. This is typically a site of air turbulence and particle deposition situated between an artery and the bronchus. BALT is formed during the postnatal period after antigenic exposure, and the follicles may often not develop discrete germinal centers. Isolated lymphoid follicles with characteristic follicle-associated epithelium can also be found in other parts of the upper respiratory tract including the trachea, larynx, and epiglottis.

Bronchus-associated lymphoid tissue (BALT) reaction is characterized by inflammation or immune stimulation causing a generalized increase in BALT cellularity which may manifest as increased numbers of germinal centers, increased T-cell areas, and more prominent high endothelial venules (HEVs). In species that do not normally contain BALT, inflammation or immune stimulation brings about the development



BALT increased cellularity, lung, rat, H&E.

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of these structures, indicating its inducibility. In addition, in the lungs of animals in which a macrophage reaction has been induced, the ingressed macrophages (or dendritic cells) are often seen in the BALT. These are particularly prominent in the case of pigmented or dust-filled macrophage responses.

Brown adipose tissue tumor, see the preferred term **Hibernoma**.

Brown fat tumor, see the preferred term **Hibernoma**.

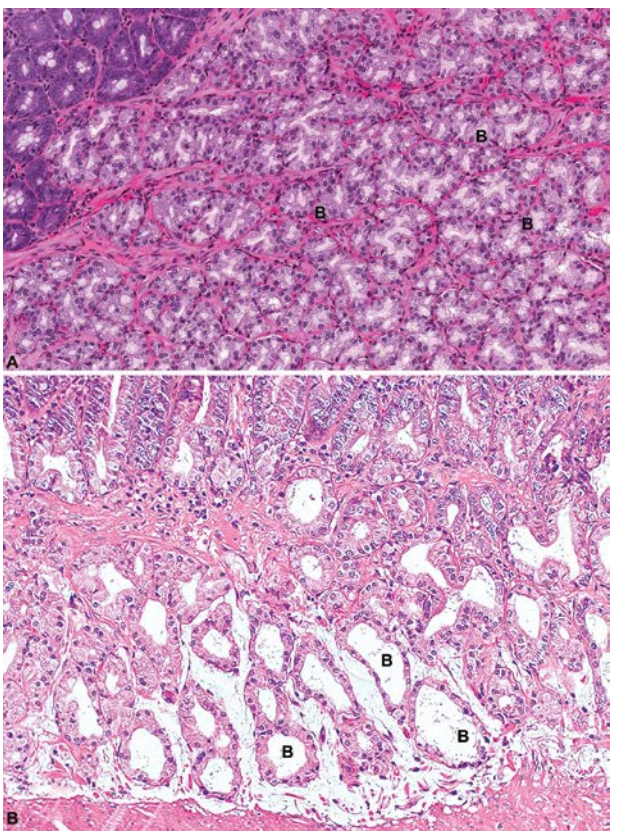
Brunner's gland carcinoma is a rare, spontaneously occurring neoplasm of the submucosal glands in the duodenum. There is partial to complete loss of glandular structures, with prominent desmoplasia and moderate pleomorphism. Neoplastic cells have intensely stained eosinophilic, amphophilic, or basophilic cytoplasm. Refer to **Gastrointestinal Tract** in Appendix 2 for further information.

Differential diagnoses: **Brunner's gland hyperplasia**; **Intestinal diverticulum**.

Brunner's gland hyperplasia is characterized by an increased number of glandular cells with an increase in overall gland size. Refer to **Gastrointestinal Tract** in Appendix 2 for further information.

Brunner's gland atrophy is characterized by a reduction in the size and number of Brunner's glands in the submucosa of the duodenum. Cystic dilatation of glands with inflammation and/or fibrosis may also be components (morphological features) of atrophy.

Differential diagnosis: **Brunner's gland degeneration/necrosis**.



Duodenum, rat (H&E). A = Brunner's gland (B), normal. B = Brunner's glands (B), atrophy. (Image reproduced with permission of the Japanese Society of Toxicologic Pathology from Nolte et al. 2016.)

Brunner's gland degeneration/necrosis is characterized by a disorganization of glandular acini with disruption of basement membranes, varying degrees of dilation, and inflammatory reaction. In the most severe lesions, inflammation extends into the surrounding mucosa and muscle layers. A mixed neutrophilic and lymphocytic inflammatory reaction with fibrosis and reactive hyperplasia of adjacent duodenal surface epithelium accompanies these changes after prolonged administration. In rats it has been described following administration of sunitinib, a multikinase inhibitor targeting VEGFR 1-3, FGFR 1-4, RET, KIT, and PDGFβ, due to their antiangiogenic actions.

Differential diagnosis: **Brunner's gland atrophy**.

Buehler skin test is an in vivo test to screen for substances that may cause human skin sensitization. It is a non-adjuvant test, whereby guinea pigs are exposed to a high dose of the substance, then given a challenge dose, defined as the highest dose that does not cause local irritation. The Buehler skin test has been superseded by the local lymph node assay (LLNA). See **Local lymph node assay (LLNA)** for further information**.**

Bulbourethral glands are small, paired mucus-secreting compound tubular glands in rodents that are difficult to evaluate grossly or dissect due to their location between the ischiocavernosus and bulbocavernosus muscles. The bulbourethral glands are poorly developed in monkeys. These glands are absent in dogs.

Synonym(s): **Cowper's gland**.

Bulla, see the preferred term **Vesicle**.

BUN is an acronym for blood urea nitrogen. See **Blood urea nitrogen** for further information.

Buphthalmos is a clinical description of enlargement of the globe, commonly found in diseases that cause an increase in intraocular pressure. See **Glaucoma, Filtration angle narrowed,** and **Filtration angle malformation** for further information.

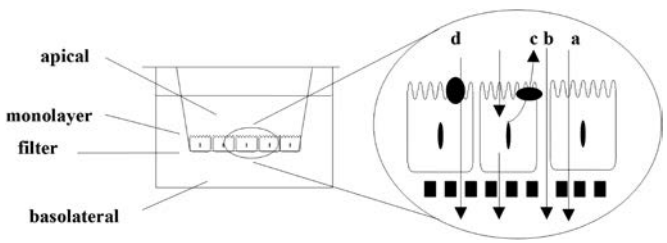
Bursal cyst is an expansion of the bursa surrounding the ovary with fluid. In mice and rats, the bursa completely surrounds the ovary and is lined by simple squamous epithelium. A bursal cyst may be differentiated from other cysts of ovarian origin because bursal cysts do not originate from the ovary. Grossly observed bursal cysts may not be identified histologically when the cyst bursts during processing.

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C

C_{max} is the maximum plasma or blood concentration of a drug after a given dose. The time to achieve this maximal concentration is T_{max}, which is dependent upon the route of administration of the drug. Following intravenous administration, it is immediately after dosing but is delayed after other routes of administration. The extent of the delay varies with the physiological and kinetic properties of the drug and may also be dose dependent.

CaCo-2 cells are cells derived from a human colon carcinoma, which express drug transporters, in particular p-glyocoprotein (pGp). CaCo cell monolayers are used as a screen for intestinal absorption of drug candidates in the early stages of drug discovery, before sufficient quantities of the chemicals are available for animal experiments.



As shown in the diagram, the cells are grown as a monolayer on filters in wells which allow administration of medium, with or without added drug candidate, on either side of the cell layer. The compounds may: a) diffuse through the cells; b) pass between the cells; c) enter the cell by diffusion and be extruded; or d) be transported into and through the cell. Compounds may be presented at the apical surface of the cells, which represents the intestinal side, or at the basolateral side. Passage through the monolayer in either direction is measured, active extrusion by pGp is assessed as a high level of basolateral permeability, and uptake from the intestine is mimicked by high apical permeability.

Calcification is the process of calcium salt deposition within soft tissues and consists of two types: dystrophic and metastatic. Dystrophic calcification is the deposition of calcium salts within injured or necrotic tissue, such as that found within a granuloma. It can also be seen as basophilic stippling due to mineral deposition within mitochondria in acutely necrotic cells. Organ dysfunction may result. Serum calcium is normal in dystrophic calcification. Calcinosis cutis is the deposition of calcium salts onto dermal collagen and epidermal and follicular basement membranes; it is almost always due to hyperglucocorticism and is often iatrogenic. If calcinosis cutis occurs in humans, a different term is used. Metastatic calcification is the deposition of calcium within multiple soft tissues due to a calcium:phosphate imbalance, typically due to hypercalcemia. As a general rule, metastatic calcification occurs when the product of the serum calcium (in mg/dL) and serum phosphate (in mg/dL) is greater than 60. The preferred sites of deposition are those where acids are excreted from the body, causing local alkalinity, and a predisposition for calcification. These sites include the gastric (glandular) mucosa, parietal pleura ("uremic frosting"), renal cortex, pulmonary alveolar septae, systemic arteries, and pulmonary veins. Causes of hypercalcemia include granulomatous disease (such as mycobacteriosis and fungal infections), bony lysis (such as fracture or intraosseous neoplasia causing bone resorption), hyperparathyroidism (nutritional secondary, renal secondary, neoplastic, or paraneoplastic), hypervitaminosis D, Addison's disease, and renal failure via both renal secondary hyperparathyroidism and failure to excrete phosphate.

Calcific band keratopathies, see the preferred term **Corneal keratinization**.

Calcitonin is a hormone produced by the C-cells of the thyroid gland. It participates in calcium and phosphorus metabolism by lowering blood calcium and phosphorus levels. Calcitonin counteracts the actions of parathyroid hormone and reduces osteoclast-induced bone resorption.

Calcium channel blockers are chemical agents (drugs) which specifically interfere with the ability of the cells calcium channel to regulate calcium movement across the cell membrane (e.g., influx and efflux). This can dramatically affect the cell function, as calcium movement across the cell membrane needs to be properly controlled for proper cell function. Contractile cells such as cardiac and smooth muscle are especially sensitive to this, so calcium channel blockers can be used to treat cardiovascular disorders and hypertension.

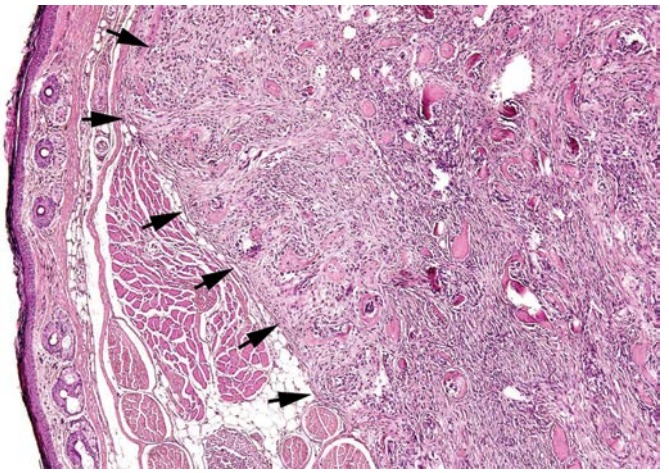
Calculus is a concretion formed from deposits typically composed of salts of organic or inorganic acids. They most often form in the urinary tract or gall bladder. They range in size from a grain of sand to a large concretion capable of obstructing the outflow of the urinary bladder. Microscopically they appear as concentric layers of basophilic and eosinophilic material, depending on the composition. Urinary calculi may form from chemicals or their metabolites or may result by altering the composition and physiology of normal urine. In rats and mice, calcium phosphate and magnesium ammonium phosphate are the most common types of calculi. In chronic toxicity studies, the presence of calculi in the urinary bladder

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may cause chronic irritation of the urothelium leading to neoplasia. Sulfosulfuron can cause the formation of urinary tract calculi in rats. See **Urolithiasis** and **Gall bladder calculi** for further information.

C

Callus is an unorganized meshwork of woven bone that forms after a fracture. Within the skin, the term callus describes a raised, irregular patch of thickened skin that develops due to friction, usually over pressure points or bony prominences.



Callus in the tail of a rat, H&E. Arrows depict the edge of callus formation consisting of bony spicules interwoven in fibrous mesh. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

cAMP is an acronym for **Cyclic AMP**. See **Cyclic AMP** for further information.

Canadian Health Protection Branch (now known as Health Canada) is the federal department responsible for helping Canadians maintain and improve their health and ensuring that they have access to safe and effective drugs and health products.

Canine ameloblastoma, acanthomatous, see the preferred term **Ameloblastoma, acanthomatous**.

Canine cutaneous histiocytoma (CCH) is a common benign cutaneous proliferative tumor in dogs, particularly young dogs less than 3 years of age. CCH most commonly presents grossly as a solitary, raised, nodular mass, most frequently on the head, and especially on the ears. Refer to **Skin** in Appendix 2 for further information.

Carboxylesterases (aliesterases; carboxylic ester hydrolase; E.C. 3.1.1.1) is a family of serine hydrolases which catalyze the hydrolysis of carboxylic acid esters to form the carboxylic acid and corresponding alcohol.

Carcinogen is a substance that can cause/increase the incidence of tumors, or a specific tumor type, in animal experiments or the clinical (human) population. Some carcinogens are genotoxic and are thought to induce tumor formation via mutagenic events, also called genotoxic carcinogens. Other compounds show no evidence of genotoxic activity and are termed nongenotoxic carcinogens. This classification is important in risk assessment since normal dose dependency with a no effect level (NOEL) for tumorigenicity at low doses is generally accepted for nongenotoxic carcinogens but not for genotoxic chemicals. Carcinogens are classified by the International Agency for Research in Cancer (IARC) into four groups, as shown in the following table.

IARC Classification of Carcinogens*

Group	Description	Definition	# Compounds
Group 1	Carcinogenic to humans	*Sufficient* evidence of carcinogenicity OR Evidence of carcinogenicity in humans is less than *sufficient* but there is *sufficient* evidence of carcinogenicity in experimental animals and *strong* evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity	111
Group 2A	Probably carcinogenic to humans[a]	*Limited* evidence of carcinogenicity in humans and *sufficient* evidence of carcinogenicity in experimental animals OR *Inadequate* evidence of carcinogenicity in humans and *sufficient* evidence of carcinogenicity in experimental animals and *strong* evidence that the carcinogenesis is mediated by a mechanism that also operates in humans OR *Limited* evidence of carcinogenicity in humans, but belongs, based on mechanistic considerations, to a class of agents for which one or more members have been classified in Group 1 or Group 2A	66
Group 2B	Possibly carcinogenic to humans[a]	*Limited* evidence of carcinogenicity in humans and less than *sufficient* evidence of carcinogenicity in experimental animals OR *Inadequate* evidence of carcinogenicity in humans but *sufficient* evidence of carcinogenicity in experimental animals OR *Inadequate* evidence of carcinogenicity in humans and less than *sufficient* evidence of carcinogenicity in experimental animals, but with supporting evidence from mechanistic and other relevant data	285

(*Continued*)

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IARC Classification of Carcinogens*

Group	Description	Definition	# Compounds
Group 3	Not classifiable as to its carcinogenicity to humans	Evidence of carcinogenicity is *inadequate* in humans and *inadequate* or *limited* in experimental animals OR Evidence of carcinogenicity is *inadequate* in humans but *sufficient* in experimental animals, but *strong* evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans OR Agents that do not fall into any other group Agents in Group 3 are not determined to be non-carcinogenic or safe overall, but often means that further research is needed.	505
Group 4	Probably not carcinogenic to humans	Evidence suggesting *lack* of carcinogenicity in humans and in experimental animals OR *Inadequate* evidence of carcinogenicity in humans but evidence suggesting *lack* of carcinogenicity in experimental animals, consistently and strongly supported by a broad range of mechanistic and other relevant data	1

[a] The terms *probably carcinogenic* and *possibly carcinogenic* have no quantitative significance and are used simply as descriptors of different levels of evidence of human carcinogenicity, with *probably carcinogenic* signifying a higher level of evidence than *possibly carcinogenic*.

* IARC website June 2018.

Carcinogenesis is the process of tumor (cancer) formation.

Carcinogenicity testing is required for all pharmaceutical agents where the expected treatment duration is greater than 6 months, including intermittent treatment for a total of more than 6 months. Two alternative approaches are available to assess carcinogenic potential: (1) studies with a treatment duration of 2 years in rats and mice, or (2) a 2-year rat study accompanied by a 6-month study in transgenic mice.

The 2-year studies (also known as cancer or carcinogenicity bioassays) usually have three-dose levels of the test compound, administered by the route to be used in the clinic, to groups of at least 50 animals per gender and a vehicle control group. All animals are subject to a full histopathological evaluation of all organs and tissues at the end of the treatment period. The studies are usually accompanied by exposure monitoring to assess plasma exposure of the test article, and in some cases, major metabolites usually in satellite animal groups. Several transgenic mouse strains are available for carcinogenicity testing that can be used in shorter-term studies to replace the 2-year mouse study.

Available strains of mice include the TSG-p53 heterozygous knockout mouse, the ras H2 transgenic mouse, v-ha-ras (TG.AC) mouse, hemizygous transgenic mouse, and the XPA homozygous knockout mouse. The first three models have mutations in known oncogenes, and the latter model is a tumor suppressor gene. As such, these transgenic animal models should be more sensitive to carcinogenic agents than standard rodent models. Although each transgenic model has advantages and disadvantages, the ras H2 model appears to be gaining in use as an alternative to the standard mouse model in the pharmaceutical industry. Transgenic studies typically use groups of 25 animals per sex with concomitant vehicle and positive controls.

Animals are treated for 6 months before sacrifice followed by a full histopathological evaluation. Carcinogenic potential is assessed from the incidence of tumors observed in the treated animals compared to that in the vehicle and historical control animal data, using appropriate statistical methodology to account for differences in longevity.

Carcinogenic potency database contains the results of carcinogenicity tests involving over 1500 compounds allowing comparison of potency as carcinogens based on the TD_{50} value, the median daily dose in mg/kg which, over lifetime exposure, would result in the induction of tumors in 50% of the animals. The latest version may be found on the NIH website (toxnet.nlm.nih.gov/cpdb/).

Carcinoid is a slow-growing type of neuroendocrine tumor (apudoma) that arises from enterochromaffin cells in the gastrointestinal tract. Refer to **Gastrointestinal Tract** and **Endocrine System** in Appendix 2 for further information.

Synonym(s): **Carcinoid tumor**.

Carcinoid tumor, see the preferred term **Carcinoid**.

Carcinoma is a malignant neoplasm derived from epithelial cells that tends to infiltrate/invade into the surrounding tissues and frequently metastasizes to other organs through vascular and frequently lymphatic invasion. Carcinomas comprise the most frequent malignant epithelial tumors of the breast, lung, pancreas, colon, and skin.

Carcinoma, primary adenoid cystic, see the preferred term **Eccrine gland carcinoma**.

Carcinosarcoma is a malignant, biphasic tumor with a carcinomatous (cancer of epithelial cells) component and a sarcomatous (cancer of mesenchymal or connective tissue cells) component. Most of these tumors arise in the background of pleomorphic adenoma; however, some arise de novo.

Cardiac arrest is a sudden cessation of the beating of the heart. This causes blood to stop flowing and often leads to sudden

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death. It is caused by a malfunction of the heart's electrical conduction system. Heart disease may or may not be present. Cardiac arrest is often confused with a heart attack. A heart attack is generally caused by a blockage of blood flow to the heart, for example by a blood clot, leading to death of myocardium which decreases cardiac function. A heart attack may result in cardiac arrest, but a heart attack may have other outcomes which do not result in a complete heart stoppage or sudden death.

Cardiomegaly is enlargement of the heart, either as a whole or part, for example one side or the other. This is a macroscopic change or one that is identified by weighing the tissue. This change may be due to an increased workload or other stimuli (e.g., pharmaceutical, hormonal).

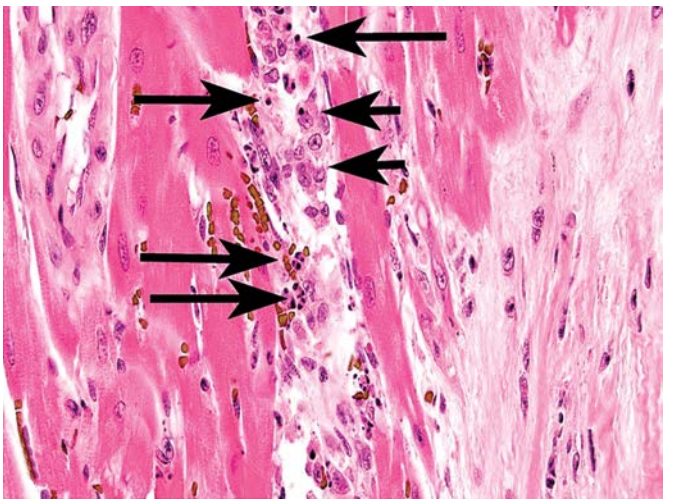


Cardiomegaly; heart from a rat treated with a compound that induced symmetrical heart enlargement and increased heart weight, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology.)



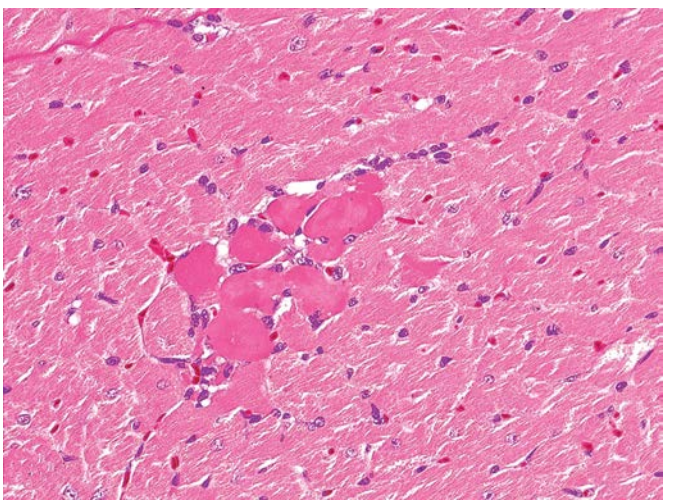
Age-matched control heart from a rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology.)

Cardiomyocyte apoptosis is death of individual cardiomyocytes without the induction of any inflammatory response. Cells are generally condensed and eosinophilic with pyknotic nuclei. Pharmaceuticals or chemicals may induce this, but definitive diagnosis can be problematic without the application of special techniques.



Cardiomyocyte apoptosis with apoptotic cells indicated by arrows, heart from ephedrine and caffeine treated rat, H&E. (Image courtesy of the National Toxicology Program; Reproduced with permission of the Japanese Society of Toxicologic Pathology.)

Cardiomyocyte degeneration appears as a variety of morphological changes, predominantly hypereosinophilia, vacuolar degeneration, and lipid vacuolation. Degeneration can result from increased workload, energy deficit, or direct toxicity, resulting in disruption of homeostasis. Unlike necrosis, degeneration is generally not associated with inflammatory cell infiltrates, as cells remain intact. Vacuolar degeneration appears as variably sized and shaped clear vacuoles within the cytoplasm of the cardiomyocyte. This change is classically seen with anthracyclines and is due to dilation of the sarcoplasmic reticulum subsequent to peroxidative damage by free radicals. Lipid vacuolation or fatty degeneration occurs due accumulation of lipid droplets in the cytoplasm. Lipids



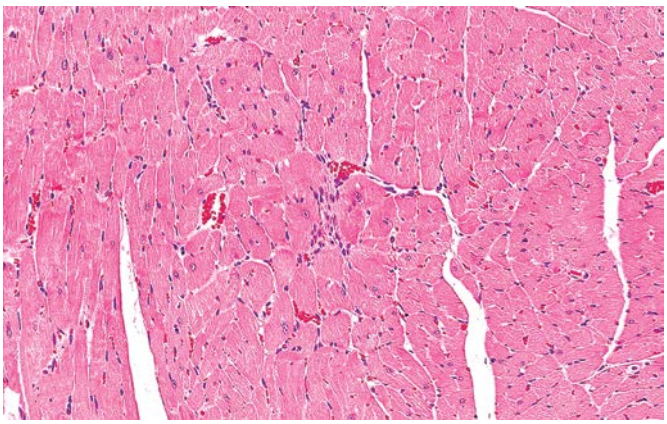
Cardiomyocyte degeneration; hypereosinophilia of peracute injury, heart, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology.)

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stain positively in oil red O in frozen sections. In severe cases, the myocardium appears pale and flaccid at necropsy. Copper deficiency, toxemia of various origins, and diets high in long-chain fatty acids can induce this change. Phospholipidosis due to cationic amphiphilic drugs results in a similar morphological picture.

Differential diagnosis: **Cardiomyocyte necrosis**.

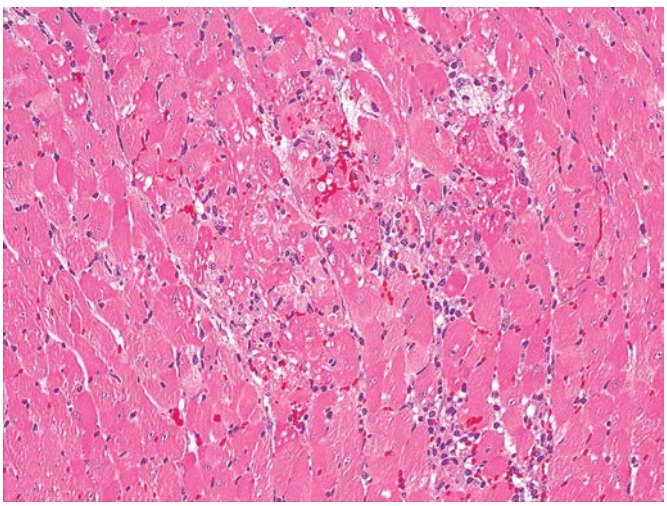
Cardiomyocyte hypertrophy is enlargement of individual cardiomyocytes that can generally be seen microscopically. This may be seen as part of a general change due to increased workload. It can also be induced by pharmaceuticals (e.g., oxfenicine) or hormones (e.g., growth hormone), and with intracellular cytoplasmic accumulation of glycogen or vacuoles.



Focal cardiomyocyte hypertrophy with minimal accompanying hypercellularity, presumed remnant of a focus of myocyte necrosis, heart, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology.)

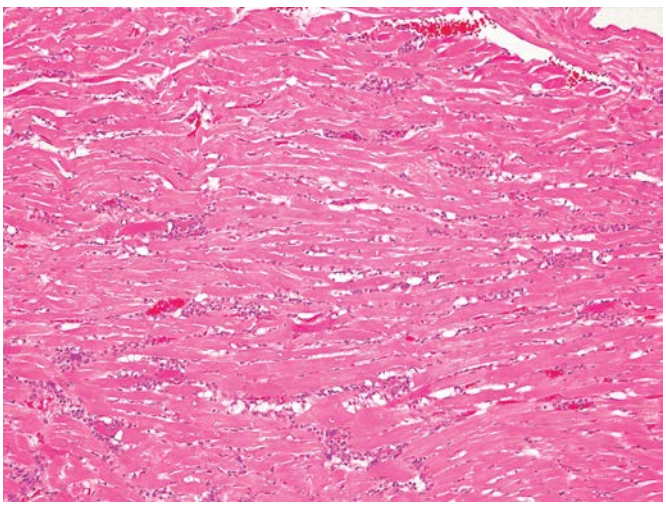
Cardiomyocyte necrosis is an irreversible process usually characterized by loss of myocyte architecture and secondary inflammatory cell infiltration. Necrotic myofibers appear hypereosinophilic with loss of striations, pyknotic nuclei and cytoplasmic basophilic granules that represent calcium accumulation in mitochondria. Broadly, necrosis can be classified into coagulation necrosis and necrosis with contraction bands. Coagulation necrosis is typically seen with ischemia. Contraction bands appear as densely eosinophilic regions of the myofiber due to hypercontraction of filaments. The latter occur due to large numbers of calcium ions passing through damaged or hyperpermeable plasma membranes causing hypercontraction of the myofibrils. Cardiomyocyte regeneration is rare.

Differential diagnoses: **Cardiomyocyte degeneration**; **Cardiomyocyte apoptosis**.



Cardiomyocyte necrosis; characterized by hyaline condensation and fragmentation of the cytoplasm, minimal hemorrhage and early inflammatory cell infiltration, heart, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology.)

Cardiomyocyte vacuolation can be due to disturbances of cell organelles or accumulation of exogenous or endogenous substances within heart muscle cells. Vacuolar degeneration can result from T-tubule or sarcoplasmic reticulum distension or from mitochondrial swelling. Morphologically, clear discrete vacuoles are seen within the cardiomyocyte, generally without distortion of cell size or shape. Necrosis and inflammation are not usually associated with the vacuoles unless cardiomyocyte injury occurs. Special stains or specialized investigations, including transmission electron microscopy, are required to investigate the content and nature of the vacuoles, and to assess their significance. Accumulation of phospholipids, associated with administration of cationic amphiphilic drugs, is a frequent cause of vacuolation in safety assessment studies.

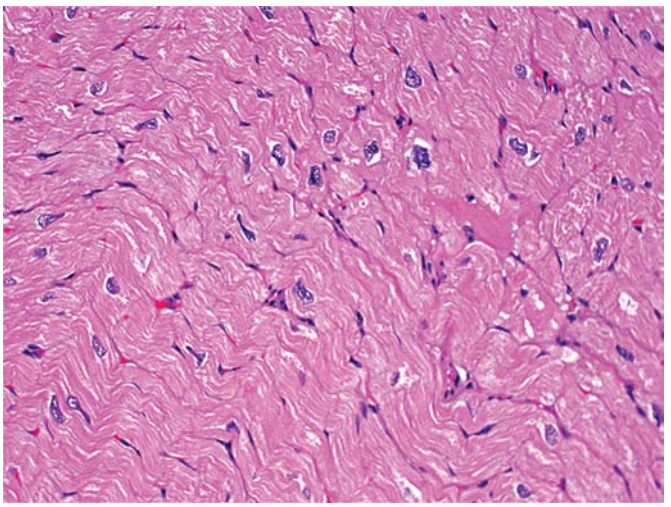


Cardiomyocyte vacuolation, heart, rat, H&E.

Cardiomyopathy is a general term used for a heterogeneous group of diseases that affect structure and function of the heart and may be secondary to other forms of heart disease, idiopathic in nature, or due to defined genetic disease, particularly in man. Cardiomyopathies are typically divided into dilated cardiomyopathy, in which the chambers of the heart are enlarged with thin walls and reduced contractile function; hypertrophic cardiomyopathy, in which the walls of the heart are thickened due to diffuse cardiomyocyte hypertrophy and disorganization that may result in inadequate filling of the ventricles during diastole and conduction abnormalities; and restrictive cardiomyopathy, in which normal relaxation of the heart chambers during

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diastole is reduced due to fibrosis within the chamber walls. In general, the term cardiomyopathy should not be used in toxicity studies and a more specific, descriptive term for the underlying lesions is preferred. Rodent progressive cardiomyopathy is a specific entity in aged rats for which the preferred term is **Myocardial mononuclear cell infiltrate/fibrosis**.



Diffuse cardiomyocyte hypertrophy and disorganization associated with hypertrophic cardiomyopathy, cynomolgus monkey, H&E. This animal had increased absolute and relative heart weight (body weight and brain weight ratio) and exhibited prolonged QRS waves on ECG. (Image courtesy of Wendy Halpern.)

Cardiotoxicity is toxicity that affects the heart. It can be observed with therapeutic agents used to treat cardiovascular and non-cardiovascular diseases (e.g., doxorubicin, COX-2 inhibitors). It can affect the heart and/or circulation by altering blood flow or causing thrombosis. Direct effects on the heart include functional abnormalities such as arrhythmias that occur without any structural changes, and developmental or other structural abnormalities. The heart can respond in limited ways to injury including hypertrophy/cardiomyopathy, degeneration/necrosis, and/or fibrosis. These changes make the heart less efficient at circulating blood and can ultimately result in congestive heart failure. Many chemotherapeutic agents carry significant risks of cardiotoxic side effects, and as such, there is ample literature regarding the clinical definition of cardiotoxicity as well as how to minimize its risk and optimize treatment.

Cardiovascular system, Anatomy and Histology, see Appendix 3 for further information.

Carrier mediated transport is the active transport of drugs or their metabolites across cell membranes. See **Drug transporters** for further information.

Cartilage is a form of connective tissue found throughout the body as part of the skeleton (e.g., joints) and provides support within soft tissues (e.g., ear, respiratory tract). Cartilage is composed of multiple components such as chondrocytes, collagen fibers (type II), and proteoglycans. Types include hyaline cartilage, elastic cartilage, and fibrocartilage.

Cartilage degeneration, see the preferred term **Chondromucinous degeneration**.

Cartilage dysplasia, see the preferred term **Physeal dysplasia**.

Cartilage hyperplasia, see the preferred term **Chondrocyte hyperplasia**.

Case-control study is a type of epidemiology study which retrospectively compares exposure to specific agents or chemicals in subjects with a certain disease or outcome as well as those who do not have the disease or outcome, to determine whether there is an association of the disease or outcome with the exposure.

Caseous necrosis is a category of necrosis grossly identified by its soft texture that easily exfoliates from a lesion. Caseous necrosis is most often associated with granulomatous inflammation, but microscopically has form similar to liquefactive necrosis with complete architectural degeneration. See **Liquefactive necrosis** for further information.

Cast nephropathy is a human condition most often associated with multiple myeloma where there is coprecipitation of immunoglobulin light chains (Bence-Jones protein) and Tamm-Horsfall protein in the descending collecting duct (DCT), resulting in homogeneous, eosinophilic material in the renal tubules in histologic sections. Tamm-Horsfall protein casts have been observed as a treatment-related effect only in cynomolgus macaques treated with therapeutic candidates having a common carboxylic acid moiety, suggesting a species-specific sensitivity.

Catalepsy is a condition of muscle rigidity, with a lack of response to external stimuli and a decreased sensitivity to pain.

Cataract is a clinical description of capsular, subcapsular nuclear, and anterior or posterior cortical lens opacity that correlates to one or more microscopic changes. See **Lens fiber degeneration** for further information.

Catecholamine is a part of a class of neurotransmitters and hormones that function in the regulation of physiologic changes related to the stress response. Catecholamines are synthesized in the central and peripheral nervous systems and the adrenal medulla from the precursor amino acid, L-tyrosine, resulting in production of dopamine, norepinephrine, and/or epinephrine, depending on enzyme availability in the cell. Epinephrine (adrenaline) is primarily produced by the adrenal gland medulla and mediates both receptor-ligand and neurotransmitter functions. Norepinephrine (noradrenaline) is primarily produced in the pons of the brain, and to a lesser extent, in the adrenal gland medulla. Epinephrine and norepinephrine secretion occurs in the "flight or fight" and "stress response," stimulating α_1, α_2, β_1, β_2, and β_3 adrenergic receptors of the sympathetic nervous system and leading to increases in blood flow, gluconeogenesis, cardiac output, respiratory rate, lipolysis, defecation, urination,

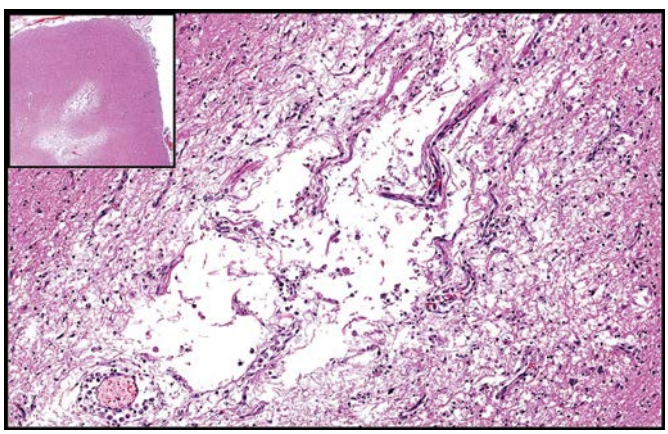
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and blood pressure. Dopamine is primarily synthesized in the brain and kidneys, with small amounts produced in the adrenal gland medulla and other locations. Dopamine is a central nervous system (CNS) neurotransmitter, modulating mood and motor function. Dopamine effects in the periphery (outside of the CNS) are less well-defined but include increasing vasodilatation, deactivating lymphocytes, increasing glomerular filtration rate, and inhibiting the actions of norepinephrine. Catecholamines are essential to normal functioning and interaction with the environment; however, persistently high levels that are unresponsive to negative feedback inhibition can lead to catecholamine toxicity and organ damage.

Synonym(s): **Dopamine, epinephrine, noradrenaline, norepinephrine**.

Catecholamine-induced cardiotoxicity can occur with sustained high levels of endogenous or exogenous catecholamines. The left ventricle and papillary muscles of the heart are typically involved. Microscopically, there is initially contraction band degeneration/necrosis followed by inflammation (composed mostly of macrophages with possible scattered neutrophils) and can ultimately result in fibrosis. The mechanism of action is complex and not entirely understood. In animals, this has been attributed to effects on the vasculature resulting in hypoxia/ischemia. In addition to cardiotoxic ischemia, recent human literature suggests that increased catecholamines also cause direct damage to cardiomyocytes resulting from mitochondrial dysfunction caused by both calcium overload and oxidative stress.

Cavitation is a macroscopic (gross) or submacroscopic term describing voids in the brain usually subsequent to infarction. Because the brain is within a rigid cranial vault, removal of dead tissue from an infarct as part of the healing and scarring process may result in cavitation. See **Infarct** for further information.



A cavitation is an empty void remaining after necrotic tissue components have been removed by phagocytes. The example here is the sequel to an infarct. In the CNS, infarcts tend to resolve by cavitation after debris has been removed by phagocytes. Cavitations are "encapsulated" by a peripheral zone of hypertrophied astrocytes (not discernible at this magnification). Fibrous scarring does not occur in the CNS unless the damage occurs adjacent to a meningeal surface. Dog. H&E.

C-cell, see the preferred term **Thyroid C cell**.

C cell adenoma, see preferred term **Thyroid C cell tumor, benign**.

C cell carcinoma, see the preferred term **Thyroid C cell tumor, malignant**.

C cell hyperplasia, see the preferred term **Thyroid C cell hyperplasia**.

C cell proliferation, see the preferred term **Thyroid C cell hyperplasia**.

cDNA (complementary DNA) designates DNA made in the laboratory by reverse transcription from mRNA, which therefore contains no introns. See **Introns** for further information.

cDNA library is a library consisting of (normally bacterial) clones that contain fragments of an organism's transcribed genes. A complete library contains all parts of an organism's transcribed genome. cDNA is the transcribed parts of the genome, in the absence of introns. The cDNA library is used to isolate genes and study their function.

Cecum inflammation is characterized by an infiltration of inflammatory cells (e.g., neutrophils, macrophages, and lymphocytes). It can be precipitated by a variety of stimuli, including mechanical, chemical, or parasitic.

Cell culture is a method to maintain cells outside of an organism. Cell cultures are employed to study or use functions of individual cell types. This method has the advantage that no experimental animals are used, and that cells can be easily manipulated.

Cell cycle is the physiological sequence of events when cells grow, divide, and as such multiply. In nondividing cells, which include the majority of cells in differentiated tissues, cells are locked in the G0 phase. If stimulated to divide, such cells would move into G1a growth phase, in which preparedness for DNA synthesis is ascertained, followed by S-phase, in which DNA is replicated, which is followed by another gap phase, G2, before mitosis (M), and finally cytokinesis or cell separation.

Cell death is cellular termination. Under the conditions in which the cell no longer performs its function or for which its function is no longer biologically relevant, programmed cell death allows the cell to be dismantled and removed from the organ system (see **Apoptosis** for further information). Severely injured cells may undergo unprogrammed cell death (see **Necrosis** for further information). The death of a cell may be part of normal biological growth, development, and regulation, or may be due to pathological influences. Programmed cell death occurs by apoptosis, necroptosis (i.e., a programmed form of necrosis), and autophagy, and is energy-dependent, while energy-independent cell death occurs by necrosis. See also **Cytotoxicity**.

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Cell transformation is the changing of a non-tumorigenic cell into a tumor cell. This is a method that is often used in vitro to predict the tumorigenic potential of cells or investigate whether nontumorigenic cells are converted into tumorigenic cells; e.g., chemical treatment. If done in cell culture, the transformed cell grows into a tumor when implanted in the appropriate animal host.

Cellular atypia describes an abnormality or deviation from the normal or typical cellular state. Histologic features of cellular atypia include nuclear abnormalities (nuclear atypia), deviations in normal nuclear to cytoplasmic ratio, changes in chromatin appearance, and changes in cytoplasm (decreased amount). Cellular atypia may or may not be associated with preneoplastic changes which may progress to malignancy, but can also be caused by infection, inflammation, or tissue irritation.

Cellular vacuolation can occur in any organ/tissue in the body. Vacuolation may be decreased or increased. Alteration of cellular vacuolation denotes a change in the size and/or number of clear spaces within the cytoplasm, usually observed in steroid-synthesizing tissues such as the adrenal gland and ovaries. Changes in vacuolation can indicate alterations in the steroid/lipid synthesis pathway.

Cementum/dentin resorption by odontoclasts occurs in the roots of deciduous teeth as a normal process during replacement by permanent teeth. Odontoclasts are multinucleate cells that arise from tartrate-resistant acid phosphatase (TRAP)-positive circulating macrophages. Dentinoclasts and cementoclasts have similar origins and play analogous roles in root resorption. Inflammatory conditions in teeth or surrounding bone and soft tissue may result in resorption of dentin and cementum, as inflammatory mediators can stimulate the formation of odontoclasts from macrophages. Certain pharmaceutical agents that affect signaling pathways in development and differentiation may stimulate abnormal resorption by odontoclasts. In some cases, depressions similar to Howship's lacunae may develop on the root surfaces. Cementum, a mineralized dental component on the outer surface of the root (except in rodent incisors, where it is normally absent), may be similarly affected, although cementum is normally very resistant to degradation because it is acellular and nonporous.

Differential diagnoses: **Dentin decreased**; **Dentin niche**.

Central chromatolysis, see the preferred term **Chromatolysis**.

Central nervous system (CNS) consists of the brain and spinal cord. The optic nerve and retina are also considered part of the central nervous system.

Centrilobular necrosis is oncotic death of hepatocytes that occurs adjacent to central veins (terminal hepatic venules) across multiple lobules of hepatic tissue. Acute necrosis may resolve by phagocytosis of the necrotic cell debris, and if the sinusoidal architecture remains intact, the hepatocellular parenchyma will regenerate by proliferation of the surviving hepatocytes within the lobule. The susceptibility of central lobular hepatocytes to toxic and ischemic injury makes this pattern of necrosis the most common of the zonal patterns of necrosis. Susceptibility of central lobular hepatocytes to toxic injury results in many instances from the requirement for metabolic activation of drugs and chemicals to toxic metabolites by certain cytochrome P450 (CYP) oxidoreductase enzymes that are preferentially expressed in central lobular hepatocytes. Examples include the activation of acetaminophen by CYP2E and CYP3A, and the activation of carbon tetrachloride by CYP2E. Susceptibility of central lobular hepatocytes to ischemic injury results in many instances from the gradient of oxygen across hepatic lobules whereby central lobular hepatocytes experience the lowest oxygen delivery. Central lobular necrosis sometimes needs to be carefully distinguished from autolytic change.

Centromere is a chromosomal position that links sister chromatids and serves as the attachment site of the cellular spindle apparatus for chromosome segregation during cell division.

Cerebrospinal fluid (CSF) circulates within the ventricular system of the brain, the central canal of the spinal cord, and within the subarachnoid space over the external surfaces of the brain and spinal cord. CSF provides nutrition and support to the brain parenchyma and serves to cushion and protect the brain, spinal cord, and the delicate structures protruding from or into the brain and spinal cord. Essentially, the brain and spinal cord are suspended within this CSF. CSF is produced by the choroid plexus epithelium, with a smaller contribution from ependymal cells. These cells actively transport some substances into CSF, which are passively followed by water, while excluding others. Compared to blood plasma, CSF has higher concentrations of sodium, chloride, and magnesium, and lower concentrations of potassium, calcium, glucose, and proteins. Normal CSF has very little protein (~14–45 mg/dL in humans) including immunoglobulins, and very few cells relative to plasma. Refer to Appendix 3 for further information.

Ceroid pigment is characterized by deposition of golden yellow pigments that represent oxidized carbohydrates, lipids, and proteins within cells. Its increased deposition, especially in the central nervous system, is associated with a variety of lysosomal storage diseases. To be accurate with this diagnostic term, additional evidence demonstrating that the pigment contains certain ceroid-related proteins (e.g., subunit c of mitochondrial ATPase or others), and/or demonstration that the pigment is positive for agglutinin stain, is necessary because lipofuscin may be similar to ceroid in color and morphology but shows negative staining for agglutinin. It is also acid-fast and autofluorescent.

Differential diagnoses: Lipofuscin pigment; **Hemosiderin pigment**; **Wear and tear pigment**.

Cervical carcinoma in situ, see the preferred term **Cervical intraepithelial neoplasia**.

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Cervical epithelial dysplasia, see the preferred term **Cervical intraepithelial neoplasia**.

Cervical inflammation is characterized by infiltration of granulocytes, lymphocytes, and/or macrophages accompanied by edema, congestion, hemorrhage, necrosis, and/or fibrosis, all dependent on the inciting cause, the severity, and the chronicity of the lesion.

Differential diagnosis: **Cervical inflammatory cell infiltrate**.

Cervical inflammatory cell infiltrate is characterized by infiltration of granulocytes, lymphocytes, and/or macrophages in the cervix that is not accompanied by edema, congestion, hemorrhage, necrosis, and/or fibrosis.

Differential diagnosis: **Cervical inflammation**.

Synonym(s): **Cervicitis**.

Cervical intraepithelial neoplasia is a papillomavirus-associated dysplastic lesion of the cervix epithelium in nonhuman primates. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Cervical stromal hypertrophy, see the preferred term **Portio vaginalis hypertrophy**.

Cervicitis, see the preferred term **Cervical inflammation**.

Cervix is the portion of the female reproductive tract bridging the vagina and uterus. The normal histomorphology is comparable to the vagina; however, the muscle layers are more prominent, and temporally, the histologic changes during the estrous cycle lag slightly behind those of the vagina.

cGMP is an acronym for **Cyclic GMP**. See **Cyclic GMP** for further information.

Chalazion, see the preferred term **Meibomian gland granulomatous inflammation**.

Chinese hamster ovary (CHO) cells is a popular cell line derived from a Chinese hamster ovary used in genotoxicity testing.

Chloracne is a manifestation of skin toxicity most typically associated with exposure to dioxin. Lesions include comedone formation, sometimes with associated inflammation. Lesions similar to chloracne have also been associated with administration of epidermal growth factor inhibitors.

Chloroleukemia, see the preferred term **Myeloid leukemia**.

CHO cells, see **Chinese hamster ovary cells** for further information.

Cholangiocarcinoma is a malignant neoplasm that originates from bile duct epithelial cells. These neoplasms are characterized by the appearance of a liver mass that histologically resembles proliferation of glands lined by atypical biliary epithelium that may form solid and papillary structures. Nuclear pleomorphism may be prominent. Refer to **Liver, Gallbladder, and Exocrine Pancreas** in Appendix 2 for further information.

Cholangiocellular adenocarcinoma, see the preferred term **Cholangiocarcinoma**.

Cholangiocellular adenoma, see the preferred term **Cholangioma**.

Cholangiocellular carcinoma, see the preferred term **Cholangiocarcinoma**.

Cholangiofibrosis is a lesion characterized by the accumulation of variably dilated glands that contain mucus and that are irregularly separated by the accumulation of connective tissue and inflammatory cells. The glands typically mimic intestinal epithelium and will replace liver tissue without forming a mass. Refer to **Liver, Gallbladder, and Exocrine Pancreas** in Appendix 2 for further information.

Cholangiole is an intralobular bile duct which is a continuation of the bile canaliculi leading to interlobular bile ducts. Cholangioles are lined by both cholangiocytes and hepatocytes.

Cholangioma is a benign neoplasm that originates from bile duct epithelial cells. These neoplasms are characterized by the appearance of a liver mass that histologically resembles a proliferation of glands lined by biliary epithelium. Refer to **Liver, Gallbladder, and Exocrine Pancreas** in Appendix 2 for further information.

Cholangioma, cystic is a benign neoplasm that originates from bile duct epithelial cells. These neoplasms are characterized by the appearance of a liver mass that histologically resembles cystic glands lined by biliary epithelium. Refer to **Liver, Gallbladder, and Exocrine Pancreas** in Appendix 2 for further information.

Cholangitis is inflammation of the bile ducts characterized by accumulation of inflammatory cells (neutrophils, eosinophils, and/or mononuclear cells) in and around the bile ducts as well as degeneration and necrosis of bile duct epithelium. Cholangitis may be generalized, but often may preferentially involve the small intrahepatic ducts or the larger extrahepatic ducts. Experimentally, cholangitis may be produced in mice by intraperitoneal injection of *Streptococcus intermedius* or by liver-specific knockout of Mdr2 (Abcb4) gene.

Cholecystitis is inflammation of the gallbladder occasionally caused by exposure to toxicants. Acute inflammation may be associated with congestion, hemorrhage, and edema of the lamina propria and serosa, mucosal ulceration, and inflammatory cell infiltration. Chronic inflammation, including granulomatous, may contain necrotic luminal cellular debris with

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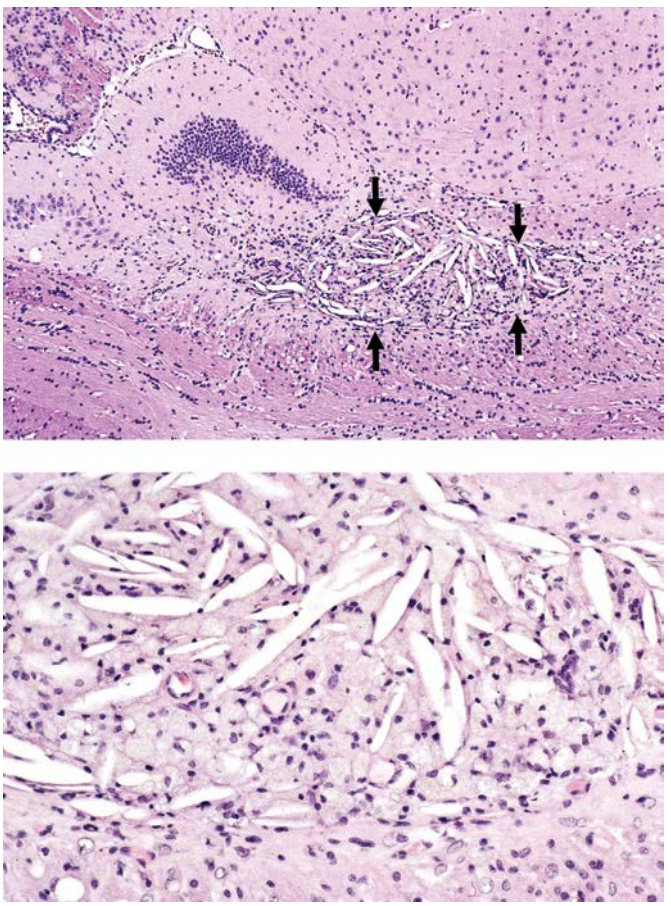
fibrosis, mucosal hyperplasia (see **Gallbladder hyperplasia** for further information) and glandular metaplasia (see **Gallbladder glandular metaplasia** for further information). Cholecystitis is rarely reported as a spontaneous change in aging mice and is reported following administration of HMG-CoA reductase inhibitors to dogs, or by bacterial and viral infections of gallbladder is several species.

Cholelithiasis, see the preferred term **Gallbladder calculi**.

Cholestasis is defined as a blockage of bile flow, although the term is commonly used in toxicology in association with clinical and/or anatomic changes resulting from a presumed stasis or a significant reduction in bile flow through hepatic canaliculi and/or the bile duct. See **Bile acids** for further information.

Cholesteatoma, see the preferred term **Cholesterol granuloma**.

Cholesterol clefts are extracellular accumulations of cholesterol-rich lipoprotein by-products left at sites of hemorrhage or necrosis, often within a tumor-like fibrovascular mass. Histologically they appear as clear, angular, fusiform, or elongate shapes within tissues, often surrounded by granulomatous inflammation or fibrous tissue. Cholesterol deposits form from degraded cell membranes, and may be incidental or associated with specific pathologic conditions. In paraffin embedded histologic sections, crystals of cholesterol are dissolved during processing leaving empty, rhomboid-shaped spaces.



Cholesterol clefts in the brain of a mouse, H&E. Arrows highlight a cluster of multiple angular, elongated clear spaces is present within the neuropil. In the higher magnification image, these spaces have variable size and shape with increased cellularity of the surrounding tissue. (Images courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

Cholesterol granuloma is a localized area of inflammatory cell accumulation (primarily macrophages) that is thought to be secondary to the irritant effect of accumulated cholesterol crystals secondary to the breakdown of blood, inflammatory tissue, or exudate. There may be accompanying foreign body giant cells and fibrosis. See **Cholesterol clefts** for further information.

Chondrocyte hyperplasia is an increase in the number of chondrocytes and/or cartilage resembling an expansile growth but is non-neoplastic. Proliferating chondrocytes are well differentiated, often hypertrophied, and observed in irregular clusters. This change often occurs focally in response to inflammation, cartilage injury, and with chondromucinous degeneration in rodents. Refer to **Bone, Muscle, and Tooth** in Appendix 2 for further information.

Chondrocytes are cells found within cartilage. These cells are round to oval and reside within a small empty space (lacuna) which is surrounded by cartilage matrix. Chondrocyte proliferation, differentiation, and cartilage matrix production is modulated by multiple molecules (e.g., TGFβ1, IGF1, Indian hedgehog, PTH, FGF).

Chondroma is a benign tumor composed primarily of cartilage-forming cells (e.g., chondrocytes, chondroblasts) occurring most commonly in the skeleton but also in extraskeletal sites. It is a well-circumscribed, expansile tumor with neoplastic chondrocytes lacking orderly arrangement, with minimal pleomorphism and rare mitotic figures. Neoplastic chondrocytes are surrounded by abundant lightly basophilic matrix. Chondromas typically do not metastasize or invade the surrounding tissues. Chondroma is rare in dogs, mice, and hamsters but is occasionally observed in the nasal turbinates of rats. Refer to **Bone, Muscle, and Tooth** in Appendix 2 for further information.

Chondromucinous degeneration is frequently observed in the sternum, growth plate, and articular cartilage of long bones and can be seen in both young and older mice and rats. Degeneration of the intersternal or xyphoid cartilage can lead to deformity and commonly, a prominent xiphoid. The condition is degenerative with no associated inflammation. Microscopically, there is necrosis, areas without chondrocytes, and fragmentation or loss of ground substance resulting in a cystic space. Small clusters of chondrocytes may be present at the periphery. In rats, the lesion increases in frequency with age. The etiology of the condition is not known, and the lesion does not appear to progress.

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Differential diagnosis: **Degenerative joint disease**.

Synonym(s): **Cartilage degeneration**; **sternal cartilage degeneration**.

Chondrosarcoma is a malignant tumor of cartilage-forming cells (e.g., chondrocytes, chondroblasts). These neoplasms arise in the skeleton but can occur in other locations such as the eyelid, larynx, and ear. Tumors typically consist of highly cellular lobules composed of large basophilic neoplastic cells in lacunae with adjacent cartilage matrix. These tumors are usually well differentiated but neoplastic cells can show variation in size (e.g., larger multinucleated) and shape (e.g., spindle-shaped). Refer to **Bone, Muscle, and Tooth** in Appendix 2 for further information.

Chordoma is a malignant tumor of primitive notochord remnants. Neoplastic mesenchymal cells are arranged in lobules and contain abundant cytoplasmic vacuolation. This invasive tumor has been reported in humans, rats, mice, ferrets, dogs, and zebrafish. Chordomas are frequently observed in the axial skeleton and at the base of the skull, with or without metastasis to the lungs. Refer to **Bone, Muscle, and Tooth** in Appendix 2 for further information.

Choriocarcinoma is a rare neoplasm in laboratory animals composed of placental cytotrophoblasts and trophoblastic giant cells, or syncytiotrophoblasts. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Chorioepithelioma, malignant, see the preferred term **Choriocarcinoma**.

Choroidal angiogenesis, see the preferred term **Choroidal neovascularization**.

Choroidal neovascularization consists of an abnormal proliferation of small blood vessels that infiltrate the choroid, usually related to ischemia or an imbalance in pro- versus antiangiogenic growth factors. New blood vessels extend through breaks in Bruch's membrane into the space below the retinal pigment epithelium (RPE) or into the subretinal space between the photoreceptors and RPE (see Appendix 3 for additional information). Neovascularization in laboratory animals is most frequently an experimentally induced lesion by laser photocoagulation to model retinopathy of prematurity, but choroidal and retinal neovascularization is a spontaneous disease in JR5558 mice.

Differential diagnosis: **Retinal neovascularization**.

Synonym(s): **Choroidal vascular proliferation**; **choroidal angiogenesis**.

Choroidal vascular hyperplasia, see the preferred term **Choroidal neovascularization**.

Choroidal vascular proliferation, see the preferred term **Choroidal neovascularization**.

Choroid plexus is a region of specialized ependymal cells that produce cerebrospinal fluid (CSF). Ependymal cells line the ventricles in the brain and central canal of the spinal cord. The choroid plexus is located along the roof of the ventricles where these specialized ependymal cells are in close contact with capillaries (forming a plexus) and where exchange of materials between the CSF and blood occurs. Villi of the choroid plexus have a core of blood vessels with a fenestrated endothelium that is surrounded by a basal lamina. The fenestrated endothelium allows diffusion of molecules from the blood into the extracellular matrix of the choroid plexus following a concentration gradient. The ventricular surfaces of the villi are lined by choroid plexus epithelial cells on another basal lamina. The choroid plexus epithelium is derived from ependymal epithelium but are joined by tight junctions (unlike ependymal cells), and thus are the primary constituents of the blood-CSF barrier. The choroid plexus epithelium produces the majority of the CSF by selective active transport of materials from the extracellular space, with passive diffusion of water.

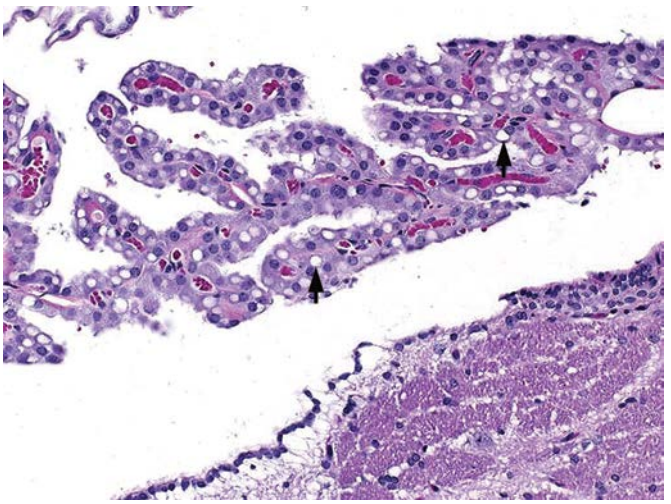
Choroid plexus carcinoma is a malignant neoplasm originating from epithelial cells of the choroid plexus, developing therefore in proximity to the ventricular system. Choroid plexus carcinomas often have a papillary morphology and often invade adjacent brain parenchyma. Refer to **Nervous System** in Appendix 2 for further information.

Choroid plexus degeneration is characterized by intracytoplasmic vacuolation involving choroid plexus epithelial cells or interstitial macrophages accompanied by evidence of cell damage such as nuclear pyknosis, cytoplasmic swelling or shrinkage, or inflammatory cell infiltration suggesting cellular dysfunction. See **Choroid plexus vacuolation** for further information.

Choroid plexus papilloma is a benign tumor originating from the epithelial cells of the choroid plexus, developing therefore in proximity to the ventricular system. Choroid plexus papillomas typically consist of papillary fronds lining an indistinct fibrovascular stroma. Papillomas grow by expansion but do not invade. Refer to **Nervous System** in Appendix 2 for further information.

Choroid plexus vacuolation is characterized by membrane-bound spaces devoid of cytoplasm within the choroid plexus. The vacuolation may involve either choroid plexus epithelial cells or interstitial macrophages, and the specific cellular component should be specified. Vacuolation is commonly observed as an incidental finding in the choroid and many other areas within the CNS but may also be increased in toxicity studies. For example, increasing the molecular weight of polyethylene glycol, either alone or conjugated with a variety of therapeutic agents, increases the chances for choroid plexus epithelial cell (ependymal cell) vacuolation. Vacuolation may occur with no apparent effect on cell function or cell viability.

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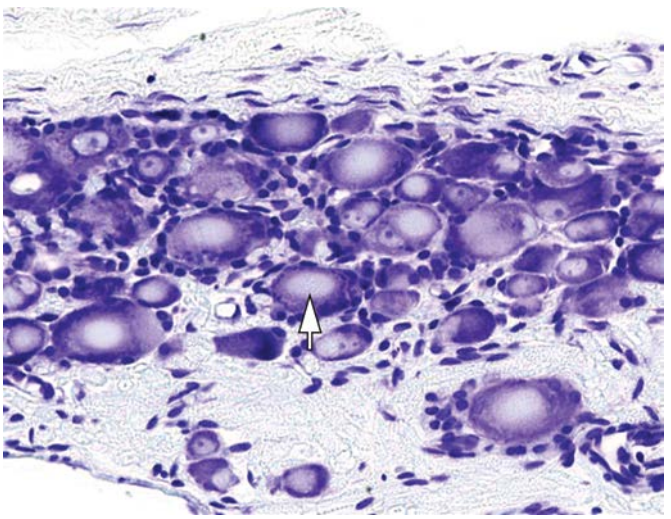
Vacuolation is characterized by clearly demarcated ovoid spaces (arrows) within the choroid plexus epithelium. Rat. H&E. (Copyright 2018 Pfizer.)

Chromatid is a chromosome consisting of two chromatids that are identical copies consisting of one DNA strand each (and accessory proteins).

Chromatin is the eukaryotic matrix responsible for the function and structure of chromosomes, compressing the DNA into a more compact form, and controlling gene expression. Chromatin contains DNA, RNA, and proteins, the main protein being histone.

Chromatin immunoprecipitation (ChIP) is a method to determine DNA-protein interaction

Chromatolysis refers to the dispersion of normally centrally located basophilic Nissl bodies (rough endoplasmic reticulum and free ribosomes) in the neuron to more peripheral portions of the neuronal cell body in an attempt to increase protein synthesis and restore the integrity of an axon following injury. It occurs in the neuroplasm following axotomy or other traumatic or metabolic injuries to neurons or their processes. Central chromatolysis is characterized by the absence of Nissl substance in the center of the cell body as an early response to cell injury. Peripheral chromatolysis, indicating a later stage of resolution, occurs when Nissl substance has reformed in the cell center but remains incomplete in the more peripheral portions of the cell body.



Central chromatolysis. Note large areas of clearing within the neuronal perikaryon (white arrow) with displacement of Nissl substance (dense blue material) to a peripheral cytoplasmic rim. Dorsal root ganglion. Rat. Cresyl violet. (Copyright 2018 Georg Krinke, AnaPath GmbH, Switzerland. Used with permission.)

Chromodacryorrhea, also referred to as "bloody tears," is an observation of a red (or reddish-brown) secretion around the eyes as a result of excessive glandular porphyrin release into the tears. In rats, the porphyrins are secreted from Harderian glands behind the eyes, with excessive release known to occur with acetyl choline administration or during periods of acute stress. As the secretions accumulate and dry near the eyes and nose, the residue resembles dried blood. When increased pigment secretions are seen originating from the nares, it is referred to as chromorhinorrhea. See **Harderian gland increased porphyrin** for additional information.

Chromorhinorrhea is increased red or reddish-brown pigment secretions seen originating from the nares. See **Chromodacryorrhea** for further information.

Chromosome is the macromolecular genetic unit of each cell. In eukaryotic cells, it contains the cellular DNA and other macromolecules (chromatin) to allow stability and functioning of the genetic machinery. The chromosome number is typical for each species. They are visible under a light microscope during the metaphase of cell division.

Chromosome aberration is damage to chromosomes, which can be structural (i.e., generation of chromosome breaks) or numerical (i.e., induction of aberrant chromosome numbers). Such damage can be induced by drugs or environmental chemicals and is an indication of carcinogenic activity. The process of inducing chromosome breaks is known as clastogenesis, and compounds inducing such breaks are termed clastogenic.

Chromosome aberration test is a mechanism to investigate the potential of agents (physical, chemical) or environmental conditions to induce damage to chromosomes. The effect is known to predispose for tumor induction and heritable diseases. Such tests may be performed in culture cell lines (CHO cells), freshly isolated cells such as peripheral blood lymphocytes, or in certain tissues in vivo. Chromosome aberration tests require cytogenetic analysis to determine changes to chromosome structure or number, which can be very time consuming. As a consequence, it is more common in drug development to detect chromosome aberrations using the micronucleus assay.

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Chromosome mutations, see the preferred term **Chromosome aberration**.

Chronic within the context of pathological processes refers to a timeframe of abnormal function or disease that has been underway for an extended period. Changes in form or function that are chronic occur following the end of the subacute phase of the condition and are specific to the type of condition. Chronicity is usually associated with gross and/or microscopic changes that differentiate it from "acute" or "subacute" changes. See **Acute** and **Subacute** for further information.

Chronic-active inflammation may occur in situations where the stimulus for inflammation remains, whether infectious or immunologic, and is characterized by repeated episodes of the acute inflammatory process, and continued tissue destruction superimposed on the chronic process.

Chronic inflammation is characterized by influx of lymphocytes, plasma cells, and macrophages, and attempts at repair with fibroplasia/fibrosis and angiogenesis. If the response has a predominance of new capillary blood vessels, this is referred to as granulation tissue.

Chronic interstitial nephritis, see the preferred term **Renal parenchymal inflammation**.

Chronic progressive glomerulonephritis, see the preferred term **Chronic progressive nephropathy**.

Chronic progressive glomerulonephropathy, see the preferred term **Chronic progressive nephropathy**.

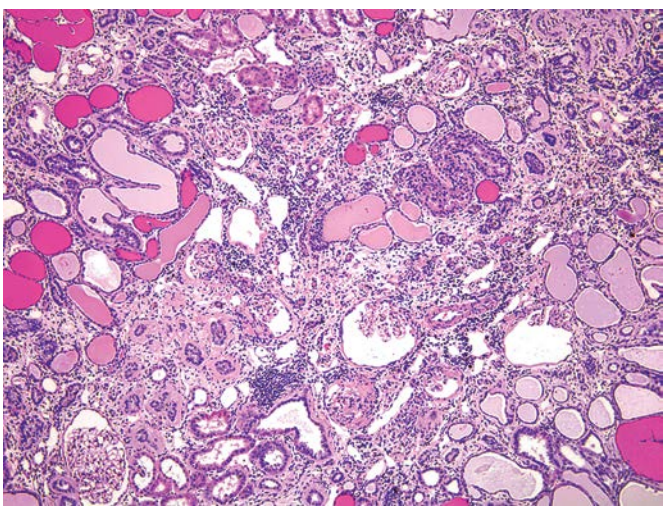
Chronic progressive glomerulonephrosis, see the preferred term **Chronic progressive nephropathy**.

Chronic progressive glomerulosclerosis, see the preferred term **Chronic progressive nephropathy**.

Chronic progressive nephritis, see the preferred term **Chronic progressive nephropathy**.

Chronic progressive nephropathy (CPN) is a spontaneous degenerative and regenerative kidney disease of the aging laboratory rat, which can be a significant confounding factor when interpreting potential compound effects in renal toxicologic pathology. It commences in early maturity and slowly progresses with aging, possibly resulting in end-stage kidney and potential death from renal failure. The early histopathologic hallmarks of CPN are discrete foci of tubular basophilia in the cortex, conspicuously thickened basement membrane lining the affected tubules, and crowding of tubule nuclei indicative of simple tubule hyperplasia. Formation of hyaline casts in the inner stripe of the outer medulla is a subsequent development. Later stages include progressive development of glomerulosclerosis, numerous tubules dilated with hyaline casts, perivascular clusters of mononuclear inflammatory cells, matrix expansion, and a characteristic form of hyperplasia of the renal papilla lining. The late stages of CPN are also associated with proliferative tubule profiles that can be confused with the hyperplastic precursor of renal tubule adenoma. Throughout its course, CPN-affected tubules undergo chronic cell degeneration and regenerative activity. The sustained tubule proliferative activity in advanced CPN is a risk factor for the development of a low incidence of low-grade renal tubule tumors. CPN can be exacerbated by certain chemicals, which represents a mode of action for the development of an increased but low incidence of low-grade renal tubule tumors, usually adenomas. Dietary factors such as protein content in feed and overnutrition modulate the incidence and severity. As there is no biological or pathological counterpart of CPN in humans, in the absence of any other cause this pathway for tumor development should be considered of no relevance for species extrapolation in hazard and risk assessment. A similar condition exists in mice, but little is known about CPN in this species. In toxicologic pathology, rat CPN should be entered and graded as a single entity and not by its individual component lesions.

Synonym(s): **Chronic progressive glomerulonephritis**; **chronic progressive glomerulonephropathy**; **chronic progressive nephrosclerosis**; **chronic progressive glomerulonephrosis**; **chronic progressive glomerulosclerosis**; **chronic progressive nephritis**; **chronic progressive nephrosis**.



CPN, rat, H&E. (Reproduced with permission of Society of Toxicology from Frazier et al., 2012.)

Chronic progressive nephrosclerosis, see the preferred term **Chronic progressive nephropathy**.

Chronic progressive nephrosis, see the preferred term **Chronic progressive nephropathy**.

Chronic renal disease is any pathologic condition that results in progressive loss of renal function over time. This is usually reflected in the development of proteinuria and renal azotemia.

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It can be due to many different inflammatory, cardiovascular, or congenital conditions.

Chronic toxicity testing involves studies in rodents of 6 months or longer, and studies in non-rodents typically of 9 months or longer. For pharmaceutical products, the European Union (EU) will accept non-rodent studies of up to 6 months in duration in support of chronic toxicity testing, and for all regions, toxicity studies of a duration longer than 6 months (rodents) or 9 months (non-rodents) are not required to support clinical trials or registration, although rodent carcinogenicity studies are required if therapeutic exposure exceeds 6 months. Protein-based therapeutics may have unique immunogenicity concerns in chronic toxicology studies, and study durations of up to 6 months satisfy the requirement for chronic testing of these products (when applicable) in both rodents and non-rodents. Chronic study designs are described in local regulatory agency (FDA Redbook) and OECD (Organization for Economic Co-operation and Development) guidelines. They generally require three dose groups plus a vehicle control, with a group size of 20 in rodent studies and 4 in non-rodent studies. Extra animals are typically included in the high-dose and control groups to assess the reversibility of any findings observed at necropsy or following histopathological evaluation. Parameters investigated during such studies include in-life parameters such as body weight gain, food consumption, cage-side observations and behavior, clinical chemistry, hematology, and at necropsy organ weights, gross lesions, and finally, histopathology. The aim of these studies is to determine target organ toxicity, dose dependence, and potential reversibility of any observed toxicities, as well as the no observed adverse effect level (NOAEL). Chronic toxicity studies generally include exposure monitoring so that the exposure of animals at the NOAEL may be compared to that observed or expected in the clinic. See **Carcinogenicity testing** for further information.

C3H10T1/2 cells is a popular cell line for mutagenicity and cell transformation assays, derived from a mouse embryo fibroblast.

Chylothorax is rarely seen in laboratory animals. It involves the accumulation of lymph in the pleural cavity and is usually a consequence of obstructed or impaired drainage by the thoracic duct. This impaired clearance may be due to neoplasia or inflammation but is most often idiopathic (of unknown etiology). The condition is characterized macroscopically by the presence of milky fluid in the thoracic cavity, which on microscopic examination is found to contain lymphocytes, neutrophils, and lipid-filled macrophages. There may be an associated mesothelial proliferation and inflammatory reaction.

Differential diagnoses: **Hemothorax**; **Hydrothorax**; **Pyothorax**.

Ciliary body atrophy is the reduction in the size of the ciliary body due to flattening, and then loss of epithelial cells, and atrophy of the supporting connective tissue and vasculature. This leads to a decrease in or cessation of aqueous production, and reduced tension in the zonular ligament. Ciliary body atrophy may occur as a genetic malformation (DBA/2J mice), as a decrease in the size or number of myofibrils within the ciliary body in aged Wistar rats and secondary to damage or diseases that affect the uveal tract.

Synonym(s): **Ciliary body degeneration**.

Ciliary body degeneration, see the preferred term **Ciliary body atrophy**.

Ciliary body epithelial cytoplasmic vacuolation consists of well-demarcated, clear spaces within the pigmented and non-pigmented epithelial cells of the ciliary body processes as a result of injury and/or metabolic change. This finding occurs in association with several diseases, including phospholipidosis, and following administration of xenobiotics (disobutamide and 6-aminonicotinamide). Vacuoles may occur in association with decreased pigmentation and be present in other ocular compartments (see **Corneal vacuolation**; **Lens vacuolation**; **Iris epithelial cytoplasmic vacuolation**; **Retinal cytoplasmic vacuolation**; **Retinal extracellular vacuolation**; **Retinal pigment epithelium vacuolation**). Vacuoles may also be an artifact from delays in fixation. See **Lysosomal storage disease**; **Phospholipidosis**; **Lipid accumulation**; **Fatty change**; and **Mucopolysaccharidosis** for further information

Ciliary body hypoplasia is a congenital malformation that results in underdevelopment and reduced numbers of folds and cellularity of the ciliary body. Hypoplasia may also involve the iris, particularly in genetically engineered mutations of molecules involving ocular morphogenesis (*Pax6, PXDN*, and *Fbn2*).

Differential diagnosis: **Ciliary body atrophy**.

Synonym(s): **Ciliary body reduced size**; **ciliary body degeneration**.

Ciliary body inflammation consists of focal or diffuse accumulations of inflammatory cells (granulocytes or heterophils [rabbit], macrophages, lymphocytes, plasma cells, and multinucleated giant cells) in the stroma and epithelium of the ciliary body accompanied by other inflammatory indicators including interstitial edema, activated vascular endothelium or perivasculitis, hemorrhage and necrosis or cellular debris, and altered pigmentation. Inflammation often involves the iris, choroid, the anterior and posterior chambers, and vitreous and retina, and may be secondary to trauma, malformations, infections, hyperglycemia, and neoplasms. The uvea is a major target of autoimmune disorders. Uveal inflammation may occur after administration of chemicals and xenobiotics such as cyclophosphamide, and after intravitreal injection or the implantation of medical devices. Severe inflammation may extend throughout the eye (endophthalmitis), and result in phthisis bulbi. Infiltration of mononuclear cells into the ciliary body and choroid in nonhuman primates is a common spontaneous finding.

Differential diagnosis: **Ciliary body inflammatory cell infiltrate**.

Synonym(s): **Uveitis**; **cyclitis**; **iridocyclitis**.

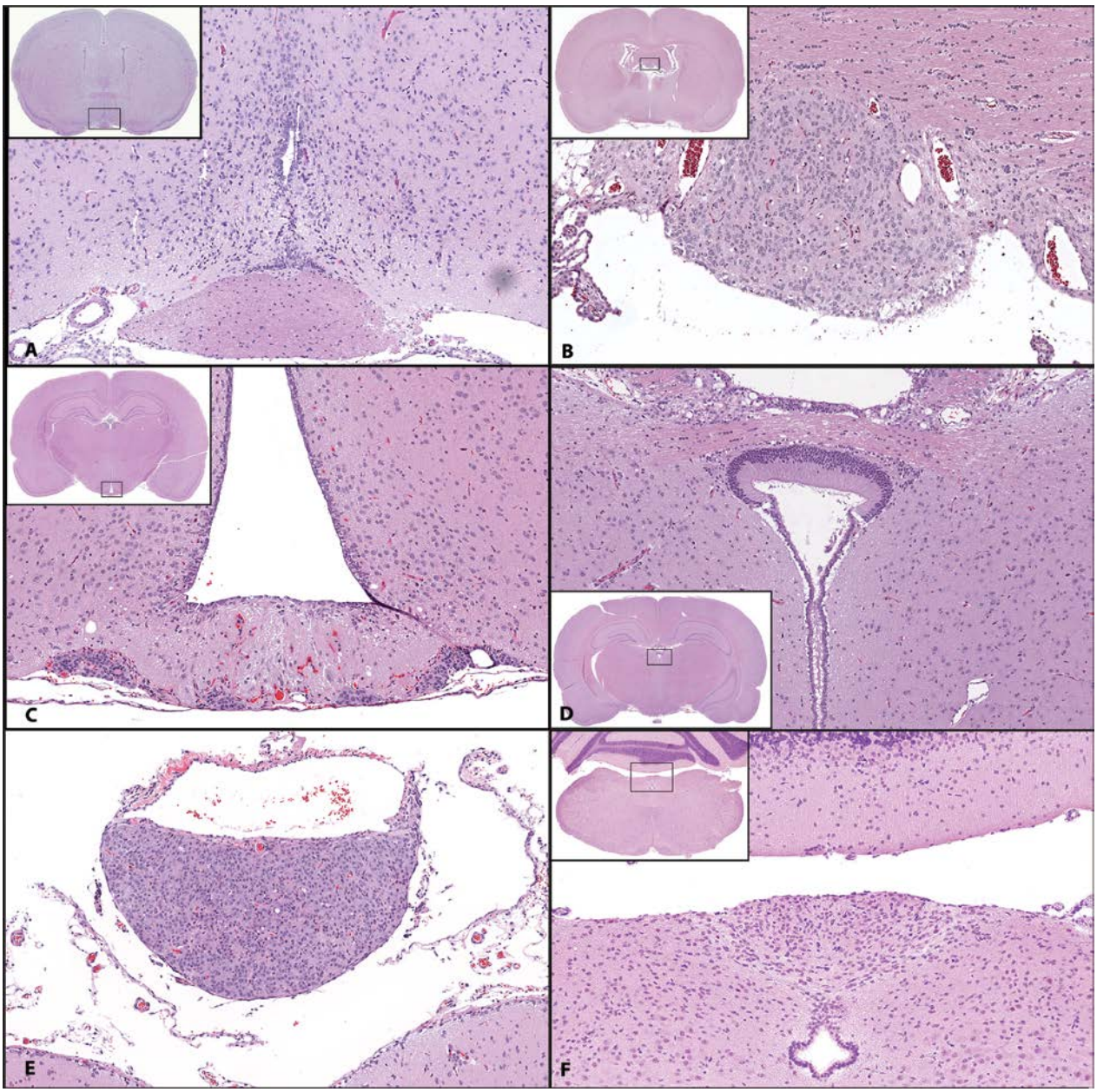
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Ciliary body inflammatory cell infiltrate is the presence of small numbers of leukocytes within the ciliary body or processes, in the absence of inflammatory changes (edema, congestion, hemorrhage, and necrosis or cellular debris).

Ciliary body reduced size, see the preferred term **Ciliary body hypoplasia**.

Circadian rhythm refers to events occurring within a period of about a day. Technically, it involves a combination of the diurnal (daytime) and the nocturnal (nighttime) activities of an organism or organ system. A circadian rhythm is thought to be controlled by the brain and the endocrine system. The eyes and the pineal gland (located on top of the brain), have been implicated in sensing photoperiod to modulate these rhythms. Daily oviposition (egg laying) in the hen is modulated by these mechanisms. The onset of light and of darkness, the daily position and length of the dark period, all determine the time of oviposition during a light–dark cycle. Due to circadian rhythms, eating habits, some hormones, metabolites, and activities are greater at specific times of the day. These can be hormonal, emotional, or behavioral. Hormone levels (for example, melatonin) may affect sleep and wakefulness or bone metabolism.

Circumventricular organs are areas within the third ventricle of the brain that are composed of a specialized ependyma with fenestrated capillaries and are therefore



Circumventricular organs, sites where the blood-brain barrier is incomplete. (A) Organum vasculosum of the lamina terminalis. (B) Subfornical organ. (C) Median eminence. (D) Subcommissural organ. (E) Pineal body. (F) Area postrema. Rat. H&E. (For additional information see *Toxicologic Pathology* 39(1):22–35, 2011.)

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an area where the blood-brain barrier (BBB) or blood-cerebrospinal fluid (CSF) barrier is incomplete. Circumventricular organs consist of the subfornical organ, the organum vasculosum of the lamina terminalis, the subcommissural organ, the median eminence, area postrema, and the pineal gland. These areas are thought to be regions where metabolites and neuropeptides can enter the CSF or cerebrovascular system. See **Ependymal barrier**, **Blood-brain barrier**, **Blood-CSF barrier**, and Appendix 3 for further information (see figure at the previous page bottom).

Clara cell, see the preferred term **Pulmonary club cell**.

Clastogenesis is the process of introducing chromosome breaks, compounds inducing such breaks are termed clastogenic, see the preferred term **Chromosome aberrations**.

Clearance is the rate at which the body eliminates a drug from the circulation, given in the units of volume of plasma (or blood) cleared of the drug per unit of time (mL/min or mL/min/kg). The clearance is calculated from the following equation:

$$\text{Clearance} = \text{Dose (mg)}/\text{AUC}.$$

Clear cell focus of altered hepatocytes, see the preferred term **Clear cell focus of cellular alteration**.

Clear cell focus of cellular alteration is a focal accumulation of hepatocytes with cytoplasm composed of clear spaces. These hepatocytes merge with the adjacent hepatocyte cords with little or no compression of the adjacent parenchyma. In some foci with basophilic or eosinophilic staining, clear cells may be observed, but the designation of such lesions is conventionally termed as basophilic or eosinophilic foci. Refer to **Liver, Gallbladder, and Exocrine Pancreas** in Appendix 2 for further information.

Clear cell hyperplasia, see the preferred term **Thyroid C cell hyperplasia**.

Clear cell preneoplastic focus, see the preferred term **Clear cell focus of cellular alteration**.

Cleft (hard) palate trauma is rare in laboratory animals, usually with evidence of fracture, necrosis, and inflammatory response at the affected site.

Cleft palate is a longitudinal defect in bone and mucosa of the midline of the hard palate in the oral cavity resulting from the failure of fusion of the lateral palatine shelves from the maxillary processes. Cleft palate is diagnosed primarily on gross observation or microscopically with no evidence of trauma. Spontaneous incidence is rare in most strains of rats and mice except in A/J mice, mice carrying the chondrodysplasia (cho) gene defect, and in cleft palate 1 (clft1) mutant mouse. Cleft palate has been induced in laboratory animals exposed to 6-aminonicotinamide (6-AN), several corticosteroids, chlorcyclizine, vitamin A palmitate, and retinoic acid.

Synonym(s): **Palatoschisis**; **cleft palate congenital malformation**.

Cleft palate congenital malformation, see the preferred term **Cleft palate**.

Clinical chemistry is the analysis of body fluids, usually plasma (or serum) and urine, for a variety of analytes such as enzyme activities, electrolytes and intermediary metabolites, to monitor the in-life function of various organs, notably liver and kidney. A typical list of parameters measured in plasma and urine is shown below. Clinical chemistry assessment is generally incorporated into all repeat-dose toxicity studies.

Clinical Chemistry Parameters Typically Measured in Plasma

Albumin	Inorganic phosphorus
Alkaline phosphatase (ALP)	Total protein
Alanine aminotransferase (ALT)	Triglyceride
Aspartate aminotransferase (AST)	Sodium
Total bilirubin	Potassium
Calcium	Chloride
Total cholesterol	Globulin
Creatine kinase (CK)	Albumin/globulin ratio
Creatinine	Blood urea nitrogen
Glucose	Gamma glutamyltransferase (GGT)

Clinical Chemistry Parameters Typically Measured in Urine

Color	pH
Clarity	Urobilinogen
Glucose	Leukocytes
Ketones	Volume
Occult blood	Specific gravity
Protein	Creatinine
Bilirubin	Total protein
Nitrites	

Clinical Pathology is the study of changes in body fluids indicative of injury or disease. In toxicology studies, clinical pathology investigations or endpoints are categorized as: (1) clinical chemistry (also referred to as serum chemistry); (2) hematology; (3) coagulation; or (4) urinalysis, with all four generally represented.

Clinical trial(s) are performed during drug development to study the disposition of a drug candidate (pharmacokinetics and drug metabolism), the efficacy, tolerability, and safety of the drug candidate, including the ability to cause drug-drug interaction with potential comedication. See preferred terms **Phase 1 clinical trial**, **Phase 2 clinical trial**, and **Phase 3 clinical trial**.

Clitoral gland is a specialized sebaceous gland in the female rodent that is frequently collected for histologic evaluation in

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GLP toxicology studies. Commonly the gland may have low-level inflammatory cell infiltrates, cysts, or less frequently hyperplastic or neoplastic changes.

Synonym(s): **Preputial gland (female)**.

Clitoral gland adenocarcinoma is a malignant neoplasm that is solid, cystic, and papillary or a mixed of multiple types. There is loss of the normal acinar structure and nuclear/cellular atypia is common. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Clitoral gland adenoma is a benign neoplasm that is circumscribed and composed of well differentiated epithelial cells. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Clonal expansion is the growth and proliferation of a group of cells stemming from the same single cell (clone). Neoplasms are believed to be of clonal origin.

Clonic is a state of complete unresponsiveness in which there is no voluntary movement or behavior (i.e., coma). The individual has no apparent awareness of or responsiveness to its environment. Both the voluntary brain functions (cerebral hemispheres), and the involuntary responses (reticular activating system [RAS]) show no symptoms of functioning. Causes of coma can be a restriction of oxygen, glucose, or sodium to the brain. Chemicals in the blood, such as alcohol (in toxic quantities), ammonia, ketones, or carbon dioxide can disrupt nerve function and lead to coma.

Cloning, molecular, see the preferred term **Molecular cloning**.

Coagulating gland in rodents is derived from the prostate and is sometimes referred to as the dorsocranial, cranial, or anterior prostate. It is adjacent and parallel to the seminal vesicle with luminal contents containing eosinophilic, proteinaceous material such as observed in the dorsal prostate. These glands are absent in dogs.

Synonym(s): **Anterior prostate**.

Coagulative necrosis maintains the tissue architecture for at least several days by blocking the proteolytic enzymes of the dead cells. Eosinophilic dead cells can persist until they are phagocytized by leukocytes and degraded by lysosomal enzymes. In tubular organs, necrotic cells may detach into the adjacent tubular lumina and form casts in smaller diameter tubes such as those in the kidney. Coagulative necrosis might release damage-associated molecular patterns (DAMPs) which act as chemotactic agents for neutrophils in the vicinity of necrotic cells. Infarction is the prototypical example of coagulative necrosis. "Single cell necrosis" is a diagnostic term used to describe a pattern of distribution of coagulative necrosis and is often observed in the liver.

Cochlear fibrosis, see the preferred term **Inner ear fibrosis**.

Codocyte, see the preferred term **Target cell**.

Codon is a genetic unit of DNA or RNA. A codon (the genetic "word") consists of three bases (the "letters") that are complementary on both strands of nucleic acids (for double-stranded molecules). Upon transcription, a codon serves to define an amino acid in the protein sequence.

Collagen fibrosis in bone marrow is an increase of collagen fibers in the bone marrow cavity visualized by special stains, most commonly trichrome stain.

Collapsing glomerulopathy is a morphologic variant of focal segmental glomerulosclerosis (FSGS) in humans, with segmental and global collapse of the glomerular capillaries, marked hypertrophy and hyperplasia of podocytes, and severe tubulointerstitial disease.

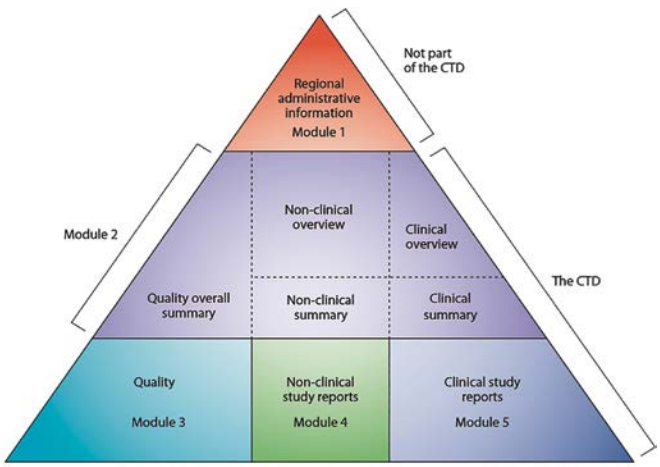
Coloboma, see the preferred term **Optic fissure malformation**.

Comedone is characterized by dilation of the hair follicle, which is filled with an excessive amount of keratin, forming as a result of keratin plugging of the hair follicle pore. Comedones are the primary feature of *chloracne*. See **Adnexal hyperkeratosis** for further information.

Comet assay is a test for primary DNA damage. The damage can be induced by clastogenic compounds, but certain variations of the assay also allow for the detection of intermediates of agents that induce point mutations, so that the assay has a relatively broad sensitivity. The Comet assay can be conducted in any tissue or cell culture system from which a single cell suspension can be obtained.

Committee on Safety of Medicines (CSM) is a United Kingdom advisory committee that conducts a premarketing assessment of new medicines for safety, quality, and efficacy.

Common technical document (CTD), is a document structure defined in the ICH M4 guideline detailing the manner in which documentation collected during the drug development process in the nonclinical studies and clinical studies, and



The CTD triangle. The Common Technical Document is organized into five modules. Module 1is region specific and modules 2, 3, 4 and 5 are intended to be common for all regions.

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during the synthesis and formulation of the drug substance and drug product should be assembled and submitted to the regulatory agencies for marketing approval. The CTD contains five modules (see the CTD triangle below, from the ICH M4 guidance. http://www.ich.org/products/ctd.html).

Module 1 contains regional administrative information, which by definition is region specific, and therefore will be different for submission to the FDA and to the EMA. The structure of the remaining modules is the same for any country accepting the ICH guidelines. The second module consists of documents that summarize the individual developmental areas, a quality overview, a nonclinical overview and summary, and a clinical overview and summary. The quality overview summarizes the synthesis of the drug substance, the properties of the drug substance and the drug product, the excipients used, stability data and impurity profiles, release specifications, and so forth. The preclinical overview gives a concise integrated summary of the pharmacology, toxicology and drug metabolism, and pharmacokinetics of the drug and is accompanied by more detailed summaries of the individual discipline. The clinical overview is a similar integrated summary of the clinical development, efficacy, and safety of the drug accompanied by individual summaries of clinical pharmacology, efficacy, and safety. Module 3 consists of the individual quality (chemical and pharmaceutical development reports), module 4 consists of the individual nonclinical study reports (pharmacology, toxicology, drug metabolism, and pharmacokinetics), and module 5 consists of the individual clinical study reports.

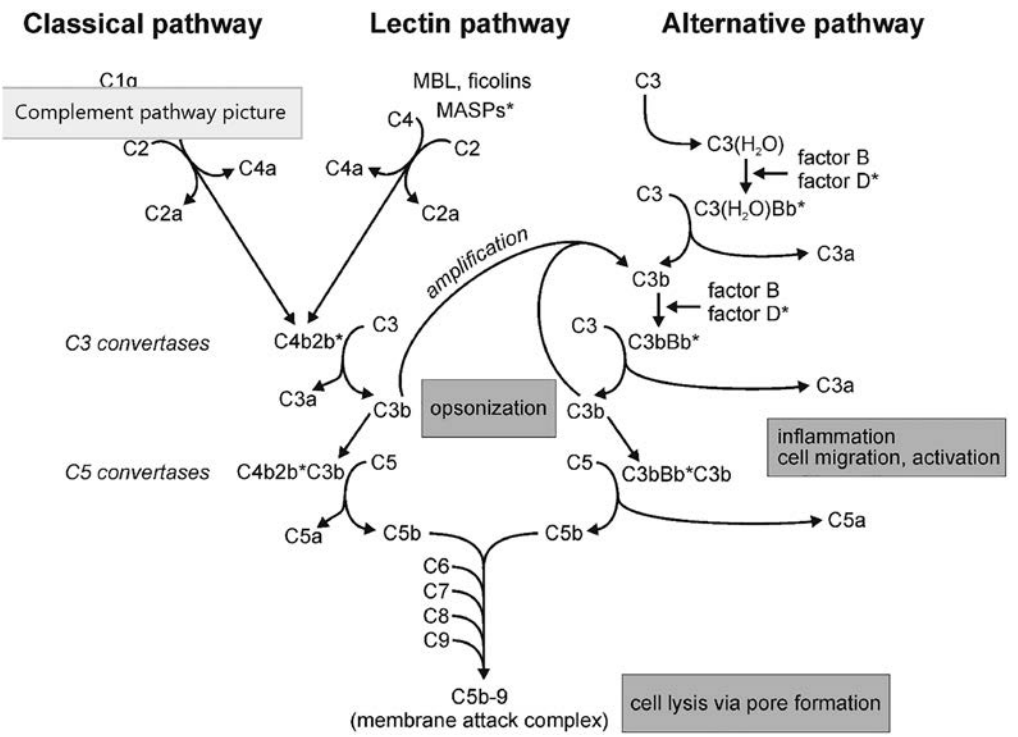
Complement is part of the innate immune system and is comprised of proteins synthesized in the liver and secreted into the plasma as inactive precursors. Complement may be activated by a variety of signals. Upon activation, proteases cleave pro-proteins forming other proteases and cytokines in an amplification cascade that eventually results in activation of phagocytes, inflammation to attract phagocytes, and formation of the cell-killing protein complexes (membrane attack complex). Complement may be activated by certain agents in toxicity studies (e.g., phosphorothioate oligonucleotides) resulting in generalized inflammation (see figure below).

Compliance refers to adherence to all applicable regulatory requirements i.e., good laboratory practice (GLP), good clinical practice (GCP), and good manufacturing practice (GMP) requirements.

Concretion (ductular or tubular), see the preferred term **Calculus**.

Conditioned avoidance refers to a specific response produced by giving a negative stimulation (e.g., electric shock) whenever the individual engages in a specific behavior. Over time the individual associates the activity with the negative stimulation and eventually avoids it in order to avert the negative stimulation.

Conditioned behavior refers to repeated administration of a signal that naturally elicits the desired response until that response is achieved with the signal alone. This is accomplished when the secondary stimulus is consistently given in association with the natural stimulus, and eventually the secondary stimulus will elicit the same response. The classic example is that of ringing a bell and feeding dogs at the same time, which eventually resulted



Schematic showing pathways of complement activation. (Khanal, S. 2017. *Complement pathways: Types Function and Regulation.* Microbe online, Nov. 5, 2017.)

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in the dogs starting to salivate at the ringing of the bell without food being presented (Pavlov response theory). The individual "learns" or "associates" what was considered a natural behavior (excitement) or involuntary response (salvation) to a natural stimulus (food) with a secondary stimulus (bell) which would not normally be associated with that response. For example, in one study telemetry-monitored animals were administered a hypotensive drug through an indwelling intravenous (IV) line daily at 0900 h for 2 weeks. On the 15th day of study when saline was substituted for drug, all animals demonstrated an increase in heart rate starting at 0900 h.

Congenital refers to a disease or condition present at birth, whether inherited or developmental) (i.e., caused by an external toxicant).

Congestion is the passive accumulation of blood within vessels in the tissues leading to dilation of capillaries and veins. This may occur due to a blockage, a thrombus for example, or due to a compromise in cardiac function, resulting in poor blood flow. It may result in tissue damage and edema potentially leading to tissue necrosis. This should be differentiated from agonal congestion in incompletely exsanguinated animals wherein blood artifactually pools in vessels following euthanasia.

Congestive heart failure (CHF) is not itself a disease, but rather a description of a clinical syndrome that can be the end result of severe heart disease. Heart disease has many causes and does not always lead to CHF. It occurs when the heart is unable to pump blood effectively to other organs and/or the rest of the body, which eventually leads to fluid accumulation outside of the circulatory system. Initially, normal circulation can be maintained as the body compensates by increasing blood pressure using several mechanisms; however, eventually this increased blood pressure can force blood out of the vessels and into the surrounding tissues, organs, and/or body cavities. Since CHF can be due to failure of the left ventricle, right ventricle, or both ventricles, the clinical presentation can vary. When output is decreased from the left side of the heart, this most commonly leads to pulmonary edema, and if it occurs on the right side, it typically causes fluid accumulation in the abdomen (ascites) or peripheral edema. Common symptoms of congestive heart failure include coughing, difficulty breathing, and exercise intolerance.

Conjugation reactions are Phase 2 reactions involving the conjugation of the parent drug or its metabolites with sugars (e.g., glucuronic acid), amino acids (e.g., glycine), peptides (e.g., glutathione), sulfate, acetyl, or methyl groups. See **Drug metabolism** for further information.

Conjunctiva-associated lymphoid tissue (CALT) is induced or acquired mucosa-associated lymphoid tissue (MALT) in the submucosa of the conjunctiva and nictitating membrane. CALT is formed during the postnatal period after antigenic exposure and can vary from loose aggregates of lymphocytes to large, organized lymphoid follicles with germinal centers adjacent to the conjunctival epithelium. CALT frequently increases with age and is not an abnormal cellular infiltrate or inflammation.

Conjunctival centripetalization, see the preferred term **Conjunctiva overgrowth**.

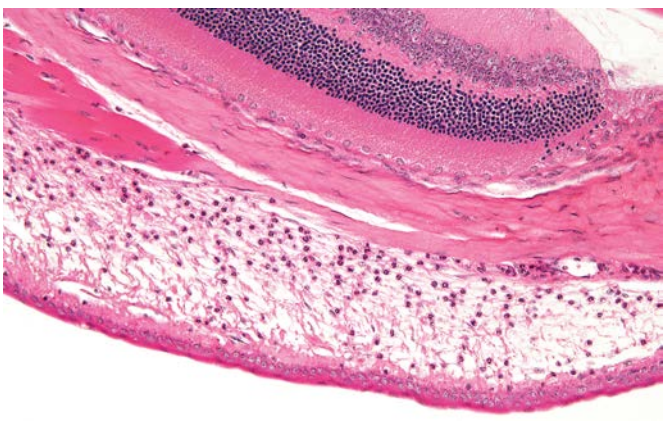
Conjunctival erosion consists of injury with partial loss of cells in the conjunctiva epithelium. These changes may be accompanied by inflammation and concurrent opportunistic infections. Physical trauma, topical and systemic administration of chemicals, radiation, corneal inflammation, buphthalmos, abnormal tear film, or eyelid denervation are initiating events.

Differential diagnosis: Conjunctival necrosis.

Conjunctival inflammation consists of focal or diffuse accumulations of inflammatory cells (granulocytes or heterophils [rabbit], macrophages, lymphocytes, plasma cells, and multinucleated giant cells) in the epithelium and submucosa of the conjunctiva, the cell types are dependent on the chronicity of the lesion and initiating agent. Often trauma, trapped particulates, age-related degeneration, topical application of chemical and xenobiotics, or infectious diseases induce epithelial damage and initiate the infiltration of inflammatory cells. Associated changes may include edema and hemorrhage, epithelial hyperplasia, necrosis, erosion, ulceration, and chronically squamous metaplasia of the epithelium. Loss of epithelium results in tear film dysfunction, which contributes to development of the disease keratoconjunctivitis sicca (see **Corneal inflammation** for further information). With a thin cornea and reduced blinking, rabbits are considered to be the most sensitive species for ocular (cornea and conjunctival) irritancy testing (Draize test) in toxicology. Inflammation needs to be differentiated from acquired conjunctiva–associated lymphoid tissue (CALT), which is a normal part of the mucosa-associated lymphoid tissue rather than abnormal infiltrates or inflammation.

Differential diagnoses: **Conjunctiva inflammation**; **Conjunctiva-associated lymphoid tissue**.

Synonym(s): **Conjunctivitis**.



Conjunctival inflammation with edema, bulbar conjunctiva, BALB/c mouse, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

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Conjunctival inflammatory cell infiltrate consists of focal to multiple loose to dense clusters of inflammatory cells that are lymphocytic, lymphoplasmacytic, granulomatous, and neutrophilic (heterophilic in rabbits) in the submucosa and perivascular areas. Causality is seldom identified, but these may include sequelae to trauma, physical irritants, topical application of chemicals, and xenobiotics and infectious organisms. Lymphocytic foci, sometimes with germinal center formation, within the palpebral conjunctiva, and occasionally in the conjunctival fornix and tarsal conjunctiva near the cornea, often occur in the absence of other tissue changes or inflammation and usually increase with age. Such foci are acquired conjunctiva−associated lymphoid tissue (CALT), which is a normal part of the mucosa-associated lymphoid tissue (MALT) rather than abnormal infiltrates or inflammation.

Differential diagnoses: **Conjunctiva inflammation**; **Conjunctiva-associated lymphoid tissue**.

Synonym(s): **Conjunctivitis**.

Conjunctival overgrowth is an idiopathic, spontaneous disease of the conjunctiva in dwarf rabbits which is characterized by a unilateral or bilateral, circumferential inward, double-layered folding of the bulbar conjunctiva. Unlike pterygium (fleshy growth on conjunctiva) in humans, there usually is no adhesion between the conjunctival fold and corneal surface. Microscopically, a sheet-like overgrowth of bulbar conjunctiva and loose connective tissue stroma of the substantia propria is covered by epithelium on both sides, and there is minimal or no conjunctival inflammation or edema.

Synonym(s): **Pseudopterygium**; **epicorneal conjunctival membrane**; **precorneal membranous occlusion**; **conjunctival centripetalization**.

Conjunctival ulcer consists of injury with complete loss of all epithelial cell layers, leaving one or more full-thickness defects. These changes may be accompanied by inflammation, mineralization, neovascularization, and concurrent opportunistic infections. Physical trauma, infections, topical and systemic administration of chemicals, radiation, excess ambient light (see **Retina light-induced atrophy** for further information), corneal inflammation, buphthalmos, abnormal tear film, or eyelid denervation are initiating events.

Differential diagnoses: **Corneal dystrophy**; **Corneal erosion**.

Conjunctivitis, see the preferred term **Conjunctiva inflammation**.

Constitutive androgen receptor (CAR) is a member of the nuclear receptor superfamily, which together with PXR acts as a sensor for xenobiotic compounds and induces the synthesis of enzymes involved in their metabolism. Many drugs induce drug-metabolizing enzymes through interaction with CAR (e.g., phenobarbital). The endogenous ligand for CAR appears to be dehydroepiandrosterone (DHEA). See **PXR (Pregnane X receptor)** for further information.

Contact dermatitis is a form of localized skin irritation and inflammation that can be immunologic in origin, referred to as allergic contact dermatitis, or nonimmunologic, referred to as irritant contact dermatitis. Irritant contact dermatitis is due to direct skin contact with toxic agents, resulting in activation of mast cells, complement, and/or prostaglandin synthesis. Irritation generally occurs within 4 hours following topical application of the irritating substance. Histopathologically, skin irritation is characterized by epidermal hyperkeratosis and hyperplasia with dermal inflammation and is frequently associated with a variety of other epidermal changes such as erosion/ulceration, necrosis, or vesicular changes. When the skin damage induced by direct contact with the initiating agent is irreversible, the lesion is referred to as cutaneous corrosion. Allergic contact dermatitis is a localized form of type IV or delayed cutaneous hypersensitivity, and its pathogenesis is complex, likely involving both innate and adaptive immune responses. A leading hypothesis is that keratinocytes sense danger-associated molecular patterns (DAMPS), such as xenobiotics, through their toll-like receptors (TLRs), which then triggers the release of antimicrobial peptides such as β-defensins, cathelicidins, and S100 proteins as well as cytokines and chemokines that in turn recruit and activate leukocytes. Completing the loop, leukocytes that are recruited to the epidermis then release cytotoxic factors, such as perforin and granulysin from CD8+ cytotoxic T cells and NK cells, as well as TWEAK, TRAIL, *Fas* ligand, and other TNF family members from macrophages and dendritic cells, which in turn induce keratinocyte death and amplify the inflammatory feedback loop.

Convulsions are body contortions caused by violent, involuntary contractions of the voluntary muscles. These uncontrolled muscular contractions may involve the extremities, trunk, and/or head. Most convulsions last only a short period (1/2–2 minutes) and are relatively harmless. They are symptoms of abnormal electrical activity in the brain. The brain activity can be induced by damaged areas in the brain or chemicals (drugs), for example antidepressants, antimalarials and antipsychotics.

Corneal angiogenesis, see the preferred term **Corneal neovascularization**.

Corneal cornification, see the preferred term **Corneal keratinization**.

Corneal descemetocele results from prolapse of Descemet's membrane through an erosion of the corneal epithelium and stroma that may progress to corneal perforation. This is a rare spontaneous finding in dogs and can be experimentally induced after ocular infections in rabbits and rodents.

Corneal Descemet's membrane hypertrophy is a spontaneous and usually focal enlargement of individual collagenous cells or thickening of the specialized basement membrane that forms Descemet's membrane between the corneal stroma and

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endothelium (refer to Appendix 3 for further information). Hypertrophy of Descemet's membrane may be caused by aging, loss of corneal endothelial cells, and mechanical injury.

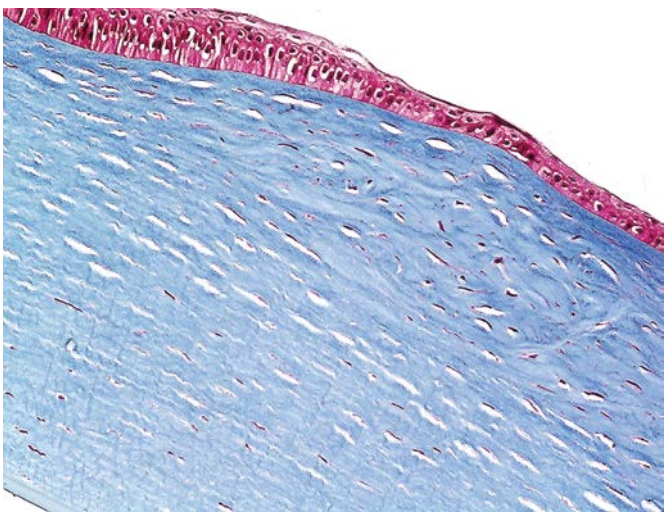
Differential diagnosis: **Fuchs endothelial corneal dystrophy**.

Synonym(s): **Descemet's membrane increased thickness**.

Corneal dyskeratosis, see the preferred term **Corneal keratinization**.

Corneal dystrophic calcification, see the preferred term **Corneal keratinization**.

Corneal dystrophy is a clinical description of a generally bilateral and genetically determined, often progressive, noninflammatory focal or multifocal corneal opacity, with many subtypes that correlate histologically to abnormalities of one or more corneal layers. Critical to diagnosis is characterization of the deposits of abnormal amorphous material and fibrillary/wavy or abnormal connective tissue using histochemical, immunohistochemical, and electron microscopic methods. Except for certain breeds of dogs (including the beagle), genetically engineered mice and the Dutch belted rabbit, most reports of corneal dystrophy in animals are epithelial, stromal, and endothelial changes secondary to other conditions, and are not a true corneal dystrophy. Genetic corneal dystrophy is most frequently a diagnostic problem in ocular toxicology studies using Dutch belted rabbits, where the defect is similar to Bowman layer dystrophy due to defects in transforming growth factor beta (TGFβ) in humans. However, unlike humans, rabbits do not have a histologically visible Bowman's layer (refer to Appendix 3 for further information). Corneal dystrophy is also used nonspecifically and inappropriately to describe any corneal opacity or discoloration, such as corneal mineralization, but histopathology is required to properly define and categorize any abnormality of the cornea. See the following for further information: **Corneal epithelial atrophy**; **Corneal edema,**



Corneal dystrophy with corneal epithelial atrophy, cornea, Dutch belted rabbit, Masson's trichrome stain.

Corneal erosion; **Corneal ulcer**; **Corneal vacuolation**; **Corneal stromal fibrosis**; **Corneal mineralization**; **Corneal pigment**; **Corneal endothelial attenuation**; **Corneal stromal neovascularization**.

Corneal edema is the presence of excess intracellular or sometimes extracellular clear to pale vacuoles or clefts that may be empty or contain eosinophilic fluid, and which may be present in the epithelium or stroma, or globally. Causes include alterations in permeability or damage to the epithelium or endothelium, stromal abnormalities (chemicals or deposition of lipid, minerals, or xenobiotics and metabolites), and abnormal vascularization of the stroma, or enhanced permeability in the limbal blood vessels. Edema is commonly associated with trauma, infections, inflammation, malformations, glaucoma, and after topical and systemic administration of irritants, chemicals, and drugs. Edema needs to be differentiated from fixation artifacts that commonly cause splitting of the stroma.

Corneal endothelial hyperplasia is an abnormal increase in endothelial cells along the inner surface of the cornea, usually to fill in a defect or loss of endothelial cells, but migration of these cells may extend over the adjacent trabecular meshwork and iris. Refer to **Special Senses** in Appendix 2 for further information.

Corneal endothelium attenuation is a decrease in the thickness of the endothelial monolayer due to flattening in order to cover defects or loss of individual endothelial cells. The endothelium has limited regenerative capacity, usually does not proliferate in response to injury, and undergoes repair by flattening and sliding of adjacent cells to cover defects in most species. Dogs have some regenerative capacity, but endothelium in rabbits will regenerate and even form multinucleated cells (refer to Appendix 3 for further information). Inflammation may be a secondary change. Attenuation occurs with aging, intraocular disease, injury to the upstream vasculature or other corneal layers, mechanical damage from devices implanted in the anterior chamber, and phototoxic agents. Endothelial attenuation is difficult to appreciate by light microscopy, and in vivo specular microscopy is a valuable adjunct tool. Cornea endothelial attenuation is a specific change that is not equivalent to cornea epithelial atrophy.

Differential diagnosis: **Corneal endothelium decreased numbers**.

Corneal endothelium decreased numbers is loss of the endothelial cells without attenuation. Corneal edema and inflammation are usually present in affected areas.

Differential diagnosis: **Corneal endothelium attenuation**.

Corneal epithelial atrophy is a decrease in the number of epithelial cells or layers. Remaining cells may be enlarged or disorganized, and edema may be present. The endothelial layer is not involved (see **Corneal endothelium attenuation** for further

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information). This may be a spontaneous change, particularly with aging, or due to trauma, infections, keratoconjunctivitis sicca, local irritants, chemotherapeutics, radiomimetics, and other inhibitors of mitosis will affect these cells. Cell layer loss is also an artifact of handling and tissue processing.

Differential diagnosis: **Corneal epithelial regeneration**. See **Corneal dystrophy** for illustration.

Corneal epithelial regeneration is identified by enlarged epithelial cells in conjunction with mitotic activity as a reparative process subsequent to a corneal erosion or ulceration.

Corneal erosion consists of injury with partial loss of epithelial cells of cornea or corneal stromal layers. These changes may be accompanied by inflammation, mineralization, neovascularization, and concurrent opportunistic infections. Physical trauma, infections, topical and systemic administration of chemicals, radiation, excess ambient light (see **Retina light-induced atrophy** for further information), corneal inflammation, buphthalmos, abnormal tear film, or eyelid denervation are initiating events.

Differential diagnoses: **Corneal dystrophy**; **Corneal ulcer**.

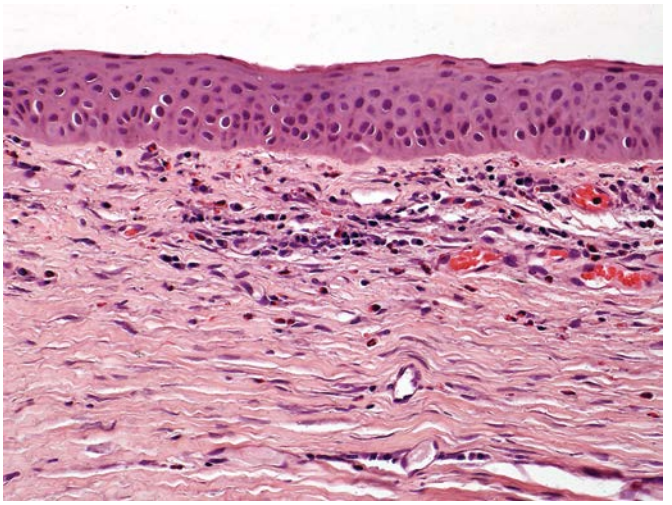
Corneal fibroplasia is the proliferation of spindle cells and fibroblasts, often in association with corneal neovascularization, into the corneal epithelium and stroma, and less frequently the endothelium. Stromal keratocytes (modified fibroblasts) or metaplastic transformation of corneal epithelial cells may be involved. Corneal clarity is dependent on a normal lattice layering of ordered collagen, and fibroplasia may temporarily impair vision (refer to Appendix 3 for further information). Fibroplasia is a common sequela to corneal injury and may progress to corneal stroma fibrosis (scarring) due to the lack of vasculature and stem cells for regeneration in the cornea.

Synonym(s): **Retrocorneal membrane**.

Corneal inclusion cyst in the dog and rabbit is a rare, usually unilateral, fluid-filled space lined by well-differentiated epithelium, sometimes filled with whorls of keratin-like material that is present in the corneal epithelium and upper stroma. Granulomatous inflammation may also be present. The origin is unknown, but these may be malformations or sequelae of epithelium trapped after repair of trauma or ulceration.

Differential diagnoses: **Ocular squamous cell papilloma**; **Ocular squamous cell carcinoma**.

Corneal inflammation consists of focal or diffuse accumulations of inflammatory cells (granulocytes or heterophils [rabbit], macrophages, lymphocytes, plasma cells, and multinucleated giant cells) within one or more layers of the cornea, with the cell types dependent on the chronicity and initiating agent. Corneal inflammation can be accompanied by edema, epithelial and keratocyte loss, hyperplasia, erosions, ulcers, mineralization, neovascularization, invasion by conjunctival epithelium ("conjunctivization"), hemorrhage, fibrosis, and extension of the inflammation into the adjacent anterior

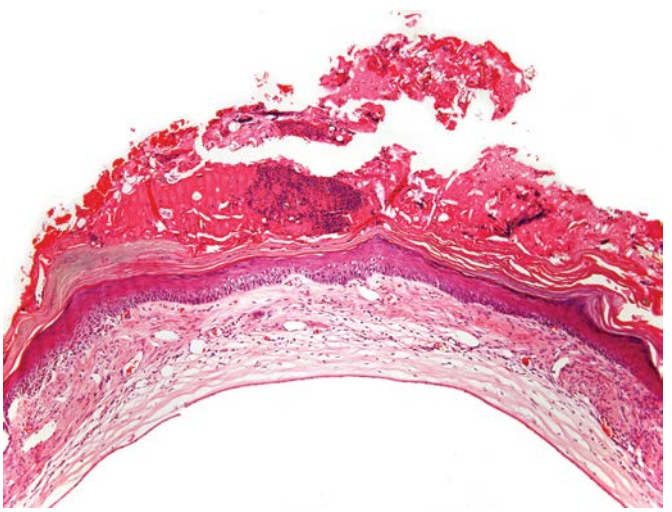


Corneal inflammation with corneal neovascularization, corneal stroma, rabbit, H&E. See **Corneal stromal fibrosis** and **Iris inflammation** for additional illustrations. (Image courtesy of L. Teixeira, University of Wisconsin.)

chamber, iris, ciliary body, lens, and vitreous. Inflammation may be a spontaneous finding or induced by chemical or physical irritants (surfactants, ammonia, and dusts from the bedding and feed), trauma, autoimmunity, ultraviolet radiation, photosensitizing compounds, hypolipidemic agents, bacterial or viral infections, secondary to reduced periorbital gland secretions, abnormalities of tear film, and exophthalmos. Spontaneous inflammation often increases with age in rodents (rats more often than mice), but is rare in dogs, rabbits, and nonhuman primates. With a thin cornea and reduced blinking, rabbits are considered to be the most sensitive species for ocular (corneal and conjunctival) irritancy testing (Draize test) in toxicology.

Synonym(s): **Keratitis**; **keratopathy**.

Corneal keratinization is thickening of the normally nonkeratinized squamous corneal epithelium by a focal or diffuse increase in cell layers and production of keratin, which may



Corneal keratinization, B6C3F1 mouse, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

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extend to form rete pegs with stromal and epithelial pigmentation. Inflammation, neovascularization, and fibrosis may be present in the adjacent stroma and endothelium. This finding occurs in response to administration of chemicals, biologics (epidermal growth factor) or physical irritants, exophthalmos, reduced tear production, nutritional deficiencies (hypovitaminosis A), infections, radiation injury, and genetic defects.

Differential diagnosis: **Ocular squamous cell hyperplasia**.

Synonym(s): **Corneal keratin metaplasia**; **corneal cornification**; **corneal dyskeratosis**; **corneal dystrophy**.

Corneal keratin metaplasia, see the preferred term **Corneal keratinization**.

Corneal lipid keratopathy, see the preferred term **Corneal vacuolation**.

Corneal lipidosis, see the preferred term **Corneal vacuolation**.

Corneal malformation, see the preferred term **Optic fissure malformation**.

Corneal mineralization consists of usually focal basement membrane, subepithelial, and stromal deposition of extracellular, focal basophilic granular or linear deposits of calcium and phosphorus that are positive with von Kossa stain. Thinning of epithelium with edema and occasionally inflammation including granulomatous inflammation and fibrosis may also be present. Mineral deposition has multiple causes, including local trauma, corneal erosion and ulceration, administration of isoproterenol, alloxan, morphine sulfate, and dihydrotachysterol, carbon dioxide laser irritation and abnormalities of the tear film, or systemic hypervitaminosis D and abnormalities in calcium-phosphate metabolism.

Differential diagnosis: Corneal sequestrum.

Synonym(s): **Corneal dystrophy**; **corneal dystrophic calcification**; **calcific band keratopathies**.

See **Corneal stromal fibrosis** for illustration.

Corneal neovascularization consists of an abnormal proliferation of small blood vessels, most frequently in the corneal stroma, usually related to ischemia or an imbalance in pro- versus antiangiogenic growth factors. The cornea is normally an avascular structure, and neovascularization by the ingrowth of vessels from the limbus adversely affects vision through changes in cornea transparency. (See Appendix 3 for additional information.) Neovascularization is often accompanied by corneal edema, erosion, ulceration, and inflammation and can be caused by injury, chemical burns, infections, autoimmunity, neoplasms of the eye or periocular structures, and administration of proangiogenic therapeutics such as vascular endothelial growth factor.

Synonym(s): **Corneal vascular proliferation**; **corneal angiogenesis**.

See **Corneal inflammation** for illustration.

Corneal opacity is a nonspecific clinical finding of a cloudy area on or in the cornea. Multiple etiologies (e.g., anomalies, genetic abnormalities, trauma, degeneration, edema, fibrosis, lipid, and inflammation) cause opacifications, and translate into a variety of histologic changes in the corneal layers.

Corneal phospholipidosis, see the preferred term **Corneal vacuolation**.

Corneal pigment is abnormal pigment deposition in the intracellular and extracellular locations of the epithelial or stroma corneal layers. The pigment may be melanin in the epithelium and stroma secondary to superficial irritation, injury, or inflammation, and due to pigment migration from damage to the iris, ciliary body, and/or corneal endothelium. After injury, pigment may be trapped within fibrotic scars. Other pigments may be hemosiderin deposits from hemorrhage, specific diseases (copper in Wilson's disease), corneal dystrophy, foreign bodies, and penetrating or systemically administered metals (gold and silver).

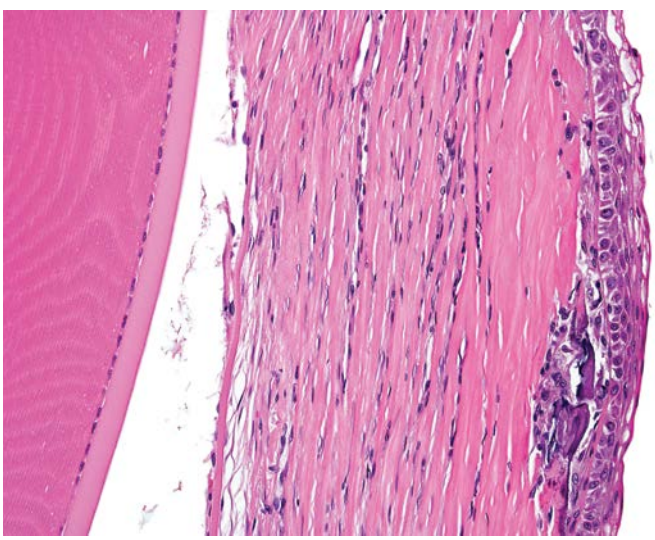
Differential diagnosis: **Uveal melanoma**.

Synonym(s): **Corneal dystrophy**.

Corneal scar, see the preferred term **Corneal stromal fibrosis**.

Corneal stromal fibrosis is the presence of mature or maturing fibroblasts originating from activated keratocytes which produce dense collagenous connective tissue and may behave like myofibroblasts in the stroma of the cornea. Corneal clarity is dependent on a normal lattice layering of ordered collagen, and fibrosis may permanently impair vision (refer to Appendix 3 for further information). Fibrotic scarring is a common sequela to corneal injury due to the lack of vasculature and stem cells for regeneration in the cornea.

Synonym(s): **Corneal scar**.



Corneal stromal fibrosis, corneal inflammation and mineralization, Hans Wistar rat, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

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Corneal stromal neovascularization is the vascularization of a normally avascular corneal stroma. It may be associated with corneal stromal edema and inflammation. Refer to **Special Senses** in Appendix 2 for further information.

C

Corneal ulcer consists of injury with complete loss of all epithelial cell layers into the deep corneal stroma and endothelium, leaving one or more full-thickness defects. These changes may be accompanied by inflammation, mineralization, neovascularization, and concurrent opportunistic infections. Physical trauma, infections, topical and systemic administration of chemicals, radiation, excess ambient light (see **Retina light-induced atrophy** for further information), corneal inflammation, buphthalmos, abnormal tear film, or eyelid denervation are initiating events.

Differential diagnoses: **Corneal dystrophy**; **Corneal erosion**.

See **Iris inflammation for** illustration.

Corneal vacuolation is a nonspecific term for usually well-delineated and round cytoplasmic spaces that may be clear or contain granules, and which present in a variety of microscopic patterns. Lysosomal accumulation of lipid or other substances that are lost during histologic processing (e.g., glycosaminoglycan, mucopolysaccharide, and others) appear as clear vacuoles within epithelial and endothelial cells and keratocytes. Phospholipidosis in corneal epithelial cells and keratocytes, and rarely endothelium, consists of foamy, lipid-like vacuoles containing bluish granules on hematoxylin and eosin (H&E) staining, irregular cytoplasmic inclusions on toluidine blue–stained thin sections, and lamellar whorls or crystalline inclusions ultrastructurally. Several cationic amphiphilic drugs produce phospholipidosis of the cornea, retina, and other tissues. The immunomodulator tilorone induces mucopolysaccharidosis and phospholipidosis in the cornea, retina, and other tissues of the rat. Corneal lipid is typified by infiltrates of large, pale macrophages with foamy cytoplasm, usually containing cholesterol esters, and often associated with necrosis. Lipid is usually present in the anterior cornea but may also be in the iris and ciliary body. Lipid may be further characterized by birefringent crystals in the outer stroma that are visible with polarized light and stain with Sudan black. Corneal lipidosis occurs most frequently in rabbits on high-fat diets and in animals with heritable lipid abnormalities (Watanabe WHHL rabbit and Zucker rat) and can be drug induced but is a rare spontaneous change in rabbits and dogs. Grossly, vacuoles may be visualized as corneal opacities, which are sometimes erroneously called corneal dystrophy. Vacuoles may also be present in other ocular compartments (see **Ciliary body epithelial cytoplasmic vacuolation**; **Lens vacuolation**; **Iris epithelial cytoplasmic vacuolation**; **Retinal cytoplasmic vacuolation**; **Retinal extracellular vacuolation**; **Retinal pigment epithelial vacuolation**). Vacuoles may also be an artifact from delays in fixation.

Differential diagnosis: **Corneal edema**.

Synonym(s): **Corneal lipidosis**; **corneal lipid keratopathy**; **corneal phospholipidosis**; **corneal dystrophy**.

Corneal vascular hyperplasia, see the preferred term **Corneal neovascularization**.

Corneal vascular proliferation, see the preferred term **Corneal neovascularization**.

Corpora amylacea are homogenous, laminar, often eosinophilic concretions within ducts and/or alveoli of specialized glands such as in mammary and nasal glands. Amyloid in the nasal cavity of mice should be distinguished from corpora amylacea, as they are similar in appearance.

Corpora lutea (CL) are composed of small and large luteal cells derived from the follicular theca (small luteal or theca lutein cells) and granulosa (large luteal or granulosa lutein cells) cells of the mature preovulatory follicle after the luteinizing hormone (LH) surge and subsequent ovulation. The CL has the primary role of producing progesterone for the maintenance of pregnancy; however, luteal cells also produce androgens (theca lutein cells) and estrogens (granulosa luteal cells). LH is luteotrophic for most laboratory animal species except for rats and rabbits where prolactin and estrogen are luteotrophic, respectively. In a nonpregnant rat, the CL survives for 12–14 days. In dogs and primates, the CL is functional for approximately 2 months and 2 weeks, respectively, irrespective of whether implantation occurs. In hematoxylin and eosin (H&E) sections, CL are basophilic when first formed, and as they age become more eosinophilic. The corpora hemorrhagicum is an early CL where the blood from follicular rupture is still present. When pregnancy does not occur, the CL completely degenerates (i.e., luteolysis/atresia), is replaced by collagenous connective tissue, and is referred to as a corpora albicans. See Appendix 3 for more information.

Corpora lutea activated, see the preferred term **Corpora lutea (CL) hypertrophy**.

Corpora lutea atresia, see the preferred term **Luteolysis**.

Corpora lutea atrophy is an ovarian lesion whereby the expected size of recently formed corpora lutea (CLs) are decreased. The change may be associated with decreased ovarian weights and ovarian atrophy because of age-related senescence, xenobiotic perturbation of the hypothalamic pituitary ovarian axis (usually feedback suppression of gonadotrophin secretion), direct damage to ovarian follicular epithelium (e.g., nitrofurantoin in mice), or interference in ovarian vascular angiogenesis (e.g., VEGF inhibition).

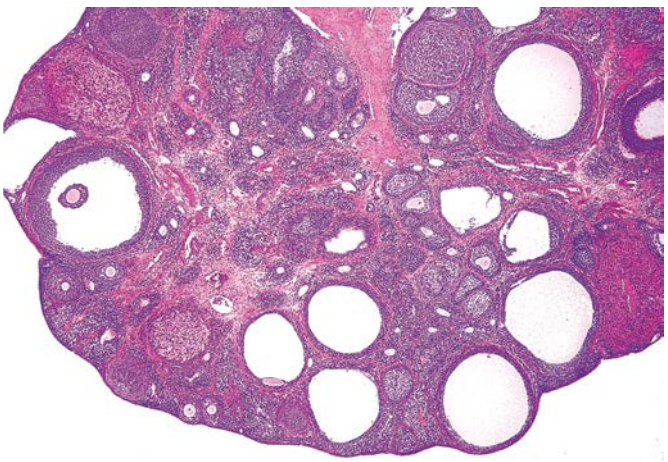
Differential diagnoses: **Anestrus**; **Corpora lutea (CL) decreased number/absent**; **Age-related ovarian atrophy**.

Corpora lutea (CL) decreased number/absent is indicated diagnostically when the expected number of ovarian corpora lutea are decreased. Decreases in CL numbers occur because of estrous cycle disruption. In rats, the estrous cycle is about 5 days, and the CL survives for approximately 2 weeks. Therefore, approximately 3 generations of CL are present at

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any one time in an ovary from a normal cycling rat. If basophilic (recent), CL are only decreased, suggesting an effect on a recent cycle; however, if only eosinophilic (older), CL are decreased and the estrous cycle disruption occurred 3–4 weeks prior. If estrous cycle disruption persists, as in the case of anestrus or senescence (see **Anestrus** for further information), eventually all CLs will be depleted.

Differential diagnoses: **Corpora luteal atrophy**; **Anestrus**; **Luteolysis**; **Age-related ovarian atrophy**.



Numerical decreases in corpora lutea, ovary, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Dixon et al., 2014.)

Corpora lutea (CL) degeneration is characterized microscopically by swollen, vacuolated, and/or hypereosinophilic CLs. Degeneration must be differentiated from the normal changes expected during the estrous cycle (i.e., corpora lutea luteolysis or atresia of the most recent CL during proestrus) (see **Luteolysis** for further information). Degeneration of the CL would be expected when there is disruption of the production or activity (i.e., receptor blockade) for the luteotrophic hormones (prolactin, rats; estrogen, rabbits; luteinizing hormone (LH) for other laboratory animals). CL degeneration may also occur if prostaglandins are induced, as prostaglandins are responsible for its initiation.

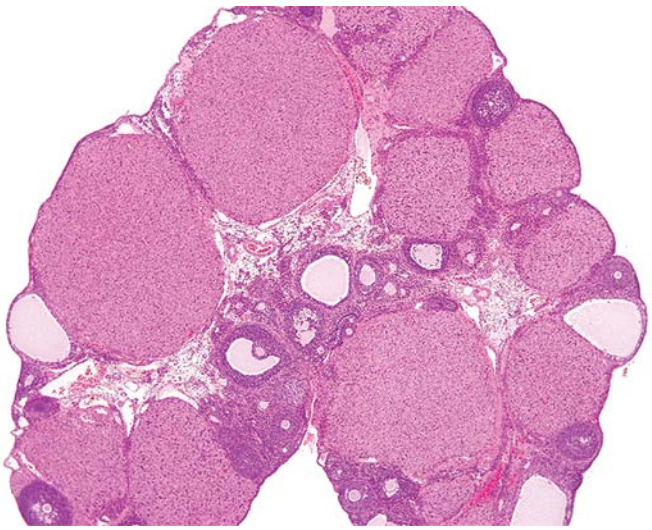
Differential diagnosis: **Luteolysis**.

Corpora lutea enlarged, see the preferred term **Corpora lutea (CL) hypertrophy**.

Corpora lutea (CL) hypertrophy describes an ovary where the expected absolute size of ovarian CL is increased. Hypertrophy may be associated with CL vacuolation as is the case in rats treated with ethylene glycol monomethyl ether (EGME) or atrazine (see **Corpora lutea vacuolation** for further information). Hypertrophy can also result from increases in or prolonged production of luteotrophic hormones (prolactin, rats; estrogen, rabbits; luteinizing hormone [LH] for other laboratory animals). For example, in rats, xenobiotics that cause hyperprolactinemia result in an early microscopic observation of increased numbers and size of CLs.

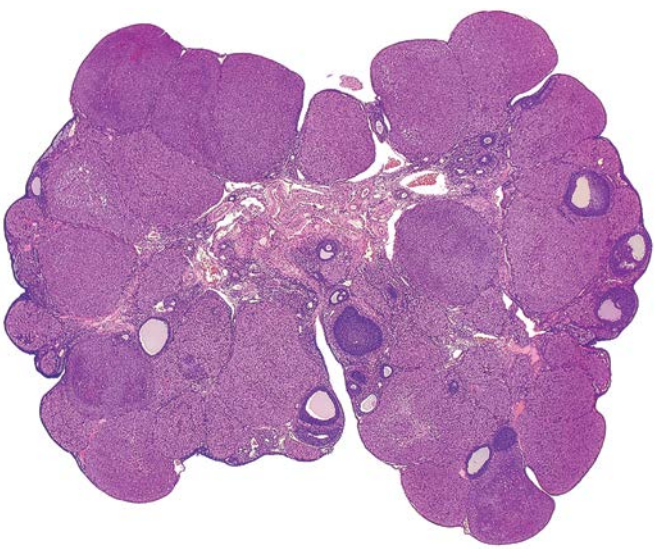
Differential diagnoses: **Corpora lutea (CL) increased numbers**; **CL vacuolation**.

Synonym(s): **Corpora lutea enlarged**; **Corpora lutea activated**.



Hypertrophic corpora lutea, rat, ovary, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Dixon et al., 2014.)

Corpora lutea (CL) increased numbers in an ovary is characterized by normal sized CLs that are increased in number. The numbers may be increased because of increased CL formation or prolonged CL life and may occur because of xenobiotic perturbation of the hypothalamic-pituitary axis. Specifically, compounds that modulate luteinizing hormone (LH), estrogen, and/or prolactin may alter CL lifespan since these hormones are luteotrophic in laboratory animal species (see **Corpora lutea** for further information). For example, in rats, both decreased and increased prolactin increase the



Numerical increases in corpora lutea, ovary, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Dixon et al., 2014.)

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number of CLs because hypoprolactinemia delays luteolysis and hyperprolactinemia is luteotrophic.

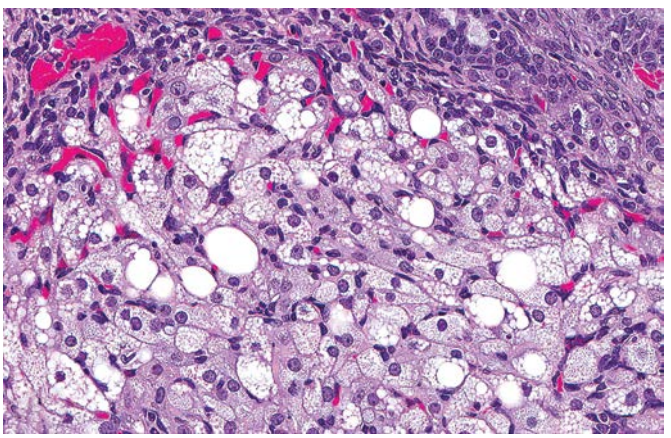
Differential diagnosis: **Corpora lutea hypertrophy**.

C

Corpora lutea (CL) mineralization describes CLs with basophilic deposits that represent mineral. The mineral is dystrophic mineralization and may reflect a xenobiotic-induced degenerative process or CL luteolysis/atresia.

Corpora lutea (CL) vacuolation is characterized by CLs that have a level of intracytoplasmic micro- or macrovesicular vacuolation beyond that expected as background. Background micro- and macrovesicular vacuolation is expected in the CL of the most recent ovulation during diestrus/early proestrus, and mid- to late proestrus, respectively. Vacuolation is also observed during luteolysis (see **Corpora lutea degeneration** for further information). Xenobiotic-induced vacuolation may affect all stages of corpora luteal development (i.e., eosinophilic, basophilic, or mixed) or be targeted to a specific stage. Vacuolation normally occurs in the regressing CL and represents lipid and autophagic vacuoles. Steroid synthesis inhibitors and phospholipidosis agents will increase vacuolation due to lipid in the CL. Ethylene glycol monomethyl ether (EGME) and atrazine cause CL hypertrophy with intracytoplasmic vacuolation in rats.

Differential diagnosis: **Corpora lutea (CL) hypertrophy**.



Corpora lutea vacuolation, ovary, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Dixon et al., 2014.)

Cortical tumor, see the preferred terms **Adrenal cortical adenoma, benign**; **Adrenal cortical carcinoma, malignant**.

Cortico-medullary ratio, decreased/increased is a change that can be observed in the thymus, adrenal glands, or kidney. In the thymus, a decrease of the cortico-medullary ratio can be secondary to immunotoxic compounds or infections and a decrease in numbers of cortical lymphocytes. In the adrenal glands, alteration of the cortico:medullary ratio can be observed due to administration of exogenous corticosteroids or an increase in endogenous corticosteroids.

Corticosteroid is a hormone product. The endogenous hormone is produced by cells of the zona glomerulosa and zona fasciculata in the adrenal cortex as glucocorticoids and mineralocorticoids (aldosterone). Exogenous corticosteroids, such as prednisone, are manufactured as medications for the treatment of inflammatory conditions, and as replacement therapeutics in cases of Addison's disease.

Corticosterone, see the preferred term **Glucocorticoid**.

Corticotroph, see the preferred term **Pituitary chromophobe cell**.

Corticotropin-releasing hormone (CRH) is a hormone secreted by the paraventricular nucleus of the hypothalamus in response to stress that stimulates the synthesis of adrenocorticotrophic hormone (ACTH) by the anterior pituitary gland. Excessive secretion of CRH can result in excessive synthesis of ACTH, leading to overstimulation of the adrenal cortex and excessive levels of cortisol and adrenal androgens (Cushing's disease). Deficiency of CRH causes adrenocortical deficiency by decreasing ACTH production (Addison's disease).

Cortisol, see the preferred term **Glucocorticoid**.

Cortisone, see the preferred term **Glucocorticoid**.

Synonym(s): **Hydrocortisone**.

Countercurrent multiplier system is the mechanism whereby the concentration of the glomerular filtrate is increased to hyperosmotic urine as it passes through the kidney. The basic structural elements comprising this system are the limbs of Henle, with the descending and ascending limbs running in opposing directions, with the medullary interstitial space between the tubules. Because of the countercurrent flow in the two branches of Henle's limbs, the osmolality of the renal interstitium increases as a gradient from cortex to the tip of the papilla. The increased osmolality of the medullary interstitium draws water from the descending thin limb, progressively concentrating the urinary fluid in the tubule lumen. The thick ascending limb lacks aquaporins (i.e., proteins that form water channels), and therefore this segment is impermeable to water, resulting in increased osmolality in the medulla. However, there is active reabsorption of sodium and chloride by the thick ascending limb. Countercurrent exchange of solutes between the ascending and descending vasa recta minimizes the loss of solutes from the medullary interstitium. As urinary fluid passes from the loop of Henle through the distal convoluted tubule into the collecting ducts, water diffuses out of the collecting system because of high osmotic pressure in the medulla, producing concentrated urine.

Covalent binding is the chemically stable binding of molecules to macromolecules such as proteins or DNA. Covalent binding of electrophilic reactive metabolites to proteins can result in cytotoxicity, or in generation of haptens and subsequent immunogenicity. In genetic toxicology, covalent

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binding results in adduct formation of chemicals with DNA bases, which can trigger mutagenic events.

Covalent binding tests are used to assess the irreversible binding of small molecular weight compounds to macromolecules (generally DNA or protein). They are usually performed using radioactively labeled ligand molecules, although covalent binding to DNA may be assessed using ^{32}P-postlabeling technology.

Cowper's gland, see the preferred term **Bulbourethral glands**.

Coxa plana (Legg-Calvé-Perthes disease), see the preferred term **Bone necrosis**.

Craniopharyngioma is an epithelial neoplasm of the sellar region of the skull (near the pituitary gland) and presumably derived from remnants of Rathke's pouch. Refer to **Nervous System** in Appendix 2 for further information.

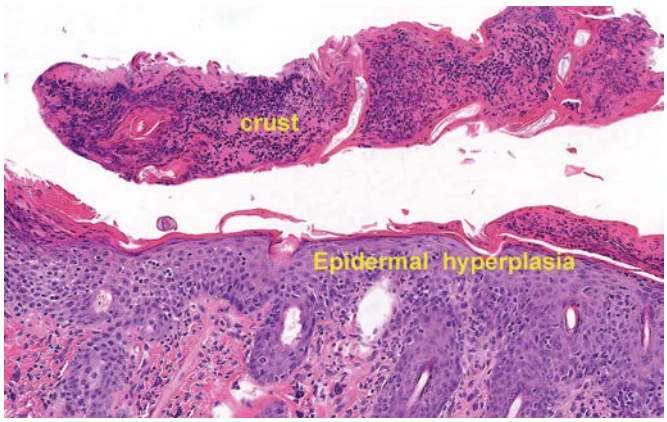
Creatinine is a nitrogenous organic acid produced at a relatively constant rate from the catabolism of creatine in muscle and excreted at a constant rate into the urine. As a consequence, the concentration of analytes in the urine may be expressed as a ratio to the creatinine concentration. This reduces errors caused by incomplete collection of urine and eliminates the necessity to collect 24-hour urine samples. Plasma creatinine levels are often monitored in repeat-dose toxicity studies as a measure of kidney function.

Creatinine phosphokinase (CPK), also referred to as creatinine kinase or CK, is an enzyme found in high concentrations in skeletal muscle, heart, and brain, and is a common component of clinical chemistry panels in toxicology studies. Although often used as an indicator of cardiac injury, levels of this enzyme may be markedly increased in toxicology studies and in pre-study evaluations, without any evidence of electrophysiological or histopathological changes in the heart. The use of other markers of skeletal muscle injury, most notably lactate dehydrogenase (LDH) and aspartate aminotransferase (AST) (especially in monkeys), can help interpret the significance of increased plasma or serum CPK activity in the absence of cardiac findings.

Crescentic glomerulonephritis is a nonspecific response to severe inflammatory glomerular injury, implying the formation of glomerular crescents. These consist of foci of cellular and/or fibrous proliferation within Bowman's space involving mainly parietal epithelial cells of Bowman's capsule and mononuclear inflammatory cells, often with fibrin deposition. Adhesions between glomerular tufts and crescents may be prominent. Crescentic glomerulonephritis has been induced in rats by administration of antiglomerular basement membrane serum.

CRISPR is an acronym for clustered regularly interspaced short palindromic repeats, a method for genetic manipulation of cells or organisms. CRISPR uses engineered nucleases that cut DNA at specific sites, which are identified by the use of a complementary RNA molecule, thus allowing the removal or insertion of DNA sequences. The method is an adaptation of a bacterial defense mechanism against viral infections.

Crust is an amalgam of desiccated proteinaceous fluid and necrotic cellular debris, including inflammatory cells (particularly neutrophils), that lies atop the skin's epidermal surface. It is an inflammatory exudate that forms as the result of an epidermal inflammatory process. Crusts often overlie epidermal erosions or full-thickness ulcerations, and sometimes form as the result of ruptured sub- and intracorneal pustules. Clinically, a crust can also be referred to as a scab.



Crust overlying an area with epidermal hyperplasia and inflammation. SKH1 mouse, H&E.

Cryptorchidism is a rare gross finding in rats, mice, dogs, and monkeys where one or both testes are present in the abdominal cavity due to failure of normal descent through the inguinal canal into the scrotal sac. Histologically, the seminiferous tubules contain degenerating or missing germ cells. For unknown reasons, tubular degeneration may be present in the contralateral descended testis when cryptorchidism is unilateral. Spontaneous cryptorchidism is reported at a higher incidence in mice mutant for Insl3 or with an androgen receptor (Ar) gene and/or Wilms tumor 1 gene deletion. It is observed in the Long Evans and the unilateral urogenital anomalies (UUA) rat, but is rare in beagle dogs and monkeys. Treatment-related cryptorchidism is reported in rodents upon in utero exposure to estrogens, phthalates, and flutamide.

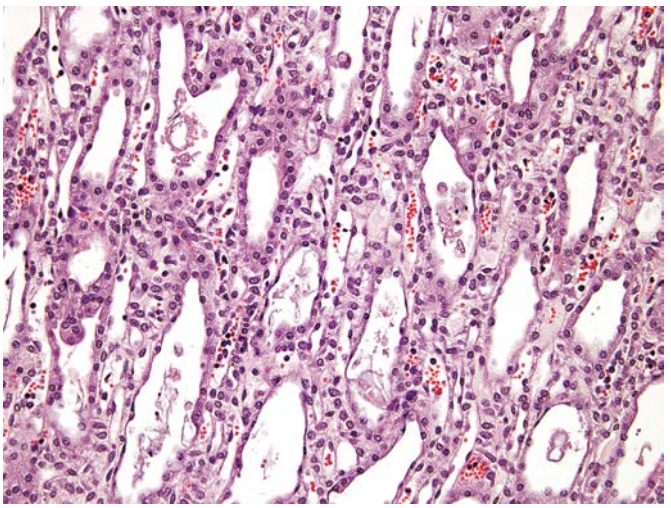
Differential diagnosis: **Testicular tubular degeneration/atrophy**.

Crystalluria, see the preferred term **Urolithiasis.**

Crystal nephropathy is a form of obstructive nephropathy caused by precipitation of crystals in the renal tubules. This elicits a granulomatous type of inflammatory change characterized by inflammation involving the interstitial infiltration

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of mainly mononuclear cells that differentiate into macrophages, epithelioid cells, and/or multinucleated giant cells of the Langhans type. There is also modest interstitial fibrosis. Crystals or crystal outlines can be observed scattered within tubules of the distal nephron and engulfed within the foreign body giant cells. Crystal precipitation with poorly soluble chemicals occurs as the urine becomes more concentrated in the distal parts of the nephron. The classic example of this process follows experimental administration to the rat or natural ingestion by dogs and cats of the antifreeze agent ethylene glycol, which leads to formation of oxalic acid crystals in the nephron. Several drugs have also induced this alteration in rats, dogs, or monkeys, including antimicrobial sulfonamides, the antiviral drug acyclovir, and some quinolone antibiotics. Similar changes have been reported in humans for some of these drugs when administered in high doses.

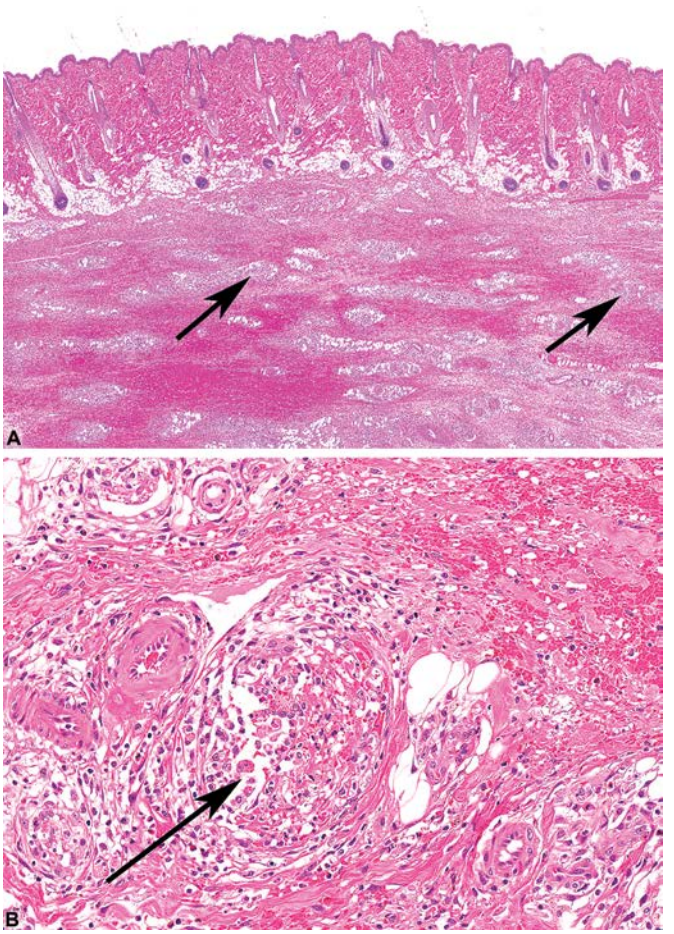


Crystals, kidney, tubules, rat, H&E.

CSF-brain barrier, see **Blood-brain barrier (BBB)**, **Ependymal barrier**, and Appendix 3 for further information.

Cushing's disease, see the preferred term **Hyperadrenocorticism**.

Cutaneous hypersensitivity is a broad term that can refer to any form of cutaneous reaction that manifests as the result of systemic hypersensitivity reactions, types I through IV. Type I hypersensitivity is acute and classically manifests cutaneously as urticaria mediated by IgE antibodies bound to the surface of mast cells and basophils. Type II hypersensitivity is characterized by cytotoxicity induced by IgG or IgM antibodies with complement activation. The various forms of pemphigus are an example of cutaneous type II hypersensitivity, with autoantibodies directed against keratinocyte antigens and inducing acantholysis, or loss of cell-cell adhesion. Type III hypersensitivity is mediated by IgG or IgM antigen-antibody immune complex deposition. Cutaneous toxicities due to type III hypersensitivity reactions are drug-induced cutaneous vasculitis and cutaneous lupus erythematosus. Approximately 20–30% of cutaneous vasculitides are drug induced, generally appearing 7–10 days following administration of the inducing drug substance. In contrast to type I, II, and III hypersensitivities, which are generally systemic, type IV, or delayed-type hypersensitivity, is often a local reaction and in the skin is referred to as allergic contact dermatitis. Different toxic agents can induce more than one immune-mediated mechanism. As an example, penicillin, which is often cited as the classic example of a drug acting as a hapten, can cause both an IgE-mediated type I hypersensitivity reaction, manifesting as urticaria as well as non-IgE–mediated reactions that manifest as systemic type IV hypersensitivity with variable degrees of epidermal keratinocyte necrosis, ranging from erythema multiforme to toxic epidermal necrolysis (TEN) (see individual terms for more information), and Stevens-Johnson syndrome, severe conditions with widespread full-thickness epidermal necrosis and detachment from the underlying dermis.



Skin and subcutis from a cynomolgus monkey administered a humanized therapeutic monoclonal antibody via repeated subcutaneous injections illustrating a type III cutaneous hypersensitivity reaction, H&E. The injection site subcutis contains relatively marked, multifocal mixed inflammatory cellular infiltration (arrows in A), often surrounding and infiltrating into subcutaneous vessels that sometimes exhibit necrosis and/or thrombosis (perivasculitis and vasculitis; arrows in B). (Figure reprinted with permission from Danilenko, D.M., 2016.)

Cutaneous lupus erythematosus (LE) can have a variety of histologic presentations but is often characterized by an

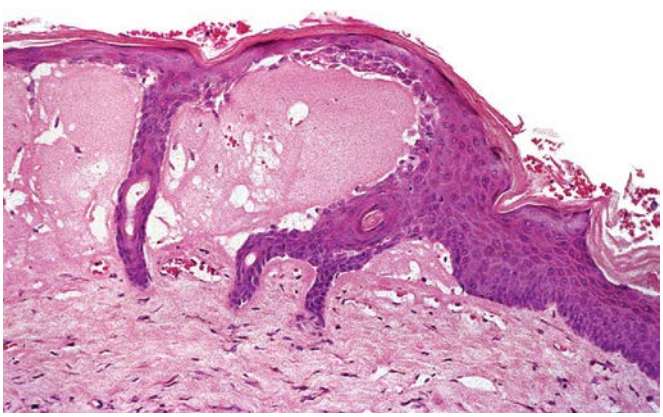
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interface dermatitis consisting of a lichenoid inflammatory cellular infiltrate at the dermal-epidermal interface. Lichenoid drug eruptions have a very similar histopathologic appearance to cutaneous forms of lupus. Drugs that are most commonly implicated in drug-induced LE are carbamazepine, chlorpromazine, hydralazine, isoniazid, methyldopa, minocycline, penicillamine, procainamide, quinidine, terbinafine, omeprazole, and the TNF-α inhibitors infliximab and etanercept, both of which are biologics. The exact pathogenesis of drug-induced LE is unknown, but reactive drug metabolites are implicated for those induced by xenobiotics. It has been hypothesized that cutaneous autoimmune inflammation as exemplified in cutaneous lupus is dependent on plasmacytoid dendritic cell (DC) activation by nucleic acid antigens via the innate immune receptors TLR7 and TLR9. In the specific case of cutaneous lupus induced by the TNF-α inhibitor biologics, nucleic acid antigens, termed nucleosomes, become detectable in the plasma of rheumatoid arthritis (RA) patients after the start of TNF-α inhibitor therapy, suggesting that this rise in plasma nucleosome levels might contribute to a break of tolerance and thereby induce autoantibodies in susceptible individuals. This hypothesis is supported by the finding that antinucleosome antibodies correlated strongly with the presence of antinuclear antibodies, a hallmark of systemic LE, in anti-TNF-α–treated RA patients.

Cutaneous lymphoma, see the preferred term **Lymphoma, epitheliotrophic (canine)**.

Cutaneous vesicle is a localized collection of acellular fluid within or beneath the epidermis. The basis of the lesion is a breach in the cell-cell adhesion of epidermal keratinocytes, or separation of the keratinocytes from the basement membrane. Such lesions are usually secondary to trauma (e.g., burn), infection (e.g., herpesvirus), or immune-mediated disease (e.g., pemphigus foliaceous, bullous pemphigoid). Histologic classification of variants of vesicle consist of bulla and cleft, primarily based on extent/size of the lesion, with bulla being the largest and cleft being the smallest and least severe.

Synonym(s): **Bulla**; **cleft**; **reticular degeneration**.



Mouse skin, H&E, vesicle.

Cut back zone is the region of metaphyseal bone that undergoes modeling resulting in the formation of cortical bone structure and contour. Osteoclasts are numerous at the periosteal surface, eliminating bone emanating from the periphery of the physis, while osteoblasts are very active within the forming cortical shell and on the endocortex, filling in gaps in the new cortical bone and thickening the endocortex. Interference with this normal process by alteration of osteoclast number or function (e.g., bisphosphonates) can result in a clubbed or flared appearance in this region.

Cyanosis is the term used to describe the bluish tint to the skin caused by low blood oxygen concentrations. The color is a result of higher levels of circulating deoxyhemoglobin but can also result from methemoglobin formation.

Cyclic AMP, or cyclic adenosine monophosphate (3′,5′-AMP, cAMP, or cyclic AMP), is a cyclic nucleotide involved in the action of many hormones, including catecholamines, ACTH, and vasopressin. Cyclic AMP acts as a second messenger activating other enzymes (e.g., kinases) within the cell. When a hormone binds to a specific receptor on the cell membrane of the target cell, it activates an enzyme, adenylate cyclase, which produces cyclic AMP from ATP.

Cyclic GMP, or cyclic guanosine monophosphate (3′,5′-GMP, cGMP, and cyclic GMP), is a cyclic nucleotide and, like cAMP, is involved as a second messenger in receptor-mediated stimulation to trigger different biochemical pathways within the cell, with biological effects as diverse as glycogen lysis, apoptosis, muscle relaxation, and vasodilation.

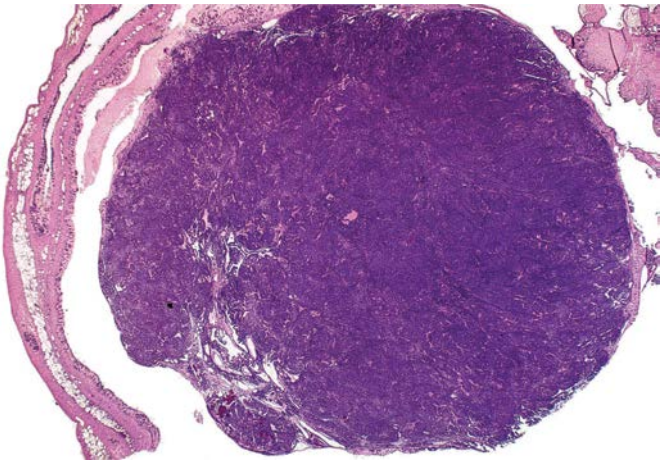
Cyclic nucleotide phosphodiesterase is a family of enzymes that act to add or remove a phosphate from a cyclic nucleotide (see **Cyclic AMP** and **Cyclic GMP** for further information).

Cyclitis, see the preferred term **Iris inflammation**.

Cyst is a sac-like expansion that typically contains eosinophilic, proteinaceous fluid and is lined by a single layer of epithelium. Cysts occur in almost all types of tissues, including bone. They are especially common findings in organs such as the pituitary gland, thyroid gland, and the female reproductive tract. A cortical cyst is a cyst occurring in the cortex of either the kidney or adrenal gland. In the kidney, dilatation of a tubule can lead to cyst formation. Cystic tubules are a common finding in the late stages of chronic progressive nephropathy in both rats and mice. Cortical cysts can occur in the adrenal gland and are more common in mice than in rats. They are also lined by a single layer of epithelium and contain similar, fluid-like material. Cortical cysts of the adrenal gland should be differentiated from cystic degeneration, which is often irregular and cavitated and lacks an epithelial lining. Newborn rats exposed to p-cumylphenol form renal tubular cysts.

Cystadenocarcinoma is a malignant epithelial neoplasm with variable cyst formation. As with cystadenoma,

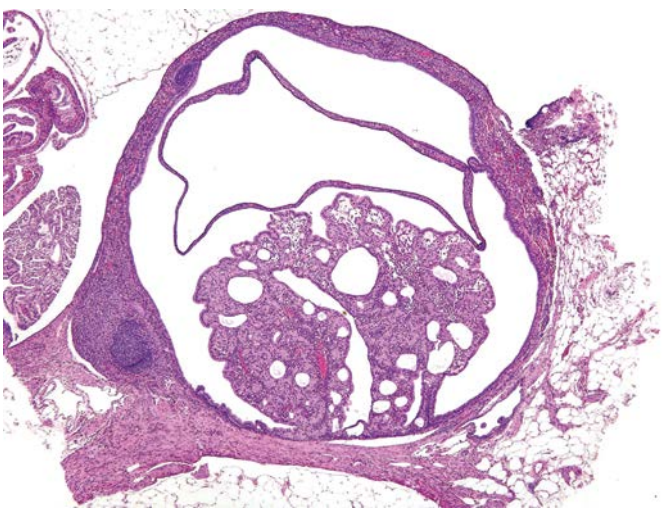
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Cystadenocarcinoma of the ovary of a mouse, H&E. Large mass with solid sheets of neoplastic cells and small cystic areas. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

cystadenocarcinoma is typically a diagnosis of the ovary or the diagnosis may be used in preputial or clitoral gland when appropriate. The neoplasm consists of a solid or cystic mass that projects from the surface of the ovary. Mitotic figures are numerous, and invasion of the underlying ovarian stroma is common. This lesion may be difficult to differentiate from malignant mesothelioma. Ovarian cystadenocarcinomas are more common in mice than in rats.

Cystadenoma is a benign epithelial neoplasm with variable formation of cysts. The diagnosis is typically made in the ovary and mammary gland, and less often in the pancreas and liver. In the ovary, cystadenomas consist of papillary structures that project from the surface and are separated by a fine stroma. Cysts, when formed, may contain fluid or blood. In general, cystadenomas of the ovary are at least the size of a corpus luteum. They are more common in mice than in rats.



Cystadenoma in the ovary of a mouse, H&E. The adenoma has a papillary appearance and projects from the surface of the ovary. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

Cystic bile duct adenoma, see the preferred term **Cholangioma, cystic**.

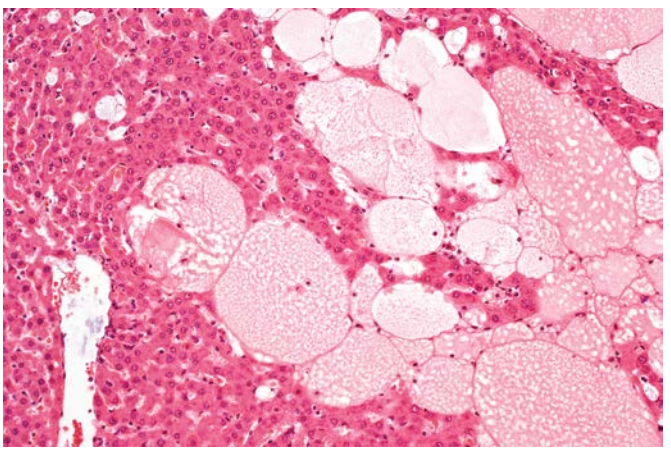
Cystic biliary adenoma, see the preferred term **Cholangioma, cystic**.

Cystic cholangiocellular adenoma, see the preferred term **Cholangioma, cystic**.

Cystic corpora lutea, see the preferred term **Luteal cyst**.

Cystic degeneration arises from altered liver stellate cells that form uni- or multilocular cyst-like structures and occurs principally in rats. These structures become filled with finely granular to flocculent acidophilic material and are lined by extracellular matrix components. Immediately adjacent to the extracellular matrix are fibroblast-like cells that contain small lipid vacuoles and express markers typical of hepatic stellate cells. Multiple cystic structures replace, rather than compress, adjacent hepatic parenchyma. The pathogenesis of cystic degeneration is not clear. It is recognized as a spontaneous aging lesion, but can also occur in carcinogen-treated rats, and may be accompanied by other treatment-related lesions (such as necrosis, regeneration, foci of cellular alteration, and/or hepatocellular neoplasms). Cystic degeneration may also occur in other densely cellular tissues such as the kidney. See **Peliosis hepatis** and **Angiectasis** for further information.

Synonym(s): **Spongiosis hepatis**.



Cystic degeneration, rat liver, H&E. (Reproduced with permission of CRC Press from Cattley et al., 2013.)

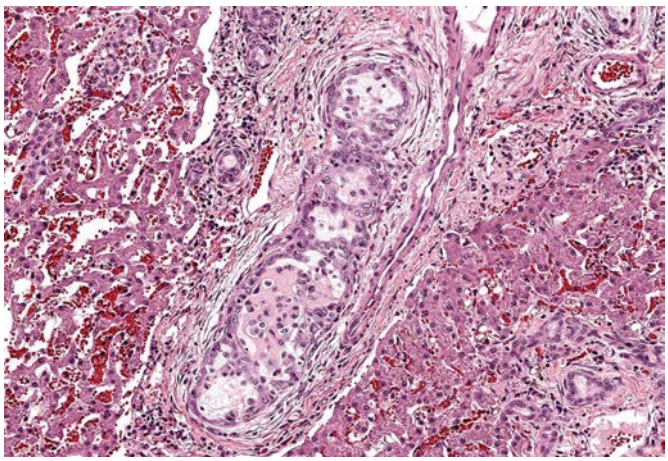
Cystic dilatation is widening of a duct resulting in a large, central, open space and probable attenuation of the lining epithelium. Causes include congenital malformation, obstruction by intraluminal material (e.g., necrotic debris, calculi), and compression (such as by a local mass).

Synonym(s): **Cystic duct**; **cystic dilation**; **ductular ectasia**.

Cystic dilation, see the preferred term **Cystic dilatation**.

Cystic duct, see the preferred term **Cystic dilatation**.

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Cystic dilatation of the bile ducts of a cat, H&E. Note attenuation (atrophy) of the epithelial cells lining the ducts.

Cystic hyperplasia is a nonneoplastic proliferation typically of epithelial cells with variable cyst formation. Cystic hyperplasia can be diagnosed in the uterus, thyroid gland, bile ducts of the liver, and the gastrointestinal (GI) tract. In the uterus, there is an increase in the number of proliferating endometrial glands. The glands expand and become cystic, and it is a common finding in aged rats and mice. In the GI tract there is disruption of the intestinal wall structures resulting in projections of the mucosal epithelium (which in some cases can become cystic) into the submucosal and muscularis layers. Compounds that are estrogenic, such as diethylstilbestrol or 17β-estradiol, can induce cystic hyperplasia in the uterus. The preferred diagnostic term for this lesion in the GI tract is **Intestinal diverticulum**.

Cystic hyperplasia, bile duct, see the preferred term **Bile duct hyperplasia**.

Cystitis, see the preferred term **Urinary bladder inflammation**.

Cytochrome b_5 is a membrane-bound hemoprotein involved in electron transport systems, including the transfer of electron to cytochrome P450 during drug oxidation. Cytochrome b_5 is reduced by the enzyme cytochrome b_5 reductase (EC 1.6.2.2), an NADH-dependent flavoprotein containing flavin adenine dinucleotide (FAD).

Cytochrome P450 is the name given to a superfamily of membrane-bound enzymes that catalyze the oxidation of a wide variety of endogenous and exogenous substrates. The heme-containing enzymes (cytochromes) were originally named because the absorption maximum of the carbon monoxide complex is at 450 nm; hence pigment 450 or cytochrome P450. The current nomenclature is based on gene structure and amino acid sequence homology. Members of the same family show at least 40% homology and subfamilies at least 55% homology. In the human genome, there are 18 CYP families with over 50 different isoforms. The superfamily is noted by the term CYP followed by the number of the family and a capital letter for the subfamily, followed by a number for the gene; thus, CYP3A4, belongs to family 3, subfamily 3A. Members of only 3 of the 18 human CYP families are involved in drug metabolism.

The CYPs are monooxygenases in that they are capable of reducing molecular oxygen, whereby one atom of the oxygen is incorporated into the substrate and the other forms into water. For this purpose, electrons are supplied from nicotinamide adenine dinucleotide phosphate-oxidase (NADPH) via NADPH cytochrome P450 reductase, giving the reaction:

$$R\text{-}H + O_2 + NADPH + H^+ \rightarrow R\text{-}OH + H_2O + NADP^+$$

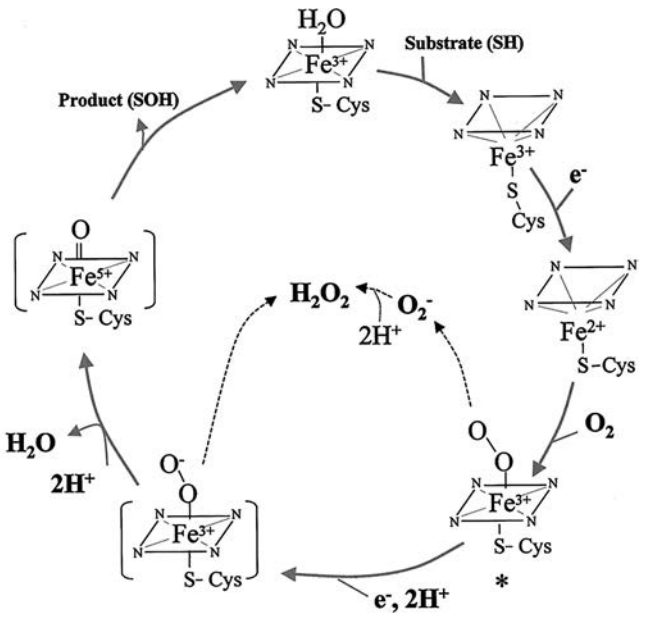
Human CYP Families and Their Function

CYP Family	# Subfamilies	# Genes	Function
CYP1	3	3 + 1 pseudo	Drug metabolism
CYP2	13	16 + 16 pseudo	Drug metabolism
CYP3	1	4 + 1pseudo	Drug metabolism
CYP4	5	11 + 10 pseudo	Arachidonic and fatty acid metabolism
CYP5	1	1	Thromboxane A2 synthesis
CYP7	2	2	Steroid 7α-hydroxylase
CYP8	2	2	Prostacyclin and bile acid synthesis
CYP11	2	3	Steroid biosynthesis
CYP17	1	1	Steroid biosynthesis
CYP19	1	1	Steroid biosynthesis (aromatase)
CYP20	1	1	Unknown
CYP21	1	1 + 1 pseudo	Steroid biosynthesis
CYP24	1	1	Vitamin D degradation
CYP26	3	3	Retinoic acid hydroxylase
CYP27	3	3	Bile acid synthesis, vitamin D3 1-α hydroxylation
CYP39	1	1	Steroid 7-α hydroxylation
CYP46	1	1	Cholesterol 24-hydroxylase
CYP51	1	1 = 3 pseudo	Cholesterol biosyntheis

The mechanism of catalysis by CYPs depends on the transfer of electrons and activation of oxygen at the heme moiety. Initially the substrate binds in close proximity to the ferric iron−containing heme distal from the axial thiolate. This binding causes a conformational change within the protein, dislodging a water molecule from coordination with the heme iron and changing the spin state of the iron atom. This binding facilitates electron transfer from either nicotinamide adenine dinucleotide phosphate-oxidase (NADPH) cytochrome P450 reductase or cytochrome B_5, reducing the iron to the ferrous state; molecular oxygen now binds as a dioxygen adduct to the ferrous iron of the heme. A further electron is transferred from an electron donor (NADPH cytochrome P450 reductase, cytochrome B_5), reducing the ferrous iron oxygen complex to an unstable peroxo complex, which rapidly reacts with two protons, releasing a water molecule and forming P450 compound 1 (a ferryl complex). The latter oxidizes the substrate, shown in the scheme as introduction of a hydroxyl group.

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Other reaction products may be formed depending on the substrate and the CYP involved. The large variety of potential drug oxidations is shown below.



(From Fleming, I. 2001. *Circ Res* 89:753–762.)

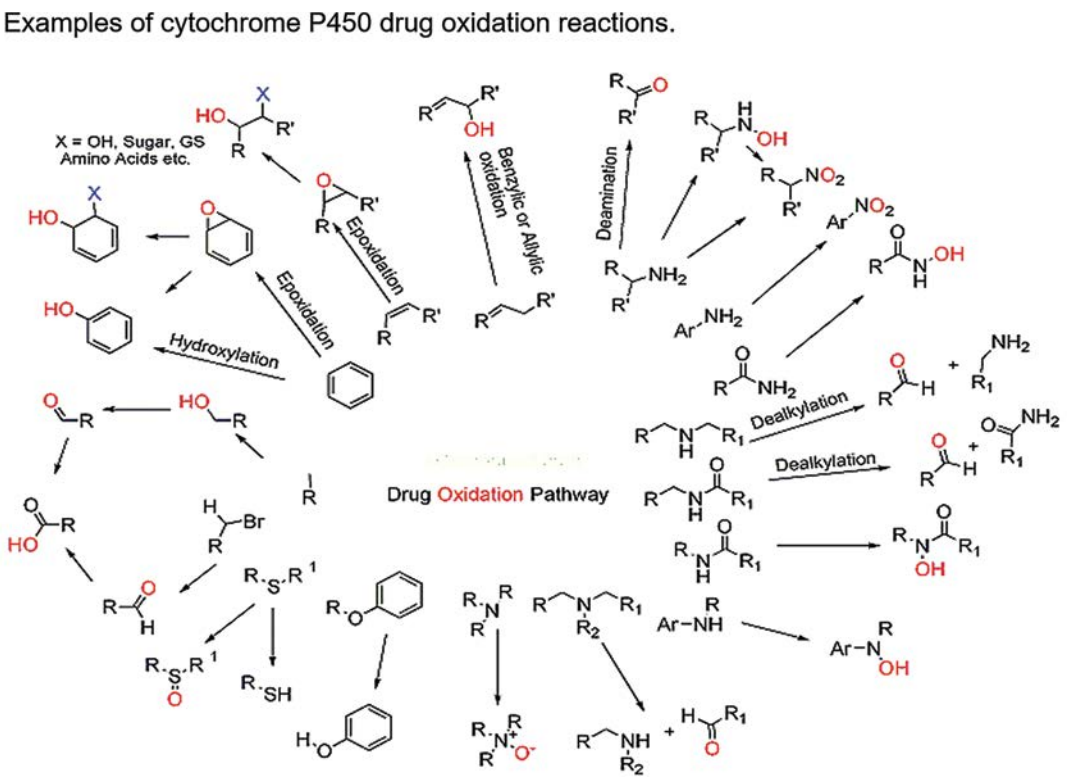
These include aromatic hydroxylation, which is often via epoxidation with rearrangement of the epoxide to form the phenol, oxidative *O*- and *N*-dealkylations, amine oxidation, and oxidative deamination (see figure below).

CYPs are the main enzymes involved in drug oxidations, consequently altering CYP activity either by enzyme induction or inhibition by co-medication or dietary supplements can result in drug-drug interactions. In the former case, a co-administered drug may be cleared more rapidly and lose efficacy (as in the case of contraceptive hormones in patients simultaneously treated with rifampicin), whereas in the latter case a co-administered drug may be cleared less rapidly resulting in exaggerated pharmacology and toxicity.

Major CYP Isoforms Involved in Human Drug Metabolism and Their Animal Homologues

Family	Human	Rat	Mouse	Dog	Marmoset	Monkey
CYP1A	1A1/2	1A1/2		1A2	1A2	
CYP2A	2A6	2A1/2	2A1/4/5			
CYP2B	2B6	2B1	2B9/10	2B11		
CYP2C	2C8/9/18/19	2C11/12		2C21		
CYP2D	2D6	2D1-5	2D9-13	2D15	2D19	
CYP2E	2E1	2E1				
CYP3a	3A4/5/7	3A1/2	3A13	3A12	3A8	3A21
CYP4A	4A9/11					

In view of this potential for drug-drug interactions, it is common practice in the profiling phase of drug discovery to subject drug candidates to CYP profiling in which the ability of stably expressed individual CYP isoforms to metabolize the compound and the ability of the compound to inhibit the activity of human liver microsomes with isoform specific substrates is assessed.



Examples of cytochrome P450 drug oxidation reactions.

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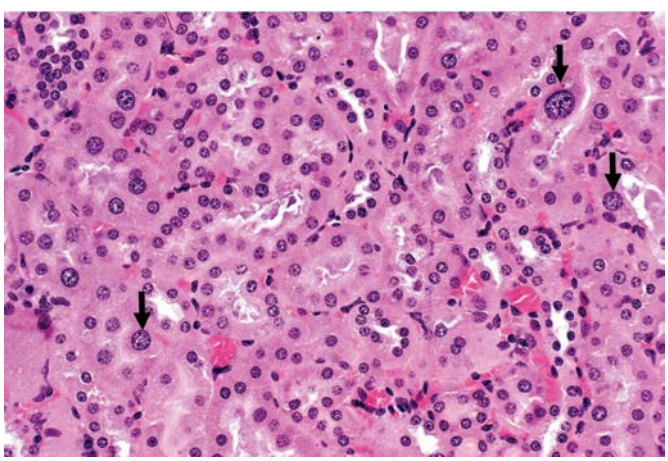
Profiling compounds as substrates for specific CYP isoforms is also important because of the known polymorphic expression of a number of CYP isoforms in the human population (for example CYP2D6, CYP1A2, CYP2C9, CYP2C19), which can affect the rate of clearance of a drug and result in large, inter-individual differences in drug clearance.

In general, most drugs are metabolized by hepatic cytochrome P450s; however, some CYP isoforms are found in high levels in extrahepatic tissues, where they can be responsible for local drug metabolism. CYP isoforms in some extrahepatic tissues are shown in the table below.

Tissue	CYP Isoforms Identified
Nasal mucosa	2A6, 2A13, 2B6, 2C, 2J2, 3A
Trachea	2A6, 2A13, 2B6
Lung	1A1, 1A2, 1B1, 2A6, 2A13, 2B6, 2C8, 2C18, 2D6, 2E1, 2F1
Esophagus	1A1, 1A2, 2A, 2E1, 2J2, 3A5
Stomach	1A1, 1A2, 2C, 2J2, 2S1, 3A4
Small intestine	1A1, 1B1, 2C9, 2C19, 2D6, 2E1, 2J2, 2S1, 3A4, 3A5
Colon	1A1, 1A2, 1B1, 2J2, 3A4, 3A5
Kidney	2B6, 3A5,4A11, 4F2, 4F8, 4F11, 4F12
Brain	1A1, 1A2, 1B1, 2B6, 2C13, 2D6, 2E1,3A5

Cytomegaly is an enlarged cell. Cell enlargement can occur for many reasons, and the increase in cell volume may be due to increases in specific organelles (e.g., peroxisomes, smooth endoplasmic reticulum, vacuoles) or cytoplasmic contents (e.g., glycogen or fluid). Cytomegaly is also typical of betaherpes viral infections (cytomegalovirus); these viruses have a predilection for salivary glandular epithelium.

Synonym(s): **Hypertrophy**.



Cytomegaly and karyomegaly of renal tubular epithelial cells in a mouse, H&E. Most tubular epithelial cells and nuclei are of uniform size, while some are two to five times this size (as indicated by arrows). (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

Cytoplasmic alteration is a descriptive term applied to a variety of hepatocellular changes. As such, it is a term that, when used, requires further characterization. It may refer to changes in the granularity or homogeneity of hepatocellular cytoplasm, including increases in numbers of organelles (i.e., endoplasmic reticulum, mitochondria, peroxisomes). However, it also may refer to cytoplasmic changes that reflect actual degenerative lesions or postmortem artifacts. (See **Hepatocellular intracytoplasmic inclusions** for further information.)

Cytoplasmic basophilia is a morphologic change that occurs in neutrophils and is attributable to altered bone marrow development, imparting a bluish-purple color to the cytoplasm associated with retained rough endoplasmic reticulum and polyribosomes. These changes may be associated with Döhle bodies and cytoplasmic vacuolation of neutrophils, and indicate increased granulopoiesis with accelerated bone marrow maturation as part of an inflammatory response.

Cytotoxicity is the property of being toxic to cells. Cytotoxic agents may reduce cell growth by inhibiting cell division, induce apoptotic pathways stimulating programmed cell death, or cause cell lysis and death. There are several screening tests for in vitro cytotoxicity to rank the toxicity of compounds/chemicals. Cytotoxicity may be an endpoint in pharmacological testing (e.g., for anticancer drugs). Cytotoxicity is also monitored in in vitro tests for pharmacological and genotoxic activity to prevent artifactual results obtained at toxic doses.

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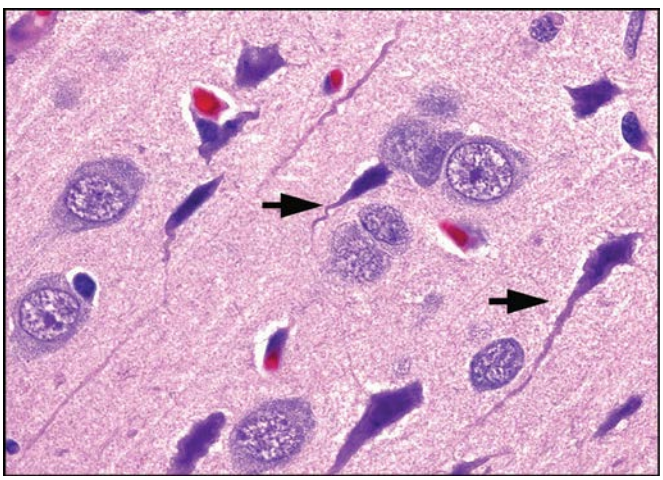
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D

Dacryoadenitis, see the preferred terms **Lacrimal gland inflammation** or **Harderian gland inflammation**.

Dark neuron artifact is an incidental finding in microscopic sections of brain and spinal cord secondary to handling pressure of fresh tissue. In hematoxylin and eosin-stained (H&E) sections, dark neurons are characterized by sharply delimited cell boundaries, cytoplasmic basophilia (dark blue to purple discoloration of the neuroplasm), including the neuroplasm of both the soma and cell processes with similar discoloration of the nucleus. Older literature sometimes used the term to describe degenerating or necrotic neurons, from which they must still be differentiated. The occurrence of dark neurons can be minimized by handling the tissues gently, or can be eliminated by perfusion fixation and leaving brain and spinal cord within bone for at least 48 hours prior to removal.

Synonym(s): **Basophilic neurons**; **dark spiky neurons**; **neuronal hyperchromatosis**.



Dark neuron artifact (two of several affected neurons are indicated by arrows). Several unaltered large pyramidal neurons are also scattered within this field. Brain, rat. H&E.

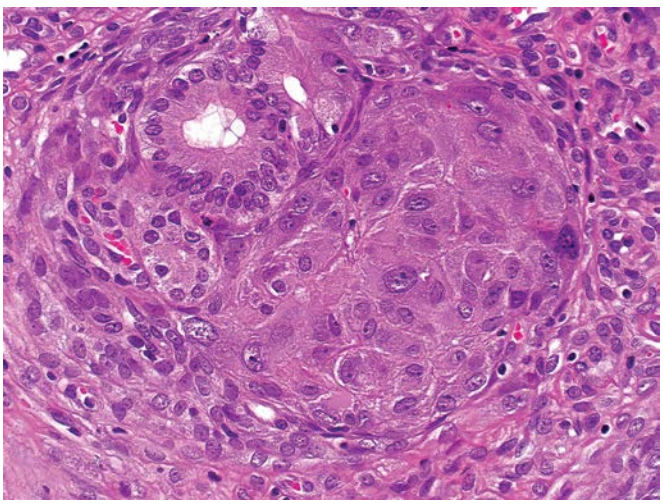
Dark spiky neurons, see the preferred term **Dark neuron artifact**.

Decidual alteration, see the preferred term **Decidualization**.

Decidualization is a focal area of stromal proliferation in the uterus or uterine intraluminal polyp characterized by stromal cells with periodic acid-Schiff (PAS)-positive cytoplasm. This lesion may be induced by progesterone treatment or prostaglandins, growth hormone, or prolactin administered at a specific time in the estrous cycle.

Differential diagnosis: **Decidual reaction**.

Synonym(s): **Decidual alteration**.



Decidualization, uterus, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Dixon et al. 2014.)

Decidual-like reaction, see the preferred term **Accessory male sex organs, mesenchymal proliferative lesion**.

Decidual-like reaction in the urinary bladder, see the preferred term **Urinary bladder mesenchymal proliferative lesion**.

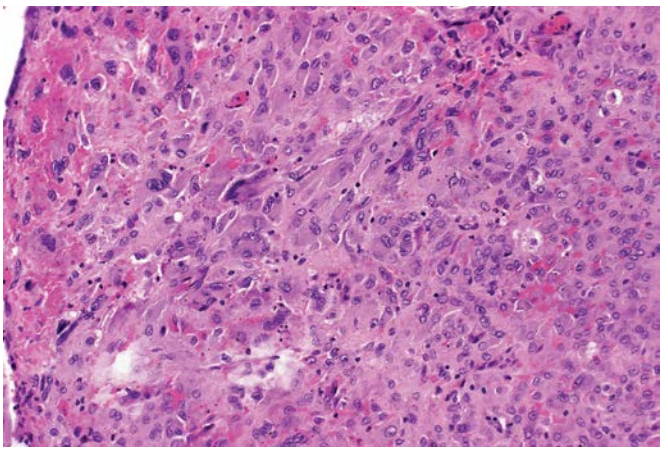
Decidual nodule, see the preferred term **Decidual reaction**.

Decidual reaction is a uterine lesion associated with pseudopregnancy (spontaneous or xenobiotic induced) that is characterized by focal stromal proliferation organized into two zones. One zone contains a dense, vascularized, and cellular mesenchyma (i.e., antimesometrial zone), while the other zone consists of a mixed population of mesometrial cells with elongated cytoplasmic processes and metrial gland cells, both with periodic acid-Schiff (PAS)-positive cytoplasm (i.e., mesometrial zone). Mechanical irritation or trauma of the uterus and progesterone treatment may induce a decidual reaction.

Differential diagnosis: **Decidualization**.

Synonym(s): **Decidual nodule**; **deciduoma**.

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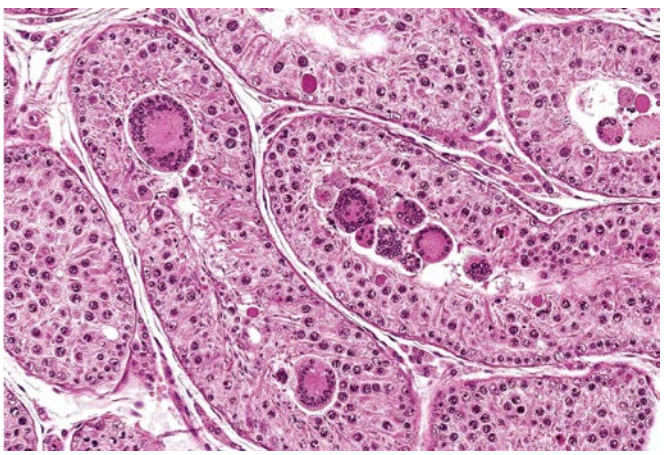
Decidual reaction, uterus, F344/N rat, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

Deciduoma, see the preferred term **Decidual reaction**.

Declaration of Helsinki is a statement related to the ethical principles of medical research involving human subjects. It was developed by the World Medical Association (WMA) in 1964 and has been modified several times, the latest version being released in 2013. It defines criteria for the ethical conduct of clinical trials and covers such topics as patient well-being (paramount), protection of minorities, protocol requirements, ethical committee requirements and defining their roles and responsibilities. It defines the requirement for informed consent, requires registration of trials in publicly accessible databases, and requires a scientific basis for trials including appropriate animal experimentation and the publication of trial results.

Decreased numbers of retinal pigment epithelium, see the preferred term **Retinal pigment epithelium atrophy**.

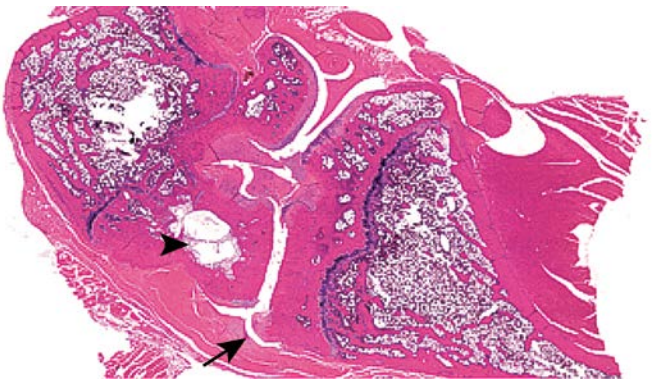
Degeneration is a generalized term referring to loss of architecture, either grossly or microscopically. Degeneration implies progression toward deterioration of cells or tissues.



Degeneration of testicular germ cells in the seminiferous tubules of a dog, H&E. There is loss of germinal epithelial cells lining tubules with accumulation of cellular debris and multinucleated cells within the lumen. (Reproduced with the permission of Germann, P. and Morawietz, G. (eds.) *Toxicopathology Case Collection CD-ROM*. European Society of Toxicologic Pathology.)

Degenerative joint disease (DJD) is an umbrella term for progressive deterioration of synovial joints caused by trauma, aging, inflammation, or congenital abnormalities such as hip dysplasia. All tissue types associated with the joint (synovium, articular cartilage, subchondral bone, menisci [if present]) are affected by the degenerative process regardless of cause. A few pharmacologic agents (e.g., quinolone antibiotics) cause DJD by inducing chondrocyte necrosis of the articular cartilage. Inflammation causes more rapid and wider degeneration of the joint than other causes (e.g., septic arthritis, autoimmune arthritis, rheumatoid arthritis). Non-inflammatory causes of DJD (e.g., trauma, aging, congenital abnormalities) are more slowly progressive.

Differential diagnosis: **Chondromucinous degeneration**.
Synonym(s): **Osteoarthritis**.



Osteophyte with degenerative joint disease (DJD), femorotibial joint, medial meniscal tear model of osteoarthritis (OA), rat. On the left side of image, the medial tibial plateau (lower bone) and medial femoral condyle (upper bone) are devoid of articular cartilage, the subchondral bone plates at those sites are thickened, an osteophyte (arrow) projects above the eburnated surface of the medial tibial plateau, and a pseudocyst (arrowhead) is evident within the medial femoral condyle. Decalcified bone, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Fossey et al. 2016.)

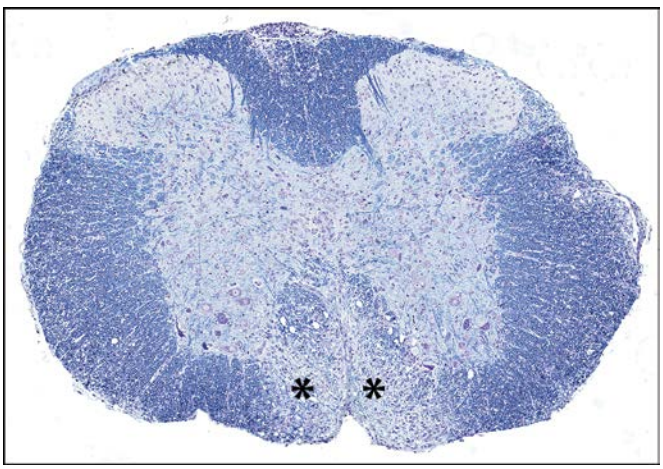
Delayed neuropathy is characterized by degeneration of distal axons in the peripheral and central nervous system and may occur 1–4 weeks after single or short-term exposure to some organophosphates. The effect is thought to be a result of inhibition of a neuropathy target esterase by acetylcholinesterase inhibitors.

Deletions refer to loss of a fragment of DNA or a chromosome. This is a type of genotoxic insult generally detected in chromosome aberration assays.

Demyelination is damage and loss of previously normal myelin, affecting oligodendrocytes of the central nervous system (CNS), Schwann cells of the peripheral nervous system (PNS), or both depending on the nature of the insult and susceptibility of myelin type. Damage and loss of myelin typically results in some degree of axonal damage; however, this is considered secondary to myelin insult.

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Demyelination has been associated with a variety of processes, including inflammatory, metabolic, viral, compressive, and toxic insults. Toxins may cause demyelination under natural or experimental conditions in a variety of species. Well-characterized examples include hexachlorophene, triethyl tin, buckthorn toxin, tellurium, cuprizone, actinomycin D, ethidium dibromide, diphtheria toxin, lead, and amphotericin B. Damage to myelin may be observed in detail by transmission electron microscopy; however, other methods may also be used to distinguish whether or not myelin is primarily affected. Some authors recommend hematoxylin and eosin (H&E) evaluation followed by examination of additional stains to distinguish myelin (Luxol fast blue stain, often in conjunction with periodic-acid Schiff [PAS] stain) and axons (Bielschowsky silver impregnation). Increasingly, immunohistochemical methods are used. For example, anti-MBP (myelin basic protein) and anti-CNP (2′, 3′-cyclic nucleotide 3′-phosphodiesterase) both label myelin sheaths (anti-CNP is also used to stain oligodendrocytes).



Demyelination in spinal cord white matter, experimental autoimmune encephalitis. Loss of myelin is indicated by decreased blue staining of the white matter of the ventral cord near the midline (asterisks). Mouse. Luxol fast blue.

Dendrites are neuronal cell processes that communicate with other neurons, forming an interlinked matrix.

Dendritic cells (DC) are bone marrow–derived cells of the monocyte lineage that are a key component of both adaptive and innate immune responses. DCs are morphologically characterized by having multiple cytoplasmic projections, or dendrites, which give these cells their name. They are found in regions of environmental contact, such as in mucocutaneous tissues including skin, gastrointestinal (GI) tract, and respiratory tract as well as in primary lymphoid tissues, such as thymus, and in secondary lymphoid tissues, such as lymph node, mucosa-associated lymphoid tissue (MALT), and spleen. DCs function in antigen presentation and thus are important in the initiation of cell-mediated immune responses such as those responsible for allergic contact dermatitis and the inflammatory response to other noxious stimuli, including toxins. Upon antigen capture and activation, DCs very quickly deliver antigenic signals to draining lymph nodes, homing to the outer paracortical region to contribute to B-cell responses as well as to T-cell activation. All DCs express major histocompatibility class (MHC) I and MHC II molecules as well as immune activation costimulatory molecules. There are several subpopulations of DCs that differ by their tissue location, the cell surface markers that they express, and their functionality. A specific type of DC, the plasmacytoid DC (pDC), named for its morphologic resemblance to a plasma cell, expresses CD45RA, CD123 and CD303 and secretes abundant type I interferons (IFNα) in response to nucleic acids via TLR7 and TLR9. pDCs may play a role in the pathogenesis of psoriasis and systemic lupus erythematosus (SLE). They have also been implicated in playing an antitumorigenic role. There is also a resident population of DCs within secondary lymphoid tissues, such as lymph nodes and spleen, called follicular dendritic cells (FDCs). These dendritic cells are distinct from the migratory DCs found in mucocutaneous tissue, as FDCs are resident, do not express MHC class II antigens, and hence do not function as antigen presenting cells. They function in the capture of opsonized antigens via complement receptors or FcγRI presentation. Upon antigen capture, FDCs produce the chemokine CXCL13, which functions to attract B-lymphocytes via the CXCR5 receptor. Binding of CXCR5 on B lymphocytes induces production of lymphotoxin-α, which further activates FDCs and produces a feedback loop. Thus, antigen-driven FDC stimulation of B lymphocytes functions to organize lymphoid follicular germinal centers. See also **Epidermal dendritic cell**.

Synonym(s): **Interdigitating cell**.

Denervation atrophy is the reduction of cross-sectional diameter and/or numbers of skeletal muscle fibers after loss of innervation. Skeletal muscle health is maintained by numerous factors, of which stress and load on the muscle during use in normal gravitational conditions is critical. Innervation of the muscle is necessary to enable action and use of the muscle, and without it the stimulus for use and load is lost. Denervation of an effector muscle can be temporary, as in the use of a neuromuscular blocking agent that does not alter the morphology of the motor endplate but does block neurotransmission. If this blockade is prolonged (e.g., botulinum toxins) there will be disuse atrophy of the muscles, which can recover once the toxin has been degraded. If the denervation is permanent (e.g., spinal cord injuries, stroke, nerve transections), disuse will lead to permanent atrophy. With these types of injuries, the denervation may not affect all muscles evenly, leading some muscles to contract while others become flaccid. Denervation atrophy may selectively affect certain muscles or muscle fiber types, depending on the neurotransmitters and specific nerves affected.

Dental calculus, see the preferred term **Dental tartar**.

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Dental cyst is a sac containing fluid or mucoid material in the jaw or soft tissue adjacent to a tooth. It has well-defined margins, but expansion of these space-occupying lesions may cause pressure and resorption of the nearby bone. Cysts generally form associated with an unerupted tooth that is in an abnormal position. Cysts may also form between the root of a deciduous tooth as it is being shed and the crown of the underlying permanent tooth, as well as at the apex of the root of a dead tooth.

Dental dysplasia is a developmental condition that can give rise to a rather chaotic mix of disordered tooth components as well as alteration of bone in the surrounding tooth alveolus. In mild dental dysplasia, the layers comprising the tooth (i.e., ameloblasts, enamel, dentin, odontoblasts, and tooth pulp layers) are recognizable, but often with reduced mass and with irregular borders. In more severe dental dysplasia, there may be no ameloblasts or enamel, very little dentin, and any odontoblasts present may be disordered and shrunken. Islands of undifferentiated epithelium may be present within the stellate reticulum of the pulp cavity. Other islands of abnormal material within the pulp cavity include dentin and bone. Denticles, resembling tiny teeth, may also develop within the stellate reticulum. The surrounding alveolar bone undergoes remodeling to compensate for the altered tooth structure, and there is generally more new woven bone replacing the normal surrounding layer of mature lamellar bone. Pharmaceutical compounds, such as smoothened inhibitors and other compounds that inhibit differentiation pathways occurring in embryonal development, cause dental dysplasia in the constantly growing incisors of rodents. Interestingly, if treatment ceases there may be recovery of normal tooth growth from the apex of the root. If treatment is prolonged, the tooth root cavity may fill with bone, at which point no recovery of normal growth can occur.

Differential diagnosis: Odontogenic neoplasia.

Dental plaque is a layer of biofilm-containing bacteria covering the surfaces of teeth within the mouth. The presence of dental plaque is normal and can be considered part of the microbiome; however, excessive plaque may be associated with the development of gingivitis, periodontal pockets, or dental caries. There may be a variety of bacteria present in plaque, including aerobic, anaerobic, filamentous, and sometimes vibrios or spirochetes. Dental plaque that develops on tooth surfaces above the gingiva (i.e., "gum line") contains predominantly aerobic bacteria, while dental plaque that extends onto the tooth surfaces below the gum line contains anaerobes. Subsequently, tartar, a mineralized layer, may develop in plaque and give tooth surfaces a yellow or brown appearance. Dental hygiene in humans includes daily tooth brushing to remove plaque. This may be done for some pets, such as dogs and cats. However, laboratory animals such as rodents are not treated this way and do not appear to be compromised from the plaque buildup. It is likely that the normal gnawing activity of rodents physically scrapes off plaque.

Differential diagnosis: **Dental tartar**.

Dental tartar is a mineralized accumulation of bacteria-derived plaque on the surface of teeth. This material can extend below the gum line contributing to inflammation of the gingiva and periodontium and can eventually contribute to periodontal disease.

Differential diagnosis: **Dental plaque**.

Synonym(s): **Dental calculus**.



Dental tartar on the teeth of a dog appears grossly as yellow to tan irregular material on the tooth surface.

Denticles are small tooth-like structures that arise from a separate island or fold of tooth developing epithelium. These may form in the tooth pulp or adjacent to a tooth, as a developmental anomaly or due to treatment with a compound that affects development of odontoblasts and ameloblasts. Denticles may contain only dentin or may have both enamel and dentin.

Differential diagnosis: **Pulp concretion**.

Dentin is mineralized dental matrix that is covered by and supports enamel. Dentin is produced by odontoblasts as predentin, which becomes mineralized after deposition. Odontoblasts extend cytoplasmic processes into dentin through dentin tubules; however, dentin does not have blood vessels or nerves.

Dentin decreased describes teeth that have an abnormally thin layer of dentin due to reduced odontoblast function or odontoblast degeneration. Affected teeth are fragile and subject to fracture during normal use.

Differential diagnosis: **Dentin niche**.

Dentin matrix alteration is a developmental defect in which odontoblasts produce dentin that lacks the normally strict, orderly appearance of straight tubules in matrix of normal thickness. The tubules may be crooked, and the dentin may contain cells or other inclusions. Dentin matrix, secreted by odontoblasts, is the collagenous material that is subsequently mineralized.

Differential diagnosis: **Dental dysplasia**.

Dentin niches are depressions or defects in the dentin surface adjacent to the pulp cavity that arise developmentally due to focal degeneration of odontoblasts. These may be multifocal and affect multiple teeth.

Differential diagnosis: **Dentin decreased**.

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Dependence is an adaptive state whereby the subject becomes dependent on something to the point where the removal of it results in a reduced ability to function, or other adverse effects on the organism. Classically, substance dependence develops with the repeated administration of that substance which provides a positive experience for the subject, whereas the withholding of that substance has a negative effect (withdrawal). Some drugs create dependence by producing a euphoric, reinforcing, or rewarding affect (e.g., heroin). Other drugs create dependence by feeding back on the body's own production of a similar chemical, and the withdrawal of the drug leaves the body unable to respond to normal stimuli (e.g., dexamethasone). This type of dependency requires the dosage to be decreased slowly to allow the patient to increase endogenous production. Dependency testing in animal models is a regulatory requirement for certain CNS active drugs, particularly those that cause animal behavioral changes associated with CNS stimulation or depression.

Depigmentation is used to denote a reduction in the amount of dark pigment (melanin) in a previously pigmented area of a tissue such as skin or hair. This may be seen in several nonclinical species when treated with molecules that target/destroy melanocyte antigens. It may also be diagnosed as a spontaneous finding in animals due to an acquired (immune-mediated) destruction of melanocytes. Depigmentation should be carefully distinguished from piebaldism, in which patchy areas of light skin result from congenital failure of melanocytes to migrate to the affected focus. Depigmentation may also be diagnosed as decreased pigment.

Dermal atrophy is characterized by the loss of dermal collagen fibers and dermal extracellular matrix components as well as by a decrease in size and sometimes number of dermal fibroblasts and mast cells. Dermal atrophy frequently accompanies epidermal and adnexal atrophy, and as such can be induced by the same agents, including corticosteroid hormones and antiproliferative compounds such as bleomycin.

Dermal edema is a change in the dermis characterized by separation of dermal collagen fibers, with the interfiber space ranging from completely clear to containing pale-staining, sometimes finely granular, eosinophilic or amphiphilic material (edema fluid). Dermal edema is most commonly found in association with dermal inflammation. It can also occur in the abdominal skin when secondary to prolonged immobility and associated vascular stasis. Dermal edema can be an incidental spontaneous finding with no apparent underlying cause in mice.

Dermal irritation tests are performed with all formulations intended for topical application; however, many pharmaceutical drug products and drug substances are also tested to ensure safe use in the production and formulation facilities. Agents suspected as being corrosive are generally tested in reconstituted human epidermal systems in vitro before in vivo experiments, for animal welfare reasons. In vivo dermal irritation testing is described in the OECD test guideline #404. Such studies are preferentially performed in rabbits, and generally with a 4-hour application period, after which skin reactions are assessed for irritation (e.g., erythema, edema, eschar formation) and graded at period intervals up to 14 days.

Dermal sensitization, see **Skin sensitization** for further information.

Dermal toxicity tests are done with topical formulations and are preferentially performed in minipigs as the non-rodent model, since minipig skin has similar anatomical and physiological properties to human skin. Such studies not only assess the local response at the site(s) of application, but also assess systemic effects in a manner similar to toxicity studies by other routes of administration. Dermal penetration of the compound is assessed by monitoring plasma levels of the agent (and/or major metabolites if applicable), and tissue levels may also be measured at necropsy. See **Minipigs in dermal studies** for further information.

Dermatomycosis is a superficial fungal infection of the skin caused by dermatophytes, yeast, or other fungi. It is more common in immunosuppressed or immunologically naïve individuals and most commonly occurs in moist or covered areas, such as within skin folds or on the feet. Common names for dermatomycosis include ringworm or athlete's foot.

Synonym(s): **Dermatophytosis**.

Dermatophytosis, see the preferred term **Dermatomycosis**.

Dermis is the collagenous layer of skin underlying the skin surface (epidermis) and attaching to the deeper subcutis. Refer to **Skin** in Appendix 3 for further information.

Dermoid cyst is a tumor of embryonic origin (teratoma) lined with epidermis, and containing hair follicles, sebum, keratin, and occasionally other tissues. Refer to **Skin** in Appendix 2 for further information.

Descemet's membrane increased thickness, see the preferred term **Corneal Descemet's membrane hypertrophy**.

Developmental toxicity refers to abnormal or impaired morphological or functional development at birth caused by exposure to toxicants or teratogens during gestation.

Development and reproductive toxicology (DART) refers to a series of preclinical animal studies needed to assess human risk for a xenobiotic's effect on male and female reproductive health, and embryonic and neonatal development.

Diabetes insipidus (DI) is a medical condition described in dogs, cats, ferrets, pigs and nonhuman primates in which there is excessive urination (polyuria) and water consumption

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(polydipsia) due to disturbances of antidiuretic hormone (ADH) production, or target organ (kidney) ADH response. When ADH production from the hypothalamus or release from the pituitary gland is decreased, the signal to concentrate urine at the level of the kidney is lost, leading to central DI. Alternatively, kidneys that are diseased may become resistant to the effects of ADH, resulting in nephrogenic DI. During pregnancy, there may be transient DI, due to the degradation of ADH by the placenta. Central DI may result from tumors, injury, inflammation, or may be idiopathic. Chronic renal fibrosis/sclerosis can result in DI due to ADH receptor loss or diminished responsiveness.

Diestrus is the phase of the estrus cycle characterized by sexual quiescence between periods of estrus. The corpora lutea develop. If there is no fertilization, this phase terminates with the regression of the corpora lutea. See **Female reproductive hormones** for further information.

Dietary nephropathy refers to the influence of diet on the incidence and severity of renal disease. An example is protein content and quality in rat diets. Low protein content is associated with less severe chronic progressive nephropathy (CPN) in the aging laboratory rat, while high protein content leads to enhanced CPN severity. Overnutrition on a caloric basis also modulates the incidence and severity of renal disease over time.

Differentiation is the process by which immature and/or pluripotent cells, tissues, organs reach a mature and/or specialized function.

Diffuse is a modifier that can be attached to a diagnosis to indicate that the specific finding is spread over a wide area of the tissue. It is an adjunct to severity grades in communicating the relative significance of a finding. For common test article–related findings such as degeneration, necrosis, and inflammation, the use of modifiers such as diffuse, multifocal, or focal often helps to communicate the likelihood that they are spontaneous or test article–mediated.

Diffuse gliosis, see the preferred term **Retinal atrophy, global**.

Dilatation of a hollow organ or vessel occurs when there is an increased amount of normally occurring (or produced) substance (e.g., fluid, ingesta) or by the presence of a substance normally not occurring or produced in this organ (e.g., air). Hollow organs such as the heart, esophagus, stomach, and intestine can show this change with expansion of the cavity, ducts, or lumen.

Synonym(s): **Dilation**.

Dilated central canal of the spinal cord, see the preferred term **Hydromyelia**.

Dilation, see the preferred term **Dilatation**.

Dismorphogenesis is the anatomical alteration of fetal external morphology.

Dissecting osteoclasia, see the preferred terms **Bone increased eroded surface** and **Osteoclasts increased**.

Distal convoluted tubule (DCT) is the portion of the nephron past the loop of Henle which then loops back to touch the associated glomerulus at the juxtaglomerular body. It then proceeds to connect to the collecting duct. Normal proximal and distal convoluted tubules are morphologically distinct and can be identified separately. See Appendix 3 for more information.

Diuresis is increased urine production by the kidneys leading in increased urine volume and decreased water in the circulatory system. The most common form is osmotic diuresis caused by excess sugar in the blood (e.g., in diabetes mellitus). Diuresis can be controlled by antidiuretics such as vasopressin (antidiuretic hormone; ADH), angiotensin II, and aldosterone.

Diuretics are substances that promote diuresis (i.e., increased urine production). Pharmacologically, diuretics such as hydrochlorothiazide and furosemide are used to help control high blood pressure by increasing the excretion of water from the cardiovascular system.

Diverticulum is an outpouching in the wall of a hollow organ or tissue. The formation of a diverticulum is generally caused by structural disruption of the wall of the organ or tissue, leading to loss of extracellular matrix integrity and projection of the surface lining into deeper layers. Diverticula may be induced by chronic infections, may be secondary to repair of ulcerative lesions, or may represent a congenital abnormality. In the gastrointestinal tract, diverticula can be cystic, with compression of surrounding structures. Diverticula can also have atypical features with clusters of dysplastic epithelial cells that appear to be "invading" into deeper layers.

DNA adducts are the products of covalent binding of a molecule to DNA. If of sufficient size and shape, such adducts can lead to mutations by disrupting DNA replication and facilitating the pairing of a different base than was originally in the opposite DNA strand.

DNA bank, see the preferred term **DNA library**.

DNA cloning, see the preferred term **Molecular cloning**.

DNA crosslinks is covalent binding of the two complementary DNA molecules to each other. Chemicals capable of crosslinking generally contain multiple functional groups. DNA crosslinking can lead to genetic damage, such as clastogenicity, but if extensive it is generally cytotoxic.

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DNA damage and repair tests are assays that use primary DNA damage (e.g., DNA fragmentation or adduct formation) to assess the genotoxic potential of agents. Examples are the Comet assay and the unscheduled DNA synthesis (UDS) assay.

DNA-dependent DNA polymerases, see the preferred term **DNA polymerases**.

DNA fingerprinting is used to determine the individual DNA sequence profile of a person. This assay uses highly variable regions of repetitive sequences, the likelihood being minimal that they are identical between two individuals.

DNA footprinting is a method to study DNA-protein interaction. The method relies on the protection of a DNA sequence from DNA-cleaving enzymes when proteins are bound to the sequence.

DNA hybridization is the binding of two strands of DNA and/or RNA by pairing of the complementary base sequences. Specific binding of this type is the basis of the in situ hybridization technique for visualizing gene expression in tissue sections.

DNA library is a collection of DNA fragments of a complete genome or genomic cDNA cloned into vectors and transferred into bacteria. The library permits isolation and analysis of distinct genomic segments.

DNA ligases are enzymes that catalyze the joining of DNA strand ends via the formation of phosphodiester bonds, a process known as DNA ligation. They are involved in the repair of both DNA single and double strand breaks.

DNA melting is the thermal separation of the two complementary strands of DNA by cleavage of the interaction of the complementary DNA bases. The temperature at which such strand separation occurs is a property of the DNA sequence, since bases that form triple bonds (guanine with cytosine) are melting at higher temperatures than double-bonded base pairs (adenine-thymine).

DNA methylation is the chemical addition of methyl groups to specific sites on DNA bases, most commonly on the C5 of cytosine to form 5-methylcytosine, a process catalyzed by DNA methyltransferases. Methylation often occurs on cytosines adjacent to guanidine residues and is often accompanied by methylation of the corresponding cytosine on the other DNA strand. DNA methylation is an important part of the epigenetic modification of chromatin to modulate transcription. Generally, DNA methylation leads to a suppression of transcription, that is, the silencing of genes.

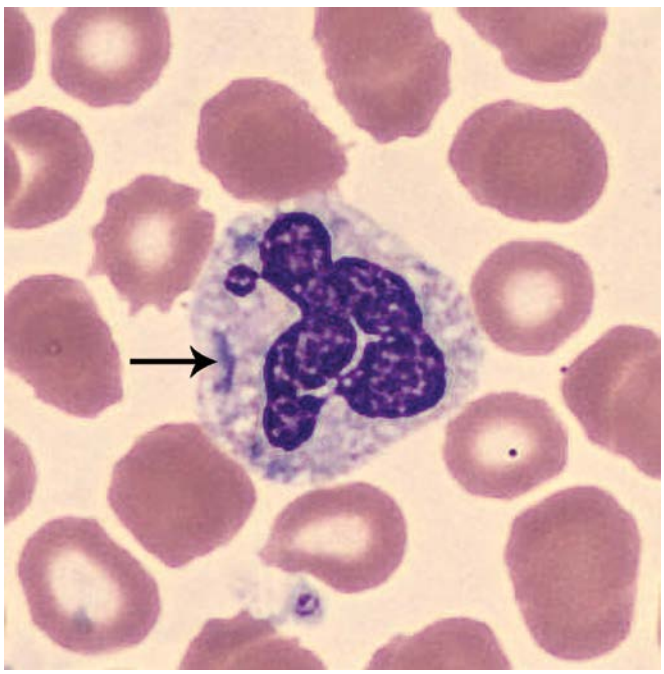
DNA polymerases are enzymes that synthesize the second DNA strand, using deoxyribonucleotides and the first DNA strand as a template, thus generating a DNA double strand. This activity is key to the process of cell division but is also involved in DNA repair.

DNA repair involves enzymatic processes to protect the integrity of the DNA by repairing DNA damage. Several different mechanisms are available, thus allowing for the repair of various types of damage. The induction of DNA repair is used as an indirect measure of the occurrence of DNA damage. See **Unscheduled DNA synthesis (UDS) assay** for further information.

DNA replication is the reduplication of the DNA strand. Both strands of the double-stranded DNA are separated, and each strand is used as a template to generate the other complementary strand, a process catalyzed by DNA polymerases that serve to multiply the DNA for cell division during S-phase of the cell cycle.

DNA vector is a genetic construct, mostly plasmid or virus, that is able to transport DNA sequences into host cells.

Döhle bodies are blue to gray, round to angular cytoplasmic inclusions approximately 1–3 μm in diameter composed of lamellar aggregates of rough endoplasmic reticulum that can be observed in neutrophils and their precursors. They are often observed following acute cases of hematopoietic injury (i.e., cytotoxic drug administration) or in the presence of inflammation. Döhle bodies and other cytoplasmic changes (i.e., basophilia and vacuolation) are caused by accelerated bone marrow maturation and development induced by inflammatory mediators and cytokines. Döhle bodies may rarely be observed in neutrophils of healthy animals.



Döhle bodies, blood smear, cynomolgus monkey.

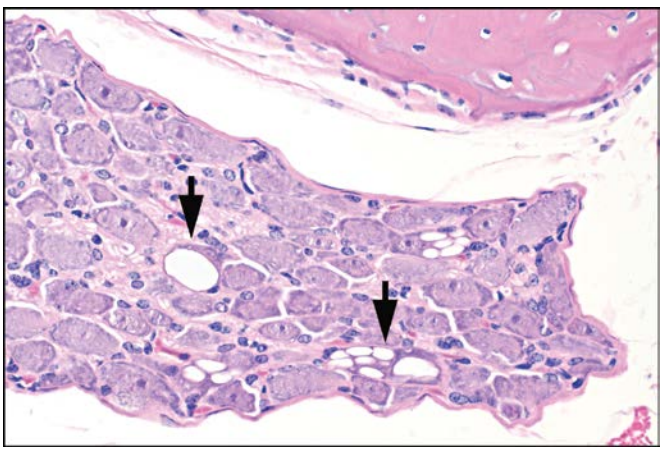
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Dominant lethal test is a rodent assay for germ cell mutations. Male animals are treated with the test compound and mated with untreated females. After mating, the females are then assessed for embryo- or fetolethal effects (implantation sites, abortions, and fetal deaths). An increased incidence of embryo-fetal mortality is an indication that mutations have been induced in the sperm-producing cells. The assay is not commonly used in drug development; rather, germ cell mutagenicity is assessed by estimating the risk on the basis of data obtained in vitro or in somatic cells in vivo.

Dominant visible mutations are generally recessive in diploid organisms, which means that when one allele is mutated, the unmutated (wild type) copy will be used for the function. However, there are cases where a mutation is dominant, that is, it will result in the mutant phenotype even in the presence of an unmutated allele.

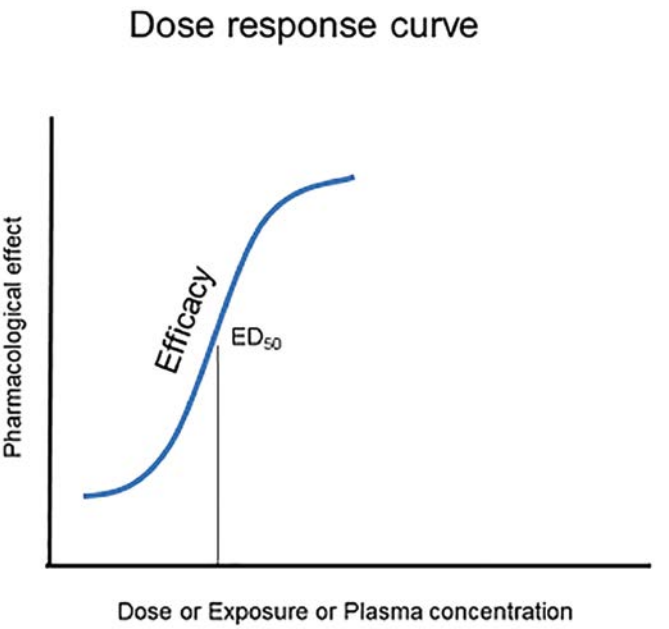
Dopamine, see the preferred terms **Catecholamine** and **Prolactin-inhibiting hormone**.

Dorsal root ganglion vacuolation is characterized by membrane-bound spaces devoid of cytoplasm within sensory neurons found in the dorsal (quadrupeds) or posterior (bipeds) spinal nerve roots. Vacuoles are also commonly found in the vestibulocochlear nucleus, in white tracts throughout the brain and spinal cord, and occasionally in gray matter. Vacuoles may be artifactual, spontaneously occurring, secondary to axonal injury, or due to the direct effects of a neurotoxin.



Cytoplasmic vacuoles (arrows) within ganglionic neurons. Dorsal root ganglion. Mouse. H&E. (Copyright 2018 Pfizer.)

Dose-response curve is a simple X-Y graphical representation of the change in effect on an organism caused by increasing levels of exposure (dose or blood concentration) of a chemical (i.e., drug, toxic agent, etc.) or other stressor (e.g., heat, ionizing radiation, infectious agent).



A dose-response curve showing the derivation of ED_{50}.

Draize scale technique has been commonly utilized for quantitatively determining the degree of irritation caused by topical application of compounds and providing a quantitative measure of comparison and differentiation of the irritation potential of various compounds (e.g., minor irritants vs major irritants). This technique was adapted in the United States by the Code of Federal Regulations (CFR 1980) and is legislated under provisions of the Federal Hazardous Substances Act. The Draize scale evaluates the degree of redness (i.e., erythema), crust or scab formation (i.e., eschar), and edema. For evaluation of dermal irritancy potential, the Draize technique involves application of test substance to a defined area on the skin of rabbits, guinea pigs, or other animal models (e.g., minipigs). Solutions may be applied directly to the skin surface, whereas solid substances are first dissolved in an appropriate solvent or moistened before application. The application site is covered by a semiocclusive dressing (e.g., gauze). The test typically involves six animals, each with four to six defined patch test areas. Testing is conducted on intact skin but may be adapted for abraded skin if dictated by the indication of use (e.g., wound healing). Observations of skin reactions are made at 4, 24, and 72 hours after application and rated according to the Draize scale. Histopathologic evaluations are not usually conducted in skin irritation evaluations using the Draize scale technique but are a critical component in repeated-dose dermal toxicity testing.

Drug-drug interactions (DDIs) occur when one drug interferes with either the pharmacology or the clearance of another drug, when patients are comedicated. Pharmacological interactions may occur when one drug potentiates or inhibits the desired pharmacology of the other. Pharmacokinetic interactions occur when one drug alters the disposition of the other by

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enzyme induction, activation, or inhibition. Pharmacokinetic DDIs are particularly problematic when the clearance of a drug with a narrow therapeutic margin is altered. Many drug-drug interactions result from inhibition of cytochrome P450 and thus it is customary to examine the ability of a drug candidate to inhibit cytochrome P450 isozymes and specific drug transporters during drug discovery using in vitro methods. If in vitro studies indicate that a drug may have the potential for drug-drug interaction, then clinical studies to examine that potential may be warranted. Both the FDA and EMA have guidance on studies to be performed during drug development to determine the interaction potential of a drug candidate. (In vitro metabolism and transporter-mediated drug-drug interaction studies. Guidance for industry. FDA, Clinical Pharmacology, October 2017; Guidance on the investigation of drug interactions, EMA June 21, 2012.)

Drug-induced glomerulonephritis, see the preferred term **Drug-induced nephrotoxicity**.

Drug-induced nephrotoxicity refers to a wide variety of chemicals, drugs in many different classes, and environmental toxins that are known, or have potential, to damage the kidney and affect renal function, especially in compromised individuals or those with comorbidities.

Drug-induced vasculitis is induced by a wide range of compound classes. Arteries and veins differ in their response to stress and xenobiotics due to structural and physiological differences. Similar blood vessels in different areas or organs also vary in their response to xenobiotics due to differences in humoral factors or innervation, surrounding cell populations, or other factors. Mechanisms are varied, and direct toxicity affecting one or more components of the vessel wall can occur. Indirect mechanisms include increased diffuse or segmental hemodynamic stress. Many pharmaceutical classes, such as B-adrenergics and PDE-4 inhibitors, exert their effects through repeated, localized dilation or contraction, causing pressure or overwork stress resulting in damage to the media. This can result in hemorrhage, fibrinoid necrosis, inflammation, and even rupture of the vessel wall. Antigen-antibody complex deposition with complement activation occurs with administration of antibodies or drug-antibody complexes.

Drug metabolism is the process involved in the metabolic alteration of drugs, generally as part of metabolic clearance and excretion. Exceptions are the conversion of prodrugs to the active pharmacological principal, and the formation of pharmacologically active metabolites. Drug metabolism often involves the incorporation of a polar group which makes the drug more water soluble. Traditionally, drug metabolism has been divided into two phases: Phase 1 metabolism involves oxidation, reduction, or hydrolysis, whereas Phase 2 metabolism involves the introduction of water-soluble groups by conjugation. More recently, the process of efflux through drug transporters has been termed Phase 3 metabolism. See **Phase 1, 2, and 3 metabolism** for further information.

Enzymes catalyzing Phase 1 metabolism include cytochromes P450 (CYPs), a family of monooxygenases which reduce oxygen in a process that results in the incorporation of one atom of molecular oxygen into the xenobiotic substrate (hence the term monooxygenase). The cytochromes P450 are heme-containing proteins that derive their name from the spectral absorption maximum of the heme-carbon monoxide complex and catalyze the oxidation of a wide variety of endogenous and xenobiotic compounds, accounting for the formation of the majority of oxidized drug metabolites. However, a variety of other oxidative enzymes including flavine-containing monooxygenases, peroxidases, monoamine oxidases aldehyde oxidase, xanthine oxidase, and dehydrogenases (alcohol and aldehyde) are also known to catalyze drug oxidation. Reductive processes may be catalyzed by aldo-keto reductases and azo-reductases and may also involve reductive dehalogenation. Hydrolytic enzymes include epoxide hydrolase and a variety of esterases and amidases.

Enzymes catalyzing Phase 2 conjugations include glutathione transferases, UPD glucuronosyl transferases, methyl transferases, sulfonyl transferases, *N*-acetyl transferases, and glycine *N*-acyl transferases, which result in glutathione conjugation, glucuronidation, methylation, sulfation, acetylation, and glycine conjugation, respectively. These conjugated metabolites are more water soluble, and therefore readily excreted.

Drug transporters are membrane-bound proteins that facilitate transport of drugs across cell membranes. Many drugs may cross biological membranes by free diffusion, in which case the amount of uptake may depend upon the pH and ionization of the compound but otherwise is governed by Fick's law of diffusion (diffusion from a high concentration to the low concentration at a rate proportional to the concentration gradient). However, for many drugs physical characteristics such as molecular weight, lipophilicity, and degree of ionization limit free diffusion such that cellular and tissue uptake is dependent on drug transporters. As a consequence, in such cases the transport proteins, which are generally integral membrane proteins, are intimately involved in the absorption, distribution, and excretion of the drugs. Comedication or dietary components may inhibit or activate transporters, altering the pharmacokinetics of the drug, resulting in drug-drug interactions leading to effects such as decreased efficacy or increased toxicity. Transporters are also involved in the disposition of endogenous substances; thus, drug candidates that affect transporter function can interrupt physiological processes, causing toxicity. For example, inhibition of the bile salt export pump (BSEP) reduces the ability to excrete bile salts, resulting in cholestasis. Consequently, it is important to characterize transporters involved in the disposition of a drug candidate and the effects of the drug candidate on transporter activity.

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Drug transporter proteins may be divided into two main categories: solute carrier transporters and ATP-binding cassette transporters. See **Solute carrier transporters** and **ATP-binding cassette transporters** for further information.

Drusen, see the preferred term **Retinal extracellular matrix deposits**.

D

Drusen-like deposits, see the preferred term **Retinal extracellular matrix deposits**.

Ductal cell tumor (benign or malignant) is considered synonymous with **cholangioma** (benign) or **cholangiocarcinoma** (malignant). See **Cholangioma** and **Cholangiocarcinoma** for further information.

Duct-associated lymphoid tissue (DALT) is the lymphoid tissue found adjacent to ducts of glandular tissues including the periorbital lacrimal glands, salivary glands, pancreatic ducts, and reproductive glands, in the absence of other indicators of inflammation. Although associated with ducts, these lymphoid aggregates are acquired, and appear to be functionally similar to mucosa-associated lymphoid tissue (MALT).

Differential diagnoses: **Periductular inflammation**; **Periductular inflammatory cell infiltrate**.

Ductular calculus refers to the formation of basophilic to eosinophilic, thickened material within the duct of a salivary gland. With time the material may form concentric whorls and appear mineralized. There may be associated ductular dilatation, fibrosis, or inflammation surrounding the calculus.

Synonym(s): **Concretion (ductular or tubular)**.

Ductular ectasia, see the preferred term **Cystic dilatation**.

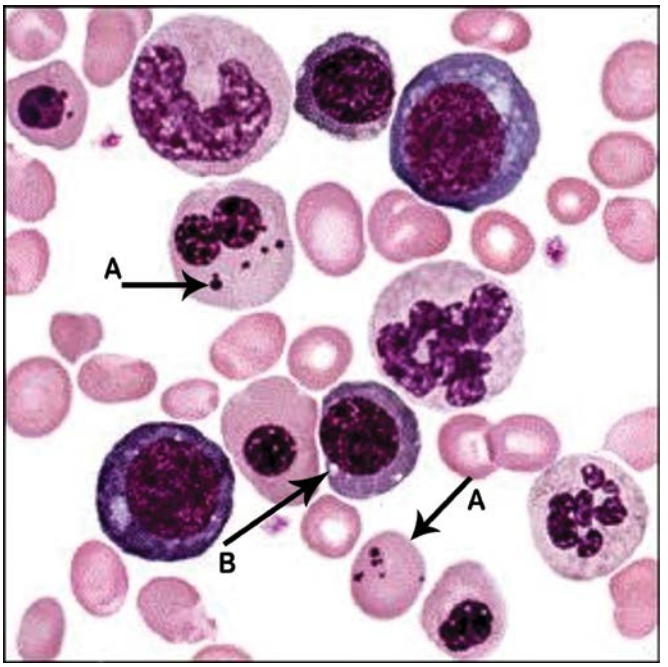
Ductular metaplasia is a transition from any normal epithelial type to a ductular phenotype. Ductular metaplasia is often a reactive change following damage to the acini of a gland, such as that caused by chronic inflammation. Ductular metaplasia occurs, for example, in the exocrine pancreas, and is comprised of variably sized ductules generally lined by flat, cuboidal epithelium. These tend to be circumscribed lesions surrounded by normal exocrine acini.

Dura mater is the third and outermost layer of the meninges that forms a thick, fibrous covering around the brain and spinal cord. The dura mater is adhered to the internal surface of the skull, but within the vertebrae of the spinal column there is a separation called the epidural space. Nerves and blood vessels that traverse the meninges do so within a cuff of dura, which in nerves becomes continuous with the external surface of the epineurium.

Dying back axonopathy, see the preferred term **Axonal degeneration**.

Dyscoria, see the preferred term **Optic fissure malformation**.

Dyserythropoiesis is a term used to describe abnormal erythroid development that can be either megaloblastic or dysplastic. Folate and B_{12} deficiency result in megaloblastic abnormalities that often contain nuclear and cytoplasmic dyssynchrony. Megaloblastic dyserythropoiesis often demonstrates an immature nucleus when compared to the degree of cytoplasmic maturation. Chromatin may be more open and immature than expected for the degree of cytoplasmic hemoglobinization present. Dysplastic nucleated red cells can have strikingly abnormal features including nuclei that are lobulated, multilobulated, fragmented, or multinucleated. At times the dysplastic nuclei can be so multilobulated that the nucleated red blood cell can resemble the nuclei of polymorphonuclear leukocytes. The cytoplasm of dysplastic erythrocytes can contain vacuoles, multiple Howell-Jolly bodies, or coarse basophilic stippling. Associated disease states and conditions include vitamin B_{12} deficiency, folate deficiency, erythroleukemia, acute myeloid leukemias, myelodysplasias, heavy metal poisoning, ethanol intoxication, and antimetabolites.

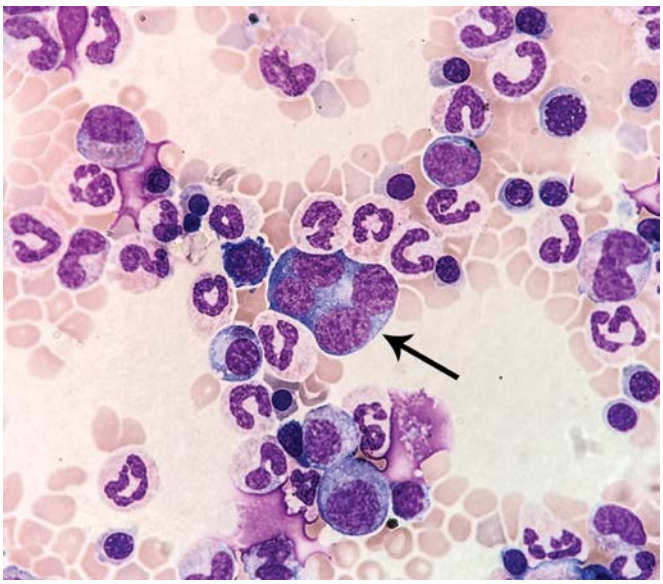


Dyserythropoiesis, bone marrow, includes features such as bilobed erythroblasts, multiple Howell-Jolly bodies (A), and vacuoles within erythroblasts (B).

Dysgerminoma is a rare ovarian neoplasm characterized by effacement of the normal architecture by a monotonous, undifferentiated round cell population. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Dysgranulopoiesis is characterized by abnormal granulocyte precursor cell maturation and/or morphology. Morphologic abnormalities include small myeloblasts and promyelocytes, asynchronous maturation, maturation arrest, abnormal granulation, abnormal mitosis, hyposegmentation, hypersegmentation,

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Dysgranulopoiesis (arrow), bone marrow, cynomolgus monkey.

and giant neutrophils. It usually occurs with myelodysplastic syndrome (especially refractory anemia with excess numbers of blasts), acute myeloid leukemia, and drugs such as lithium and valacyclovir. Diagnosis is made via a bone marrow biopsy and cytologic and/or histopathologic evaluation.

Dysplasia is a term derived from the Latin *dys*, meaning abnormal and *plasia*, meaning growth or formation. In pathologic terms, dysplasia indicates an abnormality of morphology. It may be applied to gross or microscopic changes in which the tissue or cells exhibit a form that is outside the range of normal. In some cases, dysplasia is believed to be a precursor to neoplasia.

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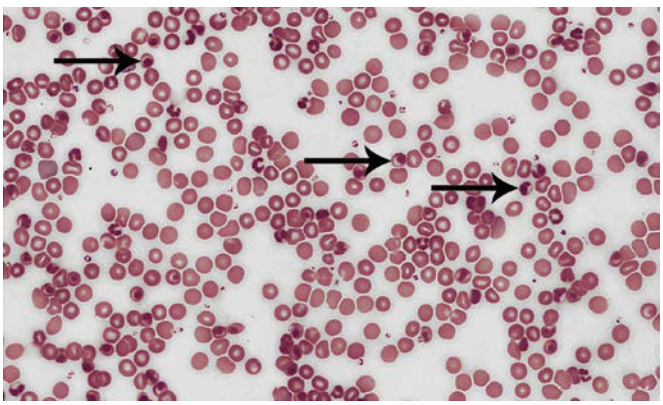


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E

Eccentrocyte is a red blood cell that has its hemoglobin shifted to one side. The abnormality is restricted to the red blood cell membrane or cytoskeleton. The condition is induced by oxidant damage. The term eccentrocyte is more commonly used in veterinary hematology cases and has been reported in dogs following ingestion of onion or garlic or other oxidant drugs. In contrast, the term "blister cell" is more commonly used in human medicine, but morphology is similar, and both are induced by oxidant damage. Subsequent staining with vital stains such as methylene blue or crystal violet typically allows the identification of Heinz bodies. It is believed that splenic removal of the precipitated hemoglobin results in tearing of the red blood cell membrane. Resealing of the membrane results in the eccentrocyte, blister cell, or bite cell morphology. Eccentrocytes are fragile red blood cells and undergo accelerated rates of destruction.

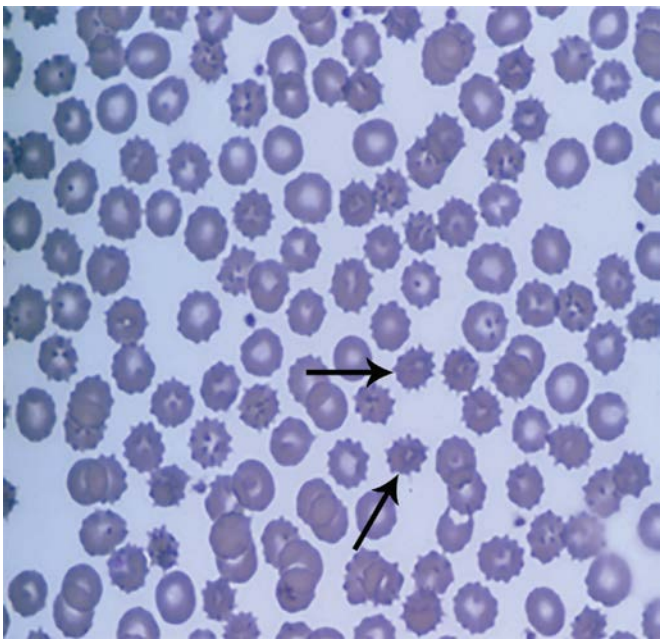


Eccentrocytes (arrows), blood smear, rat.

Ecchymosis is a type of macule or hemorrhagic patch, larger than a petechia, in the skin or mucous membrane, forming a flat, rounded or irregular, blue or purplish patch. See **Macule** and **Petechiae** for further information.

Eccrine gland carcinoma is a malignant neoplasm arising from areas where eccrine glands are present and usually in the paw area. These tumors are not common but have been reported in transgenic mice, may or may not have the cytologic features of malignancy (e.g., cellular atypia, mitotic figures), and may be cystic. Refer to **Skin** in Appendix 2 for further information.

Echinocyte is an abnormally shaped red blood cell in which the erythrocyte has short, evenly spaced spicules over the entire surface of the cell. Echinocytes are commonly observed as an artifact of EDTA blood that has had prolonged storage. However, they can also be observed in a broad variety of diseases and conditions including hemolytic anemia, burns, renal failure, doxorubicin chemotherapy, neonatal hypoxia, upper gastrointestinal hemorrhage, phosphoglycerate kinase deficiency, and pyruvate kinase deficiency.

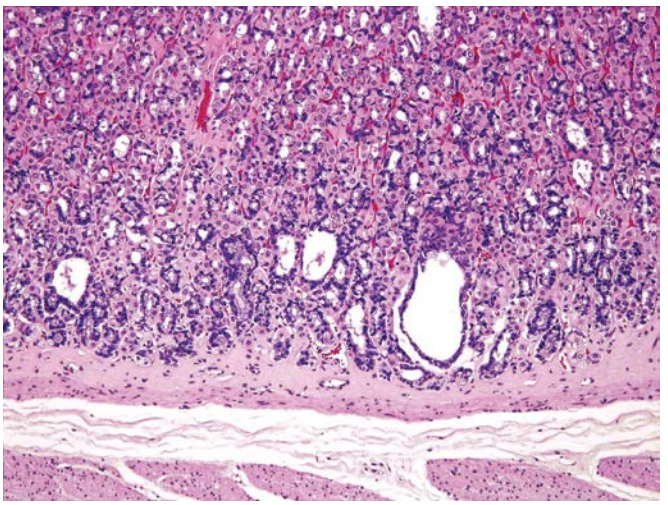


Echinocytes (arrows), blood smear, rat, following prolonged storage in EDTA. Note the even distribution of short spicules over the entire red cell surface.

Ecological risk assessment is defined by the U.S. EPA (United States Environmental Protection Agency) as "evaluating the likelihood that the environment may be impacted as a result of exposure to one or more environmental stressors such as chemicals, land change, disease, invasive species and climate change." In the pharmaceutical industry, an environmental impact assessment is required for drug registration, and defines the ecological impact of drug substance, drug product, and packaging, among other factors.

Ectasia is the expansion of a luminal space within a tissue substructure, such as a duct, sinus, alveolus, or glandular lumen.

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Ectasia of glands within the glandular portion of the stomach of a rat, H&E. The lumina of glands near the submucosal junction (bottom) are markedly expanded 2 to 10 times normal size by clear space. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

Ectopic adrenal rest, see the preferred term **Adrenal rest**.

Ectopic bone formation is bone formation outside of the skeleton. This can occur either as a result of trauma (e.g., heterotrophic ossification in skeletal muscle), toxicity, or local pharmacology (e.g., bone morphogenetic protein (BMP-2) administration).

Differential diagnosis: **Mineralization**.

Ectopic Harderian gland, see the preferred term **Harderian gland alteration**.

Ectopic lymph node, see the preferred term **Tertiary lymphoid structure**.

Ectopic lymphoid follicle, see the preferred term **Tertiary lymphoid structure**.

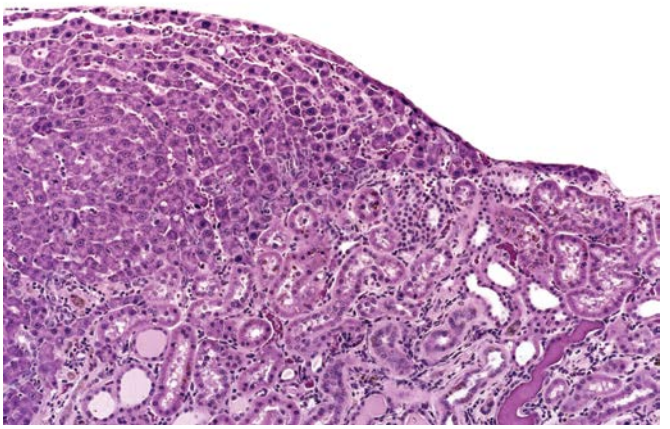
Ectopic neuron is a developmental anomaly of no functional consequence characterized by abnormal positioning of neurons in the peripheral or central nervous system.

Ectopic sebaceous gland in the oral cavity is a developmental finding in the oral mucosa of rats characterized by the presence of aggregates of ectopic dermal sebaceous glands (Fordyce granules) that are more commonly associated with the gingival mucosa of the upper incisors. This is reported primarily in male F344 rats, and is of little or no apparent pathologic significance. This may appear grossly as a white nodule or cyst in the gingival mucosa and consists of normal sebaceous gland acini with ducts opening to mucosal surface.

Differential diagnosis: **Sebaceous cell adenoma**.

Synonym(s): **Fordyce granules**.

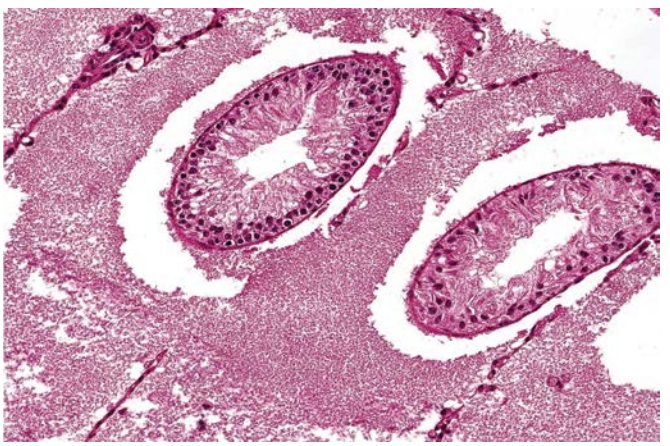
Ectopic tissue refers to the presence of a well-differentiated focus of a different adult tissue within another normal adult tissue. This is often seen in tissues that were adjacent to each other during some stage of embryogenesis. For example, islands of thymic tissue may be seen within or adjacent to the thyroid gland, while spleen (splenunculi) may be seen in the pancreas or omentum. The use of this term suggests that the focus of differentiated tissue was present at birth.



Ectopic liver tissue in the kidney of a rat, H&E. An aggregate of normal hepatocytes (upper left) sits adjacent to otherwise normal tubules of the cortex of the kidney. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

ED_{50} (median effective dose) is a measure of the efficacy of an agent. It is the concentration or dose at which the agent elicits the median biological or biochemical response (50% of the maximal positive response). The ED_{50} can be calculated as a ratio of the toxic dose to yield the therapeutic index (TI). See **Therapeutic index** for further information.

Edema is increased fluid in the interstitial tissue spaces. Edema in the lungs also accumulates in alveolar lumina. See **Exudate** and **Transudate** for further information.



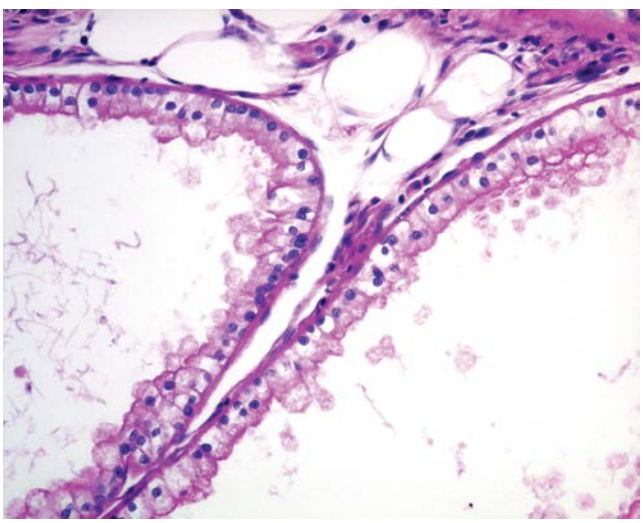
Edema in the testis of a rat, H&E. Seminiferous tubules are separated by increased space containing proteinaceous fluid. There are also decreased numbers of germinal epithelial cells lining these seminiferous tubules (atrophy). (Reproduced with the permission of Germann, P. and Morawietz, G. (eds.) *Toxicopathology Case Collection CD-ROM*. European Society of Toxicologic Pathology.)

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Effective concentration (EC) refers to the lowest concentration of an agent in the test system that will produce the desired therapeutic effect. Often the concentration showing half of the maximum response (EC_{50}) is used as a measure efficacy. The ratio of the EC and the toxic concentration is the therapeutic index. See **Effective dose** and **Therapeutic index** for further information.

Effective dose (ED) refers to the lowest dose of an agent that will produce the desired therapeutic effect. Often the dose showing half of the maximum response (ED_{50}) is used as a measure of efficacy, especially when comparing the efficacy of different compounds. The ratio of the ED and the toxic dose may also be referred to as the therapeutic index. See **Effective concentration** and **Therapeutic index** for further information.

Efferent ductal and epididymal epithelium degeneration is characterized by cellular vacuolation and/or atrophy. The subsequent breakdown in the immune-privileged blood-epididymal barrier may result in ductal sperm depositing in extraductal tissue, and the formation of sperm granulomas. In the rat, xenobiotic-induced epithelial degeneration with sperm granuloma formation has been known to occur with methyl chloride inhalation. Epithelial degeneration has also been rarely noted as a spontaneous background lesion.

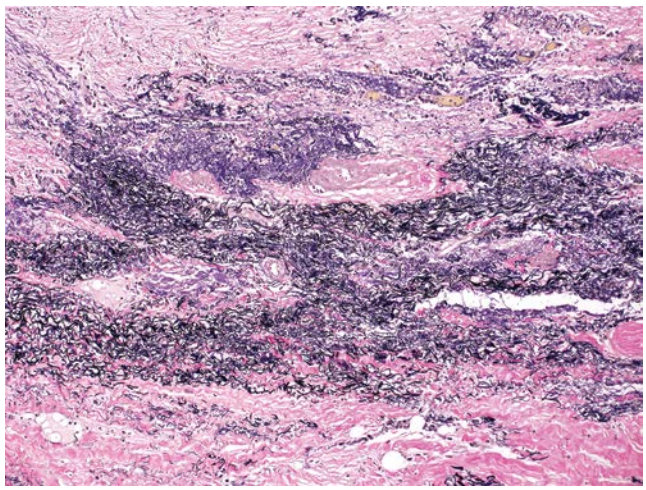


Degeneration, epididymal epithelium, rat, H&E.

Effusion is extravasation of fluid into the body cavities (e.g., hydrothorax, hydroperitoneum, hydropericardium). See **Exudate** and **Transudate** for further information.

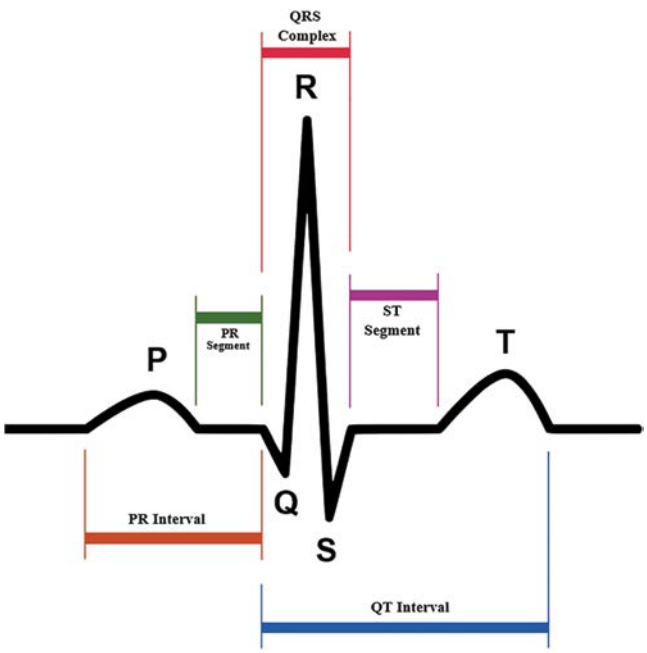
Elastosis is a degenerative change in the upper dermis of the skin with accumulation of tangled masses of abnormal elastic fibers, which are irregular, thickened, and mostly oriented parallel to each other. Elastic fibers in the skin are part of the extracellular matrix that maintains skin elasticity and recoil response after stretching, and in animals (other than humans) are involved in hair or feather movement. Degeneration of elastic fibers, coupled with their slow regenerative and repair processes, results in wrinkling of skin with aging. Elastosis is most commonly a response to excessive exposure to ultraviolet light (e.g., solar elastosis or actinic elastosis), and is seen in humans as part of photoaging. Skin with solar elastosis is prematurely aged with inelasticity, thinning or thickening, wrinkling, and drying, and is often accompanied by other changes associated with excessive UV exposure.

On hematoxylin and eosin (H&E)-stained sections, elastic fibers are lightly basophilic, but are best visualized with special stains that can include Orcein or Verhouff Van-Gieson stains.



Elastosis in photoaged human skin with solar elastosis. Elastic fibers stained black with Verhouff Van-Gieson stain.

Electrocardiogram (ECG, EKG) is a measure of the electrical activity of a heartbeat. It is recorded as a set of "waves" passing through the heart (see diagram.) The initial P wave is



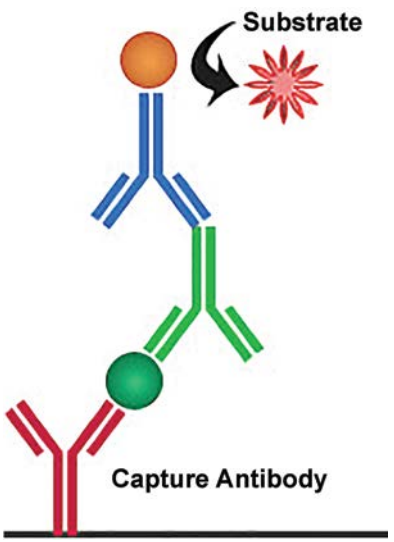
An electrocardiogram showing the different waves and intervals.

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formed by the left and right atria; this is followed by a flat line as the wave moves to the ventricles that form the QRS wave, which is followed by the T wave that represents electrical recovery and return to the resting state. Prolongation of the QT interval by drugs has been associated with drug-induced arrhythmia and torsade de points leading to sudden death, which led to a number of drug withdrawals in the 1990s.

Electrocardiograms are collected on a regular basis during routine toxicology studies in dogs and monkeys to determine effects of compounds on the cardiovascular system. Since this process requires attaching electrodes to the animals, the procedure is generally performed under mild anesthesia, which can affect the outcome. For this reason it has become common practice to measure electrocardiograms in conscious animals using telemetered devices. See also **Telemetry** and **hERG channel**.

ELISA (enzyme-linked immunosorbent assay; adsorption assay; enzyme-linked immunoassay; enzyme-linked assay) is a bioanalytical method used to detect antibodies, protein and peptide drugs, protein biomarkers, and some small-molecular-weight compounds. Several different types of ELISA exist, but capture assays are mostly used in which an antibody is immobilized in a multi-well dish. The antibody captures the antigen, which may be a small molecule, a protein biomarker, or another antibody. A second antibody to the antigen is then used to determine the amount of antigen captured from the sample. This second antibody may be directly linked to the reporter enzyme or may be linked to a reporter antibody which is conjugated to the enzyme, usually alkaline phosphatase. The amount of enzyme (which is proportional to the amount of the antigen captured from the sample) is measured using a colorimetric assay which is read spectrophotometrically or fluorometrically.



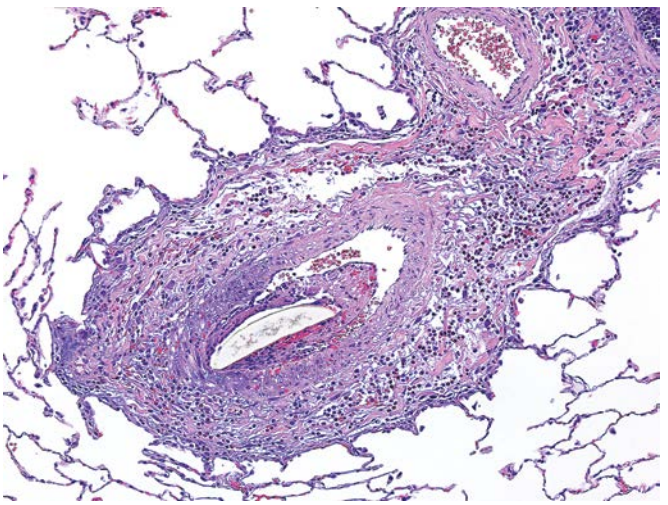
Sandwich ELISA.

Embolism, see the preferred term **Embolus**.

Embolus refers to the presence of extraneous tissue or foreign material within a blood vessel lumen. This material is usually introduced into the system via intravenous administration, and emboli are most often seen in the pulmonary capillary bed. The kidneys and brain are also common sites for embolus entrapment. Foreign materials most commonly seen in the lungs as emboli are hair shafts and skin fragments. In intravenous infusion studies, thromboemboli are frequently seen in the lungs as purplish, acellular masses, often attached to or integrated into the vessel wall. Neoplastic cells from malignant tumors that have invaded blood vessels can also form emboli, which grow into metastases at the site of their implantation, often the lungs. Septic emboli from sites of suppurative inflammation, sometimes including bacterial colonies, can also be distributed by the hematogenous route. The atrioventricular valves are particularly susceptible to deposition and colonization of these emboli, which can lead to endocarditis. See **Thrombosis** for further information.

Differential diagnosis: **Thrombus**.

Synonym(s): **Embolism**.



Embolus, foreign body; arterial shed from an infusion catheter, lung, cynomolgus monkey, H&E.

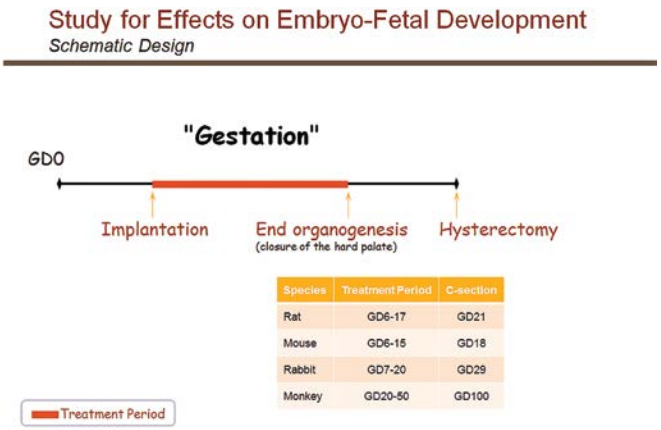
Embryo is the developing organism at the early stages of prenatal development of a female oocyte fertilized by male sperm. In humans, it is the developing organism until 8 weeks after fertilization; in rats and mice to day 13–14 after fertilization; and in rabbits to day 19–20 after fertilization.

Embryo-fetal development (EFD) refers to the developmental stages of an embryo or fetal development as well as the associated anatomic, histologic, and physiologic alterations normally observed.

Embryo-fetal developmental (EFD) toxicity studies, also known as teratogenicity studies, are generally performed in rodents and rabbits during drug development, although primate studies may be required for biopharmaceuticals. The

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aim of the study is to examine the effects of substances on the developing offspring from implantation throughout the period of organogenesis. Generally, the fetuses are delivered by caesarian section just before the end of the normal gestation period. Assessments include maternal toxicity (mortality, clinical signs, body weights, food consumption and reproductive parameters, number of corpora lutea and implants) embryo-fetal lethality, fetal weights, number of live fetuses, gender ratio, and external, visceral, and skeletal malformations.



Embryo-fetal toxicity is defined as the adverse events caused by a substance (e.g., chemical, drug), a pathogen (e.g., microorganism, virus), or any other agent (e.g., radiation) that could affect an embryo or a fetus during the gestation period.

Embryo-fetal toxicology refers to the study of a xenobiotic's effect on the developmental stages of an embryo or fetal development, as well as the associated anatomic, histologic, and physiologic alterations observed. Most commonly, rats or rabbits are used as the animal model species.

Embryo-fetal variation is a term used in development studies to identify fetal abnormalities that occur at a relatively high frequency. It represents a delay in development, a transitory alteration, or a permanent alteration, but is not believed to adversely affect survival, growth, or functional competence of the offspring.

Embryogenesis represents the early stages of prenatal development from a zygote to an embryo. These stages consist of the morula, blastocyte, and gastrula up to organogenesis when the different germ layers are defined. In humans, this phase covers the first 8 weeks of development, in rats and mice the first 13–14 days of development, and in rabbits the first 19–20 days of development.

Embryolethality refers to the severe damage of an embryo leading to death.

Embryology is the study of the embryo. For toxicologic pathology, the embryo may be evaluated histologically as part of an embryo-fetal toxicology study. See **Embryo-fetal toxicology** for further information.

Embryonal carcinoma is a rare uterine or testicular tumor that arises from a mixture of pluripotent germ cells, sex-cord stromal cells, and cells of the visceral yolk sac. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Embryonal hepatoma, see the preferred term **Hepatoblastoma**.

Embryonal nephroma, see the preferred term **Nephroblastoma**.

Embryonal tumor of liver, see the preferred term **Hepatoblastoma**.

Embryotoxicity refers to adverse events caused by a substance (e.g., chemical, drug), a pathogen (e.g., microorganism, virus), or any other agent (e.g., radiation) that could affect an embryo during the early stages of gestation.

Emesis (also referred to as vomiting) is the involuntary expulsion of the contents of the gastrointestinal (GI) tract through the mouth. Emesis may also be qualified to indicate a specific type. For example, vomiting blood is referred to as hematemesis.

Emetics are agents which give a stimulus to induce vomiting (emesis). Emetics have been used to remove stomach contents in the case of accidental ingestion of some toxins. Common agents are syrup of ipecac, strong salt solutions, or mustard water. Emetics should not be used when strong alkalis or acids have been swallowed since the esophagus wall may have been damaged (weakened) following ingestion of such caustic agents and may rupture during emesis. The potential aspiration of vapors from swallowed volatile organic solvents would also preclude the use of emetics.

Emperipolesis is the identification of an intact cell within the cytoplasm of another cell. Although its histological appearance is similar to erythrophagocytosis, where extravasated red blood cells are phagocytosed by macrophages, the processes are different. With erythrophagocytosis, red blood cells are destined to be broken down and their constituents recycled. In emperipolesis, the engulfed cell remains viable, and can exit the phagocytosing cell. Both cells (engulfed and phagocytosing) remain fully functional. Emperipolesis is seen in certain neoplastic diseases (blood cancers) and some autoimmune diseases. It is very rare in the veterinary medical context.

Differential diagnosis: **Erythrophagocytosis**.

Emphysema is characterized by the destructive enlargement of the airspaces distal to the terminal bronchioles. It may have

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a centriacinar or panacinar distribution. In the centriacinar form, the respiratory bronchioles become dilated, destroyed, and confluent with progressive loss of alveolar ducts and alveolar walls. Large bullae develop in severe forms. Spontaneous emphysema is rare in laboratory animals. One must differentiate this change from artifactual overinflation of the lung during fixation.

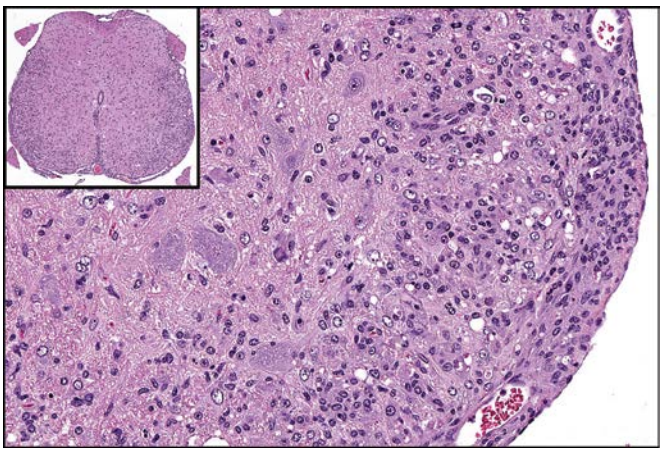


Emphysema, lung dog, H&E.

Enamel is the outer tooth layer formed by ameloblasts and is the hardest calcified material in the body—harder than dentin or bone. Enamel contains specialized proteins, enamelin and amelogenin, and the ratio of these is crucial for mineralization and the formation of the parallel, tightly packed, carbonate-rich, apatite crystals. Mature enamel is composed largely of long rods of hydroxyapatite crystals that are hexagonal in cross-section and arranged at right angles to the dentine surface. Ameloblasts initially secrete an organic matrix composed mainly of amelogenin. This is the "pre-enamel" that can often be seen in hematoxylin and eosin (H&E)-stained histologic sections as a more intensely red, eosinophilic layer immediately adjacent to the ameloblasts in developing teeth. Enamelin, an acid glycoprotein, the largest of the enamel proteins, is a minor constituent of this matrix but is essential for normal enamel formation. As mineralized enamel is formed, the organic matrix diminishes to very low levels in mature enamel. In H&E-stained histological sections that are decalcified, the mature enamel layer may be entirely removed, leaving a space, or if any remains, it is intensely basophilic. Rodent incisors do not have enamel on the tip or lingual/internal surface; rodent molar teeth do not have enamel on the cusps, unlike those in dogs and many other animals.

Encephalitis is inflammation of the brain. Evidence for inflammation may include changes such as edema and infiltration of leukocytes, similar to features of inflammation in tissues outside of the CNS or may be characterized by increases in neurospecific inflammatory cells, astrocytes and microglia. Qualification of the encephalitis such as neutrophilic, lymphocytic, or astrocytic may provide clues to the pathogenesis (e.g., bacterial, viral, etc.). See **Inflammation** and **Gliosis** for further information.

Encephalomyelitis is inflammation of the brain and spinal cord.



Inflammatory infiltrates in spinal cord white matter in experimental autoimmune encephalomyelitis. The infiltrates are comprised primarily of macrophages and lymphocytes. In this disease model, an inflammatory phase as depicted here precedes and leads to a demyelination phase that is characterized by myelin loss and cessation of inflammation. Mouse. H&E.

Endocardial schwannoma is a malignant neoplasm originating from the subendocardial Schwann cells, and may proliferate along the endocardium or invade the underlying myocardium. Refer to **Cardiovascular System** in Appendix 2 for further information.

Endochondral hypertrophy, see the preferred term **Physeal thickness increased**.

Endocrine gland, Anatomy and Histology, see Appendix 3 for further information.

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Endocrine pancreas cell hyperplasia refers to an increase in islet size with increased islet cell numbers that may occur multifocally through the pancreas of rats and mice. See **Endocrine Glands** in Appendix 2 for more information.

Endodermal sinus tumor, malignant, see the preferred term **Yolk sac carcinoma**.

Endogenous morphine, see the preferred term **Endorphin (β-endorphin)**.

Endometrial adenocarcinoma is a rare neoplasm of the uterine endometrium characterized by a malignant population of endometrial glandular epithelial cells that form nests, sheets, or glandular structures. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Endometrial adenoma is a rare neoplasm of the uterine endometrium characterized by a benign proliferation of the surface epithelium on a broad or narrow base. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Endometrial adenomatous hyperplasia, see the preferred term **Endometrial diffuse hyperplasia**.

Endometrial apoptosis is a uterine lesion characterized by glandular or luminal epithelial cells that have morphologic alterations consistent with apoptosis, including cellular and nuclear shrinkage, and nuclear fragmentation into apoptotic bodies. Endometrial apoptosis normally occurs as part of the estrous/menstrual cycle. In rats, apoptotic endometrial epithelial cells are present during metestrus and estrus. Apoptosis of endometrial gland epithelium occurs after the secretory or luteal phase if pregnancy is not established in nonhuman primates, during early diestrus in dogs, and in the proliferation phase in minipigs.

Differential diagnosis: **Endometrial necrosis**.

Synonym(s): **Endometrial single cell necrosis**.

Endometrial atrophy is characterized by a uterine endometrium with decreased numbers of glands and/or epithelial cell size (i.e., usually height) expected for the stage of estrous. The associated stromal volume may appear increased due to the decreased epithelial elements or may also be atrophic, depending on the inciting cause. Muscle layers are usually also thin. Endometrial atrophy occurs spontaneously with age-related senescence/menopause in laboratory animals, or if there is an alteration in ovarian steroid production because of direct ovarian toxicity or perturbation of the hypothalamic-pituitary-ovary axis. Body weight loss in fast growing rodents may result in estrous cycle disruption and endometrial atrophy.

Endometrial atypical cystic hyperplasia, see the preferred term **Endometrial cystic hyperplasia**.

Endometrial atypical glandular hyperplasia, see the preferred term **Endometrial diffuse hyperplasia**.

Endometrial cystic glandular hyperplasia, see the preferred term **Endometrial cystic hyperplasia**.

Endometrial cystic hyperplasia is an endometrial lesion characterized by increased numbers of normal-appearing, dilated or cystic endometrial gland profiles. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Endometrial diffuse hyperplasia is characterized by an increased number of normal or hypertrophied glands, and/or a hypercellular luminal epithelium comprising the uterine endometrium. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Endometrial focal glandular hyperplasia is characterized by a focus of disorganized, atypical glands within a normal endometrium. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Endometrial glandular hyperplasia, see the preferred term **Endometrial diffuse hyperplasia**.

Endometrial glandular hyperplasia, atypical, see the preferred term **Endometrial focal glandular hyperplasia**.

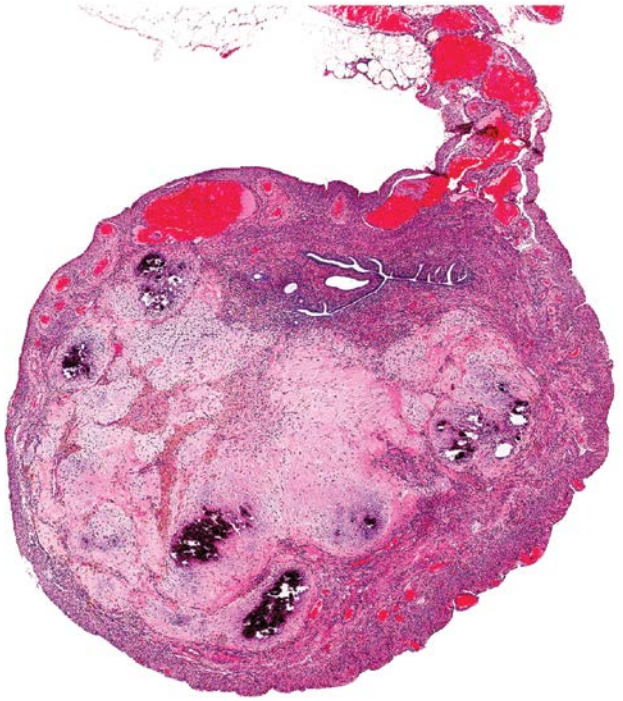
Endometrial glandular polyp is a uterine or cervical benign proliferation of normal endometrium glands and the associated fibrovascular stroma that protrudes into the uterine or cervical lumen. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Endometrial inflammation is characterized by the infiltration of inflammatory cells in the endometrium accompanied by other changes (hemorrhage, swelling, edema, tissue degeneration/necrosis/regeneration). The myometrium and uterine lumen may also be involved. The histologic appearance varies depending upon the severity and duration. This lesion often occurs as a primary endometrial insult or secondary to septicemia (e.g., *Mycoplasma* spp., *Streptococcus* spp., *Pasteurella* spp., *Corynebacterium* spp., *Klebsiella* spp.) in rodents. This condition is uncommon in dogs and the nonhuman primate (NHP).

Endometrial necrosis consists of a uterine endometrium with endometrial glands, luminal epithelial cells, or stromal cells that have morphologic changes consisting of cell shrinkage, cytoplasmic eosinophilia, vacuolation, and/or mineralization, and nuclear pyknosis or karyorhexis/karyolysis.

Differential diagnosis: **Endometrial apoptosis**.

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Necrosis, inflammation and mineralization, uterus, F344/N rat, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

Endometrial single cell necrosis, see the preferred term **Endometrial apoptosis**.

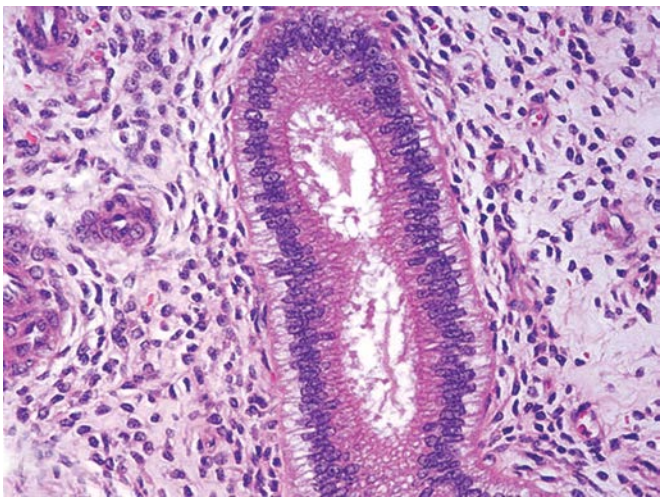
Endometrial stromal hyperplasia is characterized by a hypercellular stromal compartment (fibroblasts), with or without an increase in accompanying matrix (collagen). Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Endometrial stromal polyp is a benign uterine or cervical proliferation of the endometrial fibrovascular stroma which protrudes into the uterine or cervical lumen. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Endometrial stromal sarcoma is an invasive uterine neoplasm characterized by the proliferation of undifferentiated endometrial stromal cells. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Endometrial stromal tumor, benign, see the preferred term **Endometrial stromal polyp**.

Endometrial subnuclear vacuoles in the nonhuman primate are periodic acid-Schiff (PAS)-positive cytoplasmic vacuoles found in the secretory epithelium of the macaque endometrium during the late follicular (periovulatory) phase of the menstrual cycle. These remain prominent through the early to mid-luteal phase of the cycle, are high in glycogen content, and expand to also include supranuclear vacuoles as the secretory phase progresses, with apical blebbing of the glandular epithelium.



Subnuclear vacuoles, endometrial gland, cynomolgus monkey, H&E. (Reproduced with permission of the Academic Press from Rudmann et al. in *Haschek and Rousseaux's Handbook of Toxicologic Pathology,* 3rd ed. 2013.)

Endometriosis in the sexually mature, nonhuman primate uterus is the presence of normal-appearing endometrial epithelial and stromal structures within the myometrium and serosa. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Endoneurium is the innermost of three layers surrounding and protecting the axons that compose peripheral nerves. Endoneurium is an extracellular matrix composed of type III collagen and some fibroblasts. The next layer is the perineurium, which is composed of multiple layers of specialized fibroblasts with tight junctions, and a basement membrane, that surround bundles of axons. The nerve fascicles are bundled together and surrounded by an external connective tissue layer called the epineurium. See **Blood-nerve barrier** and Appendix 3 for further information.

Endorphin (β-endorphin) is an opioid neurohormone produced by the hypothalamus and pituitary gland, among other organs, from its precursor, proopiomelanocortin (POMC) during stressful conditions. Endorphin makes up one of the three classes of endogenous opioids (along with enkephalins and the dynorphins) and is an agonist for opioid receptors, generally leading to analgesia. Endorphins are implicated in addictive behaviors, such as alcoholism and overeating syndromes.

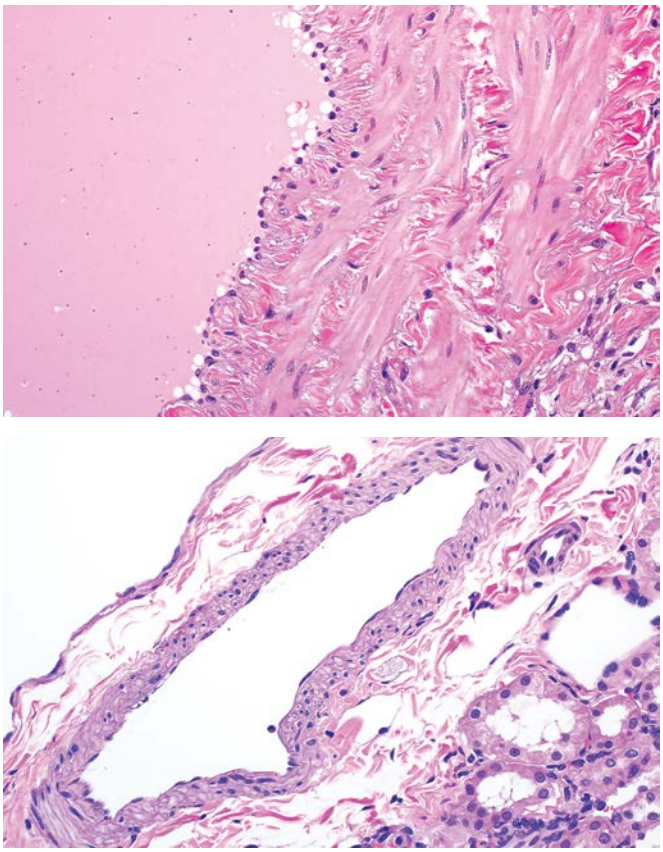
Synonym(s): **Endogenous morphine**.

Endothelial cell hypertrophy appears as increased size and prominence of the endothelial cells lining a blood vessel. Endothelial cell hypertrophy often accompanies endothelial cell hyperplasia (increased numbers of endothelial cells), as in treatment with 1,3 butadiene. In intravenous infusion studies, the presence of an indwelling catheter often results in endothelial hypertrophy and hyperplasia, which develop as an

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adaptive change. Hypertrophy of the endothelial cells lining blood-filled channels and spaces is a common feature in hemangiomas and hemangiosarcomas.

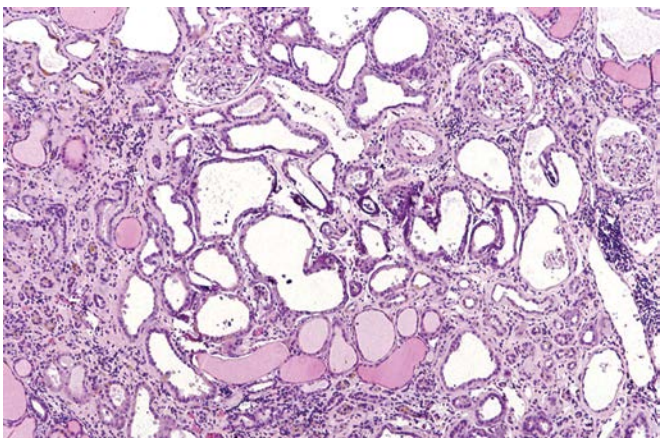
Differential diagnosis: **Hemangioendothelial hyperplasia**.



Endothelial cell hypertrophy (top) of the vein at an infusion site (renal vein) as compared to a normal vein endothelium (bottom), cynomolgus monkey, H&E.

Endothelial hyperplasia, see the preferred term **Hemangioendothelial hyperplasia**.

End-stage kidney is the final stage of kidney degeneration caused by progressive kidney disease, particularly chronic progressive nephropathy (CPN) in the aging laboratory rat. Virtually all the kidney parenchyma is involved in the disease process, and this stage is a prelude to death from renal failure. In end-stage CPN, the renal changes are accompanied by systemic, nonrenal organ pathology, including compensatory hyperplasia of the parathyroid glands, renal osteodystrophy of the skeletal system, and generalized mineralization occurring in the lungs, gastric mucosa, and other tissues.



End-stage kidney, rat kidney, H&E. (Reproduced with permission of Society of Toxicology from Frazier et al., 2012.)

Enlarged retinal pigment epithelium, see the preferred term **Retinal pigment epithelium hypertrophy**.

Enteric nervous system is a fairly autonomous subdivision of the autonomic nervous system that controls the movement and secretions in the gastrointestinal tract.

Enteritis, see the preferred term **Intestinal inflammation**.

Enterochromaffin-like cell tumor, see the preferred term **Stomach neuroendocrine cell tumor, benign/malignant**.

Enterohepatic recirculation is the reuptake from the intestine of drugs that are excreted in the bile unchanged or as direct glucuronide conjugates, and which may be hydrolyzed back to the parent drug by the intestinal bacteria. See **Biliary excretion** for further information.

Enzyme induction is an increase in enzyme activity caused by increased synthesis of enzyme protein. In toxicology studies, enzyme induction is often an adaptive response to the drug load in the liver. Most commonly, the induction involves increased levels of cytochrome P450 in a pleiotropic response triggered by interaction of the chemical with a receptor protein such as CAR (constitutive androgen receptor), PXR (pregnane X receptor), Ah receptor, or PPARα (peroxisome proliferator activated receptor alpha). Once formed, the receptor ligand complex moves to the nucleus and binds to response elements on the DNA initiating the transcription of a set of response genes, which code for proteins involved in drug metabolism, thereby increasing the rate of compound metabolism. Such autoinduction leading to increased clearance of a compound results in decreased systemic exposure. Since many of the proteins that are induced are found in the endoplasmic reticulum, such enzyme induction may be associated with increased amounts of smooth endoplasmic reticulum within hepatocytes, and consequently, increased cell size (i.e., hepatocellular hypertrophy). See **PPAR (peroxisome proliferator–activated receptor)** and **PXR (Pregnane X receptor)** for further information.

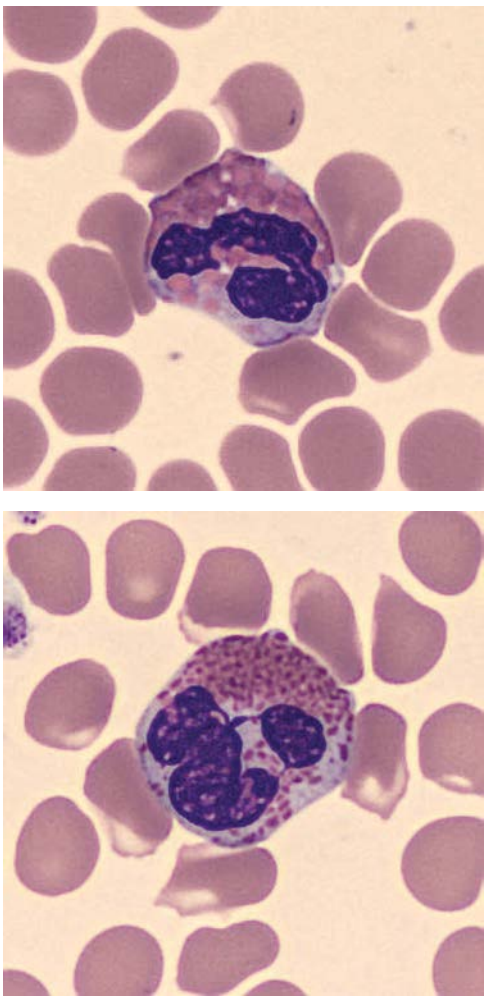
Enzyme inhibition is a decrease in the activity of an enzyme, either through interaction with a competing substrate or a nonsubstrate–inhibiting molecule. Inhibition may be competitive (i.e., with the substrate and the inhibitor competing for the same site), noncompetitive, or uncompetitive. Inhibition of enzymes involved in the clearance of a drug can result in increased exposure and consequent toxicity. If the inhibitor were a comedication, this would lead to a drug-drug interaction. For this reason,

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it has become common practice to look at the potential for drug candidates to inhibit the activity of a panel of cytochrome P450 isoenzymes during the candidate profiling phase of drug discovery. See **Cytochrome P450** for further information.

Eosinopenia (decreased eosinophils) has limited significance because eosinophil numbers in healthy animals are generally low. Eosinopenia can be caused by corticosteroid administration leading to decreased survival and increased attraction of eosinophils into lymphoid tissues.

Eosinophil is a type of leukocyte (white blood cell) with an affinity for eosin dye. They develop primarily in the bone marrow over a period of 2–6 days and are responsive to GM-CSF, IL-3, and IL-5, which drive commitment of eosinophil progenitor cells, terminal differentiation, proliferation, and maturation. They typically have 2–3 segments in their nuclei and contain prominent orange to pink granules that vary in size, shape, and number, depending on the species. Eosinophils are usually present within tissues, predominantly in the skin, respiratory tract, and gastrointestinal tract. They guard against parasites, protozoa, and bacteria, and promote mast cell degranulation through release of preformed proteins, including major basic protein, eosinophil peroxidase, and eosinophil cationic protein. They suppress hypersensitivity reactions by inhibition of chemical mediators released by mast cells during allergic and anaphylactic reactions. Eosinophils can phagocytose immune complexes, antibody-coated red blood cells, mast cell granules, inert particles, yeast, and bacteria, and help regulate other inflammatory cells, endothelial cells, and fibroblasts through the release of cytokines including IL-1, IL-4, IL-5, IL-6, IL-10, TNFα, and TGFβ.



Eosinophil, blood smear, dog (top) and monkey (bottom). Note eosinophilic granules are often larger in the dog than in the monkey.

Eosinophilia (increased numbers of eosinophils) is most commonly associated with parasitism, infections, immediate or delayed hypersensitivity, and some tumors such as eosinophilic leukemia (acute and chronic), mast cell tumors, and T-cell lymphoma.

Eosinophilic change describes an increase in eosin staining in routine hematoxylin and eosin (H&E)-stained tissue. Eosin stains intracellular proteins (e.g., enzymes, actin, myosin) and extracellular proteins (e.g., collagen, extracellular matrix) a red or pink color. Hepatocellular eosinophilic change can be induced by clofibrate leading to peroxisome proliferation in rodents. Peroxisomes contain enzymes that stain pink.

Eosinophilic crystalline pneumonia is a murine condition characterized by a massive alveolar infiltration of strongly eosinophilic macrophages (in hematoxylin and eosin [H&E]-stained sections) which contain crystals of an immunohistochemically detectable chitinase-like protein, Ym1.

Differential diagnosis: **Pulmonary alveolar macrophage aggregation**.

Eosinophilic droplets, see the preferred term **Eosinophilic globules**.

Eosinophilic focus, see the preferred term **Eosinophilic focus of cellular alteration**.

Eosinophilic focus of altered hepatocytes, see the preferred term **Eosinophilic focus of cellular alteration**.

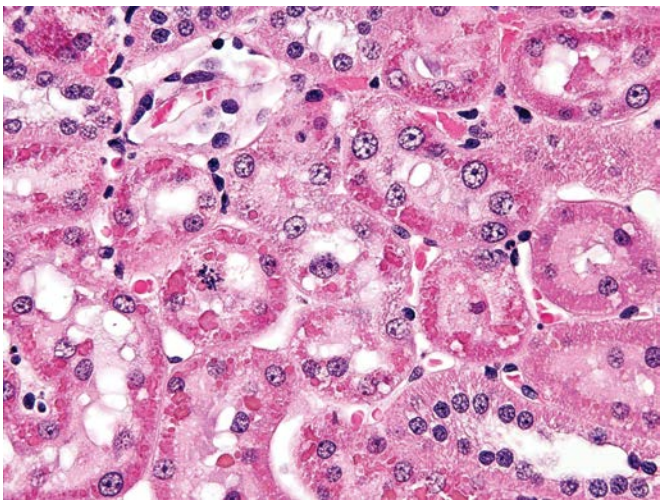
Eosinophilic focus of cellular alteration is a focal accumulation of hepatocytes with increased cytoplasmic eosinophilia compared to the surrounding hepatocytes in the liver. Hepatocytes in an eosinophilic focus merge with the adjacent hepatocyte cords, with little or no compression of the adjacent parenchyma. Refer to **Liver, Gallbladder, and Exocrine Pancreas** in Appendix 2 for further information.

Eosinophilic globules in male rat kidneys are lysosomes containing alpha 2-microglobulin protein in proximal tubular epithelial cells. Chemicals can cause increases in globule size and number and can be associated with tubular epithelial cell degeneration. Mallory-Heidenhain stain enhances their identification. Rodents with histiocytic sarcoma may also

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demonstrate renal tubular epithelial hyaline globules. See also **Basophilic granules** for further information.

Synonym(s): **Hyaline droplets**; **eosinophilic droplets**.



Eosinophilic globules in the renal tubular epithelium of a rat, H&E. Renal tubular epithelial cells have cytoplasmic accumulation of variably sized bright eosinophilic globular droplets. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

Eosinophilic leukemia is a tumor of the eosinophilic granulocytic lineages. It has not been reported as spontaneous finding in rodents. See **Myeloid leukemia** for further information.

Eosinophilic preneoplastic focus, see the preferred term **Eosinophilic focus of cellular alteration**.

Ependymal barrier is the barrier between the brain parenchyma surrounding the ventricles and the cerebrospinal fluid (CSF) within the ventricles, which occurs at the ependymal lining of the ventricles. The ependymal barrier is also called the CSF-brain barrier. This is functionally different from the blood-brain barrier (BBB) and the blood-CSF barrier, which serve as barriers between blood and the brain parenchyma or CSF, respectively. Ependymal cells line the CSF-filled ventricles of the brain (lateral ventricles, third ventricle, and fourth ventricle) and the central canal of the spinal cord and have cilia at the apical surface in contact with the CSF. These cilia are responsible for circulation of CSF within the ventricular system. Unlike the BBB and blood-CSF barrier, the ependymal barrier does not have tight junctions but does serve as a partial barrier between the CSF and the brain parenchyma. Large molecules such as proteins can pass between ependymal cells into the extracellular space. There is not a continuous basal lamina between the ependymal cells and subjacent glial processes, allowing further diffusion into the extracellular matrix around glial processes. Within the ependymal layer are patches of specialized ependymal cells called tanycytes. Tanycytes are joined by tight junctions between tanycytes and adjacent ependymal cells. Tanycytes have basal processes that extend through the subjacent astrocyte processes to form end feet on parenchymal blood vessels, thus allowing transport of substances between the ventricles and the blood vessels. Elsewhere surrounding the perimeter of the third ventricle are specialized patches of ependyma called the circumventricular organs. Circumventricular organs have fenestrated capillaries and are therefore areas where the BBB or blood-CSF barrier is incomplete, and are thought to be regions where metabolites and neuropeptides can enter the CSF or cerebrovascular system. See **Blood-brain barrier (BBB)**, **Blood-CSF barrier**, **Circumventricular organs**, and Appendix 3 for further information.

Ependymoma, benign is a tumor arising from ependymal cells lining the ventricular system of the brain and the central canal of the spinal cord. These tumors are usually located within proximity to the anatomic locations of the ventricle, aqueduct, and/or the central canal of the spinal cord and are composed of polygonal ependymal cells often arranged in rows and rosettes (luminal and perivascular). Refer to **Nervous System** in Appendix 2 for further information.

Ependymoma, malignant is a neoplasm arising from ependymal cells lining the ventricular system of the brain and the central canal of the spinal cord. These neoplasms are usually located within proximity to the anatomic locations of the ventricle, aqueduct, and/or the central canal of the spinal cord with invasion of the adjacent brain parenchyma. The malignant ependymal cells exhibit cytologic atypia and have high mitotic activity. Refer to **Nervous System** in Appendix 2 for further information.

Epicorneal conjunctival membrane, see the preferred term **Conjunctiva overgrowth**.

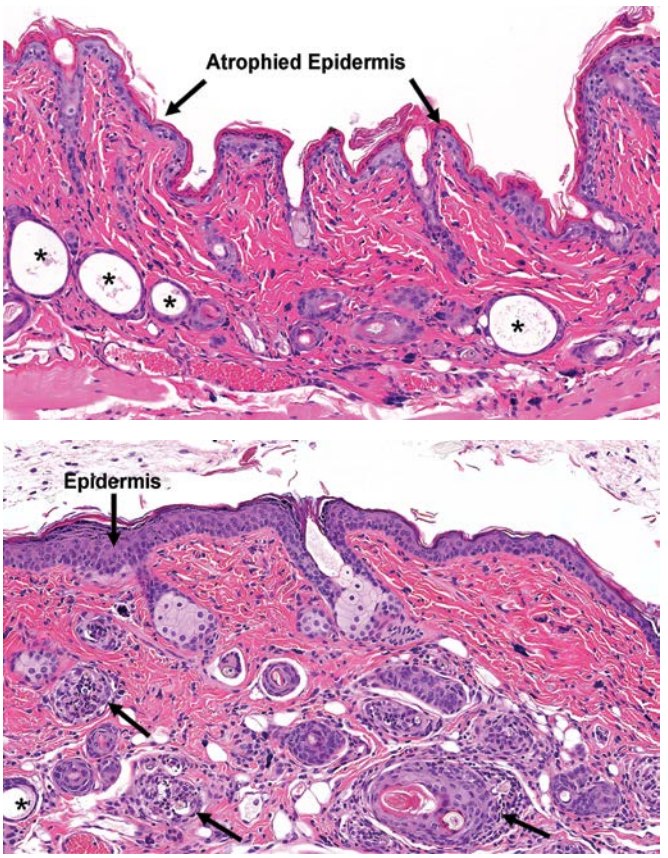
Epidemiology is the study of factors involved in the frequency, incidence, and distribution of disease. Epidemiology utilizes statistics and models in the study of health in populations to understand the causes and patterns of disease. This is most often used by public health services to seek methods for predicting and avoiding pandemics or epidemics or determining the potential detrimental effects of environmental pollutants.

Epidermal atrophy is a reduction in the number, size, and layers of nucleated epidermal cells as a result of decreased basal cell turnover. Compounds that reduce the metabolic activity of the stratum basale, including corticosteroids (endogenous or exogenous), can result in epidermal atrophy. Epidermal atrophy can be difficult to detect in laboratory rodents due to the normally thin epidermis in these species. In addition, in all species, the thickness of the epidermis normally varies between different regions of the body and will vary with age and strain. Therefore, before making this diagnosis based on comparison to a sample of normal skin, it is important to ensure that the comparison is from a similar area of the body in an age- and strain-matched individual. Hairless rodents in general will have thicker epidermis than normally haired

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rodents. Epidermal atrophy may also develop locally over a subcutaneous, expansile mass.

Synonym(s): **Epidermal thinning**.



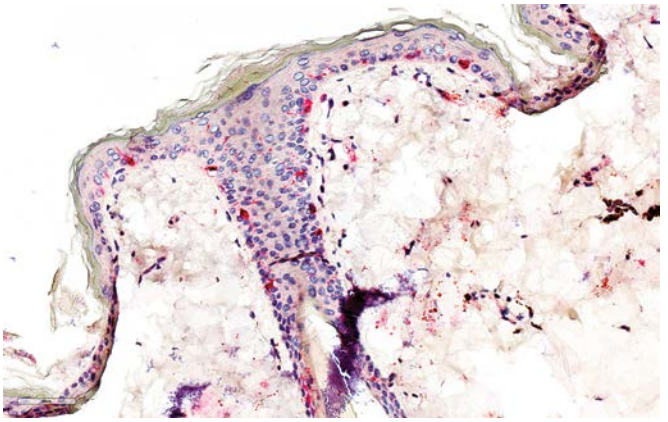
Epidermal atrophy (top) compared to typical epidermal thickness (bottom) for the strain in SKH1 hairless mice, H&E. Note that this strain of mouse has adnexal dysplasia resulting in abnormal orientation of hair follicles with granulomatous folliculitis (arrows), and formation of follicular cysts (*).

Epidermal cleft, see the preferred term **Vesicle**.

Epidermal cyst, see the preferred term **Squamous cyst**.

Epidermal dendritic cell is a resident, antigen-presenting cell that originates from the primitive hematopoietic progenitor cells in the yolk sac/fetal liver. These cells migrate prenatally to the epidermis where they retain a low rate of proliferation for renewal in situ. In cases of high demand (e.g., inflammation and cell death), Langerhans cells can differentiate from monocytes recruited from the bone marrow. These cells are usually located within the lower layers of the epidermis and have long dendrites that project between keratinocytes for immune surveillance. During immunologic responses, they can sample antigens, migrate to lymph nodes, and present these antigens to naive T cells. They also play roles in immune tolerance and epidermis repair. Interdigitating epidermal cells are identified by immunohistochemical staining of langerin (CD207) or CD1a and by identification of Birbeck granules by transmission electron microscopy. Birbeck granules have apparently not been identified in dogs.

Synonym(s): **Langerhans cell**; **interdigitating cell**.



Immunohistochemistry photomicrograph of monkey skin. In red are Langerhans cells labeled with an anti-CD207 antibody. Note that cell dendrites extend between epithelial cells.

Epidermal diffuse, full-thickness, necrosis, see the preferred term **Toxic epidermal necrolysis**.

Epidermal hyperkeratosis is an increase in the number of layers of keratinized cells of the epidermis that results in an increased thickness of the stratum corneum. Grossly, this may appear as flaky or scaly skin, or as a callous. Hyperkeratosis can result from increased epidermal turnover or decreased desquamation of corneocytes (keratinocytes). Hyperkeratosis can be a primary change but most commonly accompanies other epidermal changes, especially as a sequel to chronic epidermal disease or irritancy. Orthokeratotic hyperkeratosis is increased numbers/layers of typical, non-nucleated corneocytes, whereas in parakeratotic hyperkeratosis, corneocytes retain their nuclei. Parakeratotic hyperkeratosis is normal in mucous membranes lining the mouth or vagina. Otherwise, parakeratosis implies rapid and abnormal turnover of the epidermis, and is seen with scaling dermatoses such as psoriasis. It can also be seen with nutritional imbalances such as zinc deficiency. Hyperkeratosis can be accompanied by crusts (scabs), which are desiccated accumulations of inflammatory cells, corneocytes, plasma proteins, and sometimes erythrocytes. Similar to the epidermis, the thickness of the stratum corneum normally varies in different parts of the body and can be very thick in some areas such as the footpads or callouses. In addition, the stratum corneum can become thicker as a result of environmental exposure and will vary between species and strains. Therefore it is critical to know where the skin was sampled to know if true hyperkeratosis is present. Normal skin comparisons should be from the same area of the body and from an age- and strain-matched control in a similar environment. See **Orthokeratotic hyperkeratosis** and **Parakeratotic hyperkeratosis** for further information.

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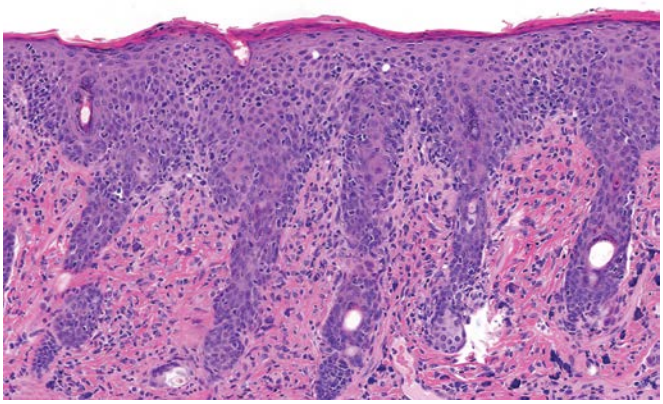


Parakeratotic hyperkeratosis from SKH1 mouse with epidermal hyperplasia, H&E. Note the retention of nuclei within the thickened condensed layer of keratin (arrows). Underlying epidermis and hair follicles are hyperplastic.

Epidermal hyperplasia is an increase in the thickness of the epidermis resulting from increased numbers of layers of nonkeratinized cells, usually the stratum spinosum and the stratum granulosum. An increase in thickness of the keratinized layer is called hyperkeratosis and is commonly seen concurrently with epidermal hyperplasia. Epidermal hyperplasia is usually an adaptive response to injury and is part of the wound healing response. Refer to **Skin** in Appendix 2 for further information.

Epidermal inflammatory cell infiltrate is characterized by an infiltration of leukocytes into the epidermis between epidermal cells. The epidermis is nonvascular, so any leukocytes present have come from the dermis, and dermal inflammation commonly accompanies epidermal leukocytic infiltrates. Inflammatory cell infiltrates are also commonly accompanied by other changes, including intercellular edema and hyperkeratosis or epidermal hyperplasia. An epidermal inflammatory cell infiltrate diagnosis is usually named by the type of infiltrating leukocyte, which can give information as to possible pathogenesis or etiology. The presence of neutrophils or eosinophils in the epidermis may indicate the presence of bacteria, fungi, or parasites. Lymphocytic or mononuclear cell infiltrates can indicate immune mediated epidermal disease. A monomorphic lymphocytic infiltrate can indicate an epitheliotrophic lymphoma. Refer to **Lymphoma, Epitheliotrophic (Canine)** under **Skin** in Appendix 2 for further information.

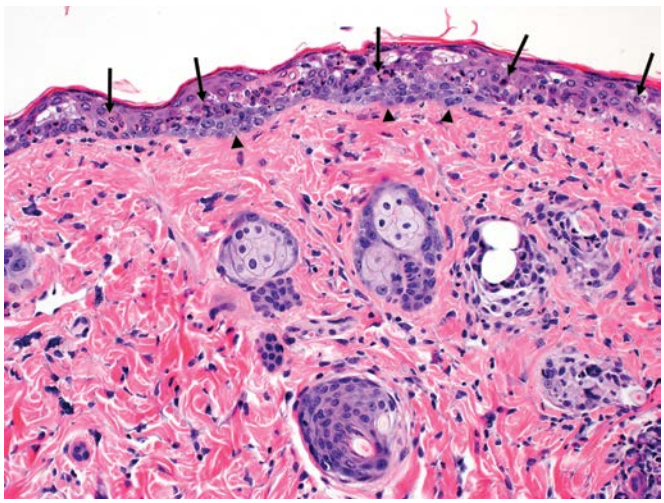
Synonym(s): **Exocytosis**.

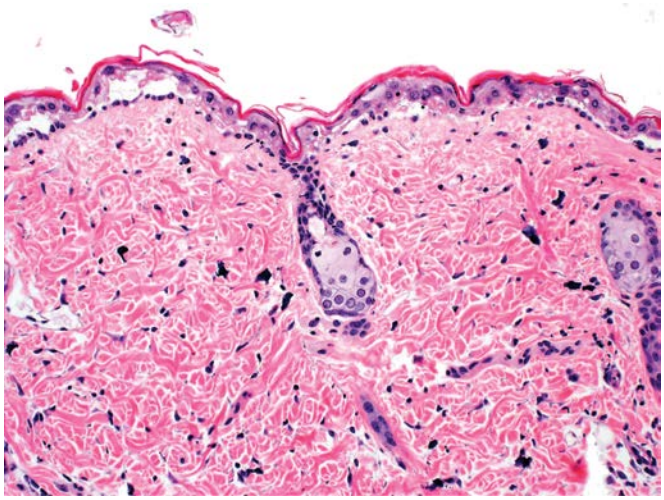


Epidermal inflammatory cell infiltrate, within hyperplastic epidermis. Rat, H&E.

Epidermal layers/epidermis, refer to **Skin** in Appendix 3 for further information.

Epidermal necrosis is death of the surface epithelium overlying the dermis of the skin. Single cell type of epidermal necrosis is characterized by individual epidermal cells with hyalinized, hypereosinophilic cytoplasm and pyknotic nuclei. Apoptosis should only be used when there has been molecular demonstration of the apoptotic pathway. Since the production of the stratum corneum involves a normal process of programmed cell death to produce the corneocytes,





Top: Epidermal necrosis, single cell type, with beginning proliferation of basilar layer (large arrowheads) in response to epidermal necrosis. Single cell necrosis ("sunburn cells") are visible in upper layers of epidermis (small arrows). Bottom: Epidermal necrosis, full thickness. Both images SKH1 mouse, H&E, following UVB exposure.

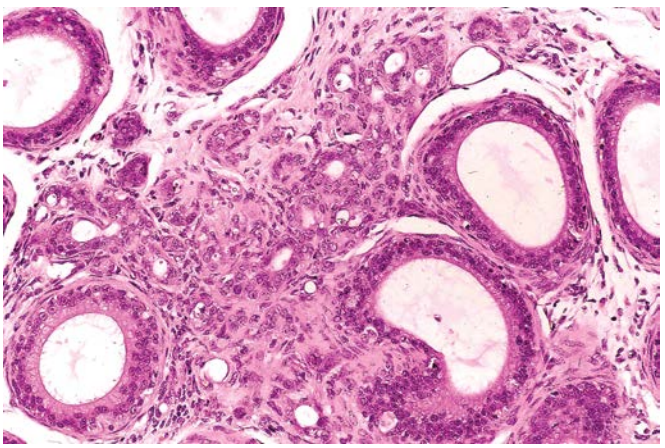
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apoptosis can be misleading. Erythema multiforme refers to multiple epidermal cells undergoing single cell necrosis and indicates that either toxic- or immune-mediated mechanisms were at play and should not be used if it is known that UV exposure was the cause. "Sunburn cells" refer to single cell necrosis of the epidermis following exposure to ultraviolet light. Due to the implied cause of single cell necrosis resulting from the use of either term, especially if the cause is uncertain, the preferred term is epidermal necrosis, single cell type, with qualifiers. The use of the modifier satellitosis in reference to an epidermal change means that individual necrotic epidermal cells are surrounded by lymphocytes. (Note that this is different from satellitosis in the central or peripheral nervous systems.) Diffuse epidermal necrosis refers to all or the majority of epidermal cells in a specified layer or area having undergone necrosis, characterized by loss of cellular detail. Full thickness epidermal necrosis refers to necrosis of all cell layers (necrolysis), often accompanied by separation of the epidermis from the dermis. Toxic epidermal necrolysis (TEN) is immune mediated, diffuse, full thickness necrosis of the epidermis; due to the implied cause in this term, the use of the term "epidermal necrosis" with qualifiers is more appropriate.

Epidermal thinning, see the preferred term **Epidermal atrophy**.

Epidermoid carcinoma, see the preferred term **Squamous cell carcinoma**.

Epididymal adenosis is a common spontaneous lesion in aging mice but rarely noted in rats. Histologically, adenosis is characterized by small aggregates of epithelial cells with a small lumen in close association with the epididymal duct, often in between the ducts. It may be associated with periductal fibrosis and epithelial vacuolation. Drug-induced adenosis is reported in mice exposed neonatally to diethylstilbestrol.

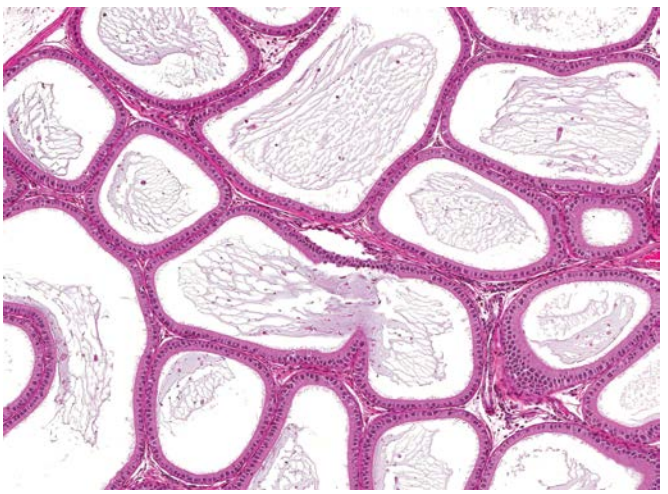


Adenosis, mouse epididymis, H&E. (Reproduced with permission of Society of Toxicologic Pathology from Creasy et al., 2012.)

Epididymal and efferent duct agenesis, see preferred term **Epididymis and efferent duct aplasia**.

Epididymal aspermia is a complete absence of sperm in the epididymides because of severely reduced sperm output by the testis, due to long term germ cell injury, androgen deficiency, and rarely, congenital testicular hypoplasia/agenesis. The reduction may be throughout the epididymis or limited to specific regions depending on timing after insult. Aspermia is usually accompanied by tubular degeneration/atrophy or atrophy and decreases in testes and epididymal weights. Aspermia is commonly observed in the laboratory beagle dog and nonhuman primate in toxicology studies (<1 month for dogs; all studies in nonhuman primates) due to the use of sexually immature animals. In sexually mature rhesus monkeys, oligospermia/aspermia in the epididymis may be observed because they are only seasonal breeders. See **Testicular tubular degeneration/atrophy** and **Testicular tubular atrophy** for further information.

Differential diagnosis: **Sexual immaturity**.



Aspermia, epididymis, F344/N rat, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

Epididymal ductal atrophy is generally associated with diffuse tubular degeneration/atrophy of the testis secondary to a xenobiotic-induced reduction of androgens or androgen receptor blockade, and subsequent decreased fluid and sperm output from the testis; however, androgen receptor antagonists and 5α-reductase inhibitors may cause epididymal atrophy without appreciable testicular morphological effects. Both diffuse and segmental (i.e., junction of the corpus and cauda) epididymal atrophy are common age-related findings in rodents, secondary to testicular degeneration.

Differential diagnosis: **Sexual immaturity**.

Epididymal histiocytic lymphoma, see the preferred term **Epididymal histiocytic sarcoma**.

Epididymal histiocytic sarcoma is a rare tumor restricted to the mouse, is the equivalent of the female uterine histiocytic sarcoma, and is typically confined to the cauda epididymis. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

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Epididymal histiogenic tumor, see the preferred term **Epididymal histiocytic sarcoma**.

Epididymal hypoplasia, see preferred term **Epididymis and/or efferent duct hypoplasia**.

Epididymal karyocytomegaly, see the preferred term **Epididymal karyomegaly**.

Epididymal karyomegaly is a commonly observed, self-limiting lesion in the cauda epididymis of the B6;129 transgenic mouse strain. It is often accompanied by cytomegaly and pseudostratification such that the ductal cells may extend into the lumen. Cells may be single- or multinucleated, and nuclei may be larger, deeply basophilic, and folded with cytoplasmic invaginations.

Synonym(s): **Epididymal karyocytomegaly**.

Epididymal luminal sperm, reduced is usually related to decreased spermatogenesis in the testes, but can also result from an obstruction in the efferent ducts, in which the testes often appear normal histologically. There may be a reduction (i.e., oligospermia), or a total absence (i.e., aspermia) of sperm in the ductular lumens, diffusely or segmentally, depending on the chronology of the spermatogenic disruption. Because it takes 3–5 days for sperm to arrive at the cauda, where they are stored for a week or more, some toxicants can cause a reduced transit time, thereby reducing normal sperm content without consequences to spermatogenesis. Reduced testosterone diminishes epididymal sperm survival. A reduction in sperm is often accompanied by an increase in sloughed testicular germ cells and cell debris due to associated spermatogenic disturbances in the testis and reduced lumen size of the ducts, the latter resulting from a reduced volume of sperm and fluid. Peripubertal animals may have normal-appearing testes and normal numbers of sperm in the caput and corpus but reduced numbers of sperm in the cauda because they have not built up full sperm reserves. Some toxicants accelerate (e.g., chloroethylmethanesulphonate, hydroxyflutamide) or decrease (e.g., guanethidine sulphate) transit time through the epididymis, or can alter epididymal function via decreasing androgen status.

Synonym(s): **Epididymis and efferent duct reduced luminal sperm**; **epididymis, hypospermia**; **epididymis, oligospermia**; **epididymis, spermatids reduced**.

Epididymal mesothelial hyperplasia is a proliferative lesion localized to the serosa of the epididymis in the rat. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Epididymal reticulum cell sarcoma, see the preferred term **Epididymal histiocytic sarcoma**.

Epididymal sperm retention cyst, see the preferred term **Spermatocele**.

Epididymis (ductus epididymidis) is a part of the integrated sperm transport system that includes the efferent ducts, initial segment, caput, corpus, cauda, and vas deferens. It is a highly coiled, tortuous duct which links the efferent ducts to the vas deferens. In rodents, the efferent ducts are long, thin, tortuous, and located within the epididymal fat pad. In the dog, they are collected with the initial segment of the epididymis. In cynomolgus monkeys, the efferent ducts share a connective tissue capsule with the head of the epididymis but are located slightly proximal and may be present in a routine epididymal section. The epididymis itself is relatively long and loosely attached to the testis in the rodent, whereas in man and other domestic animals it is comparatively shorter and attached more tightly. It is lined by pseudostratified, ciliated columnar epithelium, which is surrounded by loose connective tissue and smooth muscle cells. Periductal smooth muscle fibers increase in number toward the cauda, while epithelial height decreases toward the cauda. Cell types within the epididymal epithelium include principal cells with apical stereocilia (the primary cell type), basal cells, halo cells (a subset of T lymphocytes and monocytes), and clear cells. The epididymis serves several functions, including sperm maturation, protection, concentration, and storage. Spermatozoa are relatively immotile in the caput but transition to fully motile and capable of recognizing and fertilizing an oocyte in the cauda.

Epididymis and efferent duct agenesis, see the preferred term **Epididymis and efferent duct aplasia**.

Epididymis and efferent duct aplasia is the complete absence of one or both epididymis/epididymides, and efferent duct(s) on gross and histological examination. It is an uncommon congenital anomaly due to testosterone deficiency and failure of the development of its primordium during embryogenesis. Xenobiotic-induced aplasia is reported with in utero exposure of compounds that disrupt testosterone biosynthesis or testosterone binding (e.g., various phthalate esters, linuron, and flutamide). Unilateral aplasia of the epididymis is reported in TW inbred rats and male August X Copenhagen Irish (ACI) rats. Mice with null mutations of the androgen receptor, Pax2, or Emx2 have aplasia of the epididymis and vas deferens.

Differential diagnosis: **Epididymal hypoplasia**.

Synonym(s): **Epididymis and efferent duct agenesis**.

Epididymis and efferent duct apoptosis, see the preferred term **Epididymis and efferent duct single cell epithelial necrosis**.

Epididymis and efferent duct atrophy is characterized by a reduced diameter of the epididymal ducts and efferent ducts, and is often associated with cribriform change. Diffuse ductal atrophy associated with testicular degeneration and segmental atrophy at the corpus and cauda junction is observed spontaneously in aged rodents. Causes of diffuse atrophy include reduced testosterone production from steroid biosynthesis inhibitors, decreased metabolism of testosterone to dihydrotestosterone from 5α-reductase inhibitors (i.e., the major effective androgen for epididymal function), antagonism of

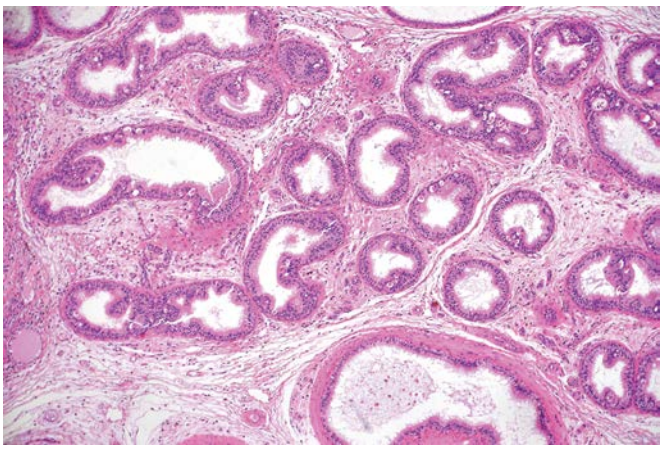
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the androgen receptor, or decreased fluid and sperm output secondary to severe tubular degeneration/atrophy in testis. See **Testicular tubular degeneration/atrophy** for further information).

Differential diagnosis: **Sexual immaturity**.

Epididymis and efferent duct cribriform changes are pseudoglandular luminal structures within the epididymal epithelium that form after segmental contraction and subsequent in-folding and bridging of the duct epithelium. Cribriform change is generally seen at the junction between the distal corpus and the cauda epididymis and may be observed spontaneously and/or be associated with decreased sperm content and ductular atrophy. In the caput epididymis, it is rare, segmental, and usually secondary to efferent duct blockage.

Synonym(s): **Epididymis and efferent duct pseudoglandular formation**.



Cribiform change, rat epididymis, H&E.

Epididymis and efferent duct dilation occurs because of increased ductal fluid pressure due to reduced fluid reabsorption or fluid obstruction distal to the dilation. Affected ducts may be lined by a flattened epithelium and appear empty or contain cellular debris. Cystic dilation with atrophy of the epithelial lining of the epididymis is occasionally seen as a background incidental finding in aging rodents and caused by drugs that interfere in resorption of the seminiferous tubule fluid, which is the major function of the efferent ducts. Rodents treated with 5-hydroxytryptamine agonists or estrogen antagonist, and estrogen receptor knockout mice develop dilation of efferent ducts that are associated with these testicular changes.

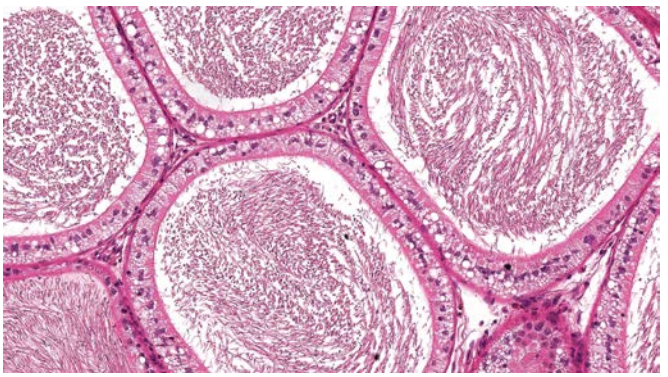
Differential diagnosis: **Spermatocele**.

Epididymis and efferent duct edema is an occasional background lesion in prepubertal rats and occurs because of extravasation of clear, slightly eosinophilic or basophilic fluid, often with small numbers of inflammatory cells into the interstitial space. Test article–related effects on the vasculature or altered ductal fluid reabsorption are the most frequent causes of epididymal edema. L-cysteine treatment in maturing rats produces edema (unilateral and/or bilateral), and sperm granuloma formation in the epididymis.

Epididymis and efferent duct epithelial vacuolar degeneration, see the preferred term **Epididymis and efferent duct epithelial vacuolation**.

Epididymis and efferent duct epithelial vacuolation may be induced by xenobiotics or occur spontaneously in the aging rodent. Vacuoles may be formed due to buildup of epididymal secretory fluids, or because of lipid, phospholipid, or glycoprotein accumulation. When due to test article−induced phospholipidosis, such as in rats given spinosad or selective dopamine 3 antagonists, vacuoles are typically small (i.e., microvesicular), and restricted to specific regions of the epididymis depending on the test article. Age-related vacuolation is also commonly microvesicular in appearance and has been noted in both the aging rat and mouse. The proximal end of the cauda epididymis is most commonly affected in the aging rat; however, basophilic foamy vacuolation may also be age related and is most likely due to secretory product accumulation. In the dog, intracellular vacuolation is commonly noted as a background lesion at the junction of the corpus and the cauda.

Synonym(s): **Epididymis and efferent duct epithelial vacuolar degeneration**; **epididymis and efferent duct epithelial vesicular or hydropic degeneration**.



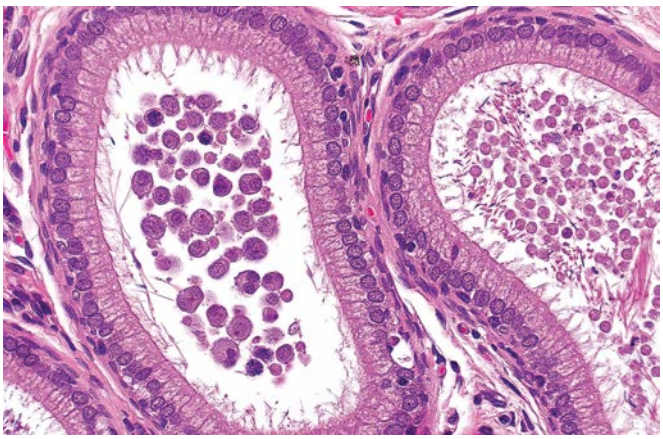
Epididymal epithelial vacuolation, rat, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

Epididymis and efferent duct epithelial vesicular or hydropic degeneration, see the preferred term **Epididymis and efferent duct epithelial vacuolation**.

Epididymis and efferent duct luminal cell debris is characterized by cell and cell debris admixed with sperm in the lumen of the epididymis or efferent ducts, and generally reflects sloughing of germ cells from the testis. This finding is characterized by the presence of intact cells (often recognizable as round spermatids or spermatocytes) and/or cell debris intermixed with mature sperm within the ductular lumen. In the mature rat, this is a sensitive indicator of spermatogenic disruption in the testis since there are normally few sloughed cells. Sloughed cells are more frequently seen in the normal mouse

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and are quite common in the dog. They are also common in peripubertal, and sometimes aging animals of any species, which reflects the higher background level of germ cell degeneration and exfoliation during the first wave of spermatogenesis. If cell debris is associated with degeneration or necrosis of the epididymal or efferent duct epithelium, a primary lesion in the epididymis should be considered. The efferent ducts are generally not collected in routine rodent toxicity studies, but they are an important potential target for toxicity and may need to be examined. The epithelium of the efferent ducts is composed of principal and ciliated cells in most species.

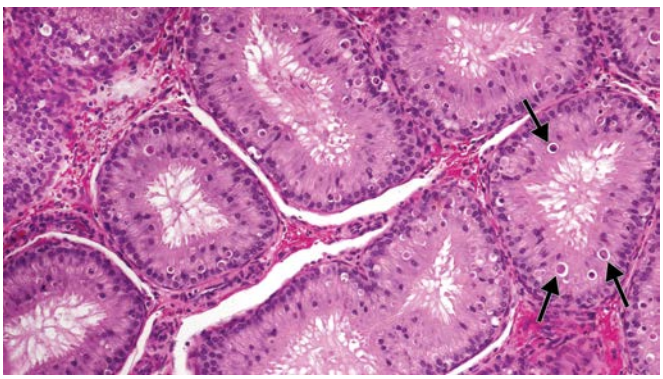


Luminal germ cell debris, epididymis, rat, H&E. (Reproduced with permission of Society of Toxicologic Pathology from Creasy et al. 2012.)

Epididymis and efferent duct pseudoglandular formation, see the preferred term **Epididymis and efferent duct cribriform changes**.

Epididymis and efferent duct reduced luminal sperm is a synonym for epididymal luminal sperm, reduced. See the preferred term **Epididymal luminal sperm, reduced**.

Epididymis and efferent duct single cell epithelial necrosis is characterized by shrunken, hypereosinophilic individual epithelial cells with condensed or fragmented nuclei, and the absence of associated inflammation. There is a background level of single cell necrosis (i.e., apoptosis) that is accentuated with decreased androgen levels or occlusion of the efferent duct. When associated with decreased androgen levels, location is time-dependent; preliminary changes occur in the initial segment, which transition to the caput, corpus, and subsequently the cauda epididymis. If due to efferent duct occlusion, epithelial single cell necrosis is restricted to the initial segment of the duct without any further downstream effects.



Single cell necrosis (arrows), epididymal epithelial cells, rat, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

Synonym(s): **Epididymis and efferent duct apoptosis**.

Epididymis and efferent duct squamous cell metaplasia is an adaptive response that results in replacement of the normal epididymal or efferent duct epithelium with multiple layers of stratified squamous epithelium that may contain laminated keratin whorls or debris. Squamous cell metaplasia may be secondary to inflammation or sperm granulomas. In rodents, squamous metaplasia of the epididymis and/or vas deferens occurs with hypovitaminosis A and is observed in specific genetically modified mice.

Epididymis and/or efferent duct hypoplasia consists of a congenital absence or a segmental reduction in development. Hypoplasia of one or more efferent ducts is a relatively common incidental finding in the rat. Diffuse epididymal hypoplasia is uncommon, and usually results from a low androgen environment during critical periods of organogenesis. It has been observed in rats given linuron, dibutyl phthalate, and dithylhexl phthalate. Macroscopically, there may be distension and/or discoloration of the tissue proximal to the hypoplastic area. Microscopic changes include fewer efferent or epididymal ductal structures, sperm stasis, spermatoceles, and/or the formation of sperm granulomas.

Synonym(s): **Epididymal hypoplasia**; **epididymis and efferent duct aplasia**.

Epididymis, hypospermia, see the preferred term **Epididymal luminal sperm, reduced**.

Epididymis, oligospermia, see the preferred term **Epididymal luminal sperm, reduced**.

Epididymis, spermatids reduced, see the preferred term **Epididymal luminal sperm, reduced**.

Epigenetics is a discipline that investigates DNA function not associated with a change in DNA sequence. Such alterations result in changes in phenotype without alteration of the genotype. Epigenetic changes involve DNA modifications such as C5 methylation of cysteine or chromatin changes such as histone acetylation. These specific alterations result in gene expression changes, which generally are maintained within the cell type of a particular organ in the absence of genotypic (DNA sequence) changes.

Epinephrine, see the preferred term **Catecholamine**.

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Epineurium is an external connective tissue layer that surrounds peripheral nerves. See **Blood-nerve barrier** and Appendix 3 for further information.

Epiretinal membranes, see the preferred term **Retina fibroplasia**.

Episcleritis, see the preferred term **Scleral inflammation**.

Epithelial alteration is a focal to diffuse flattening of respiratory epithelium with loss of cilia and a slight increase in the number of cell layers. This change may be a precursor to squamous cell metaplasia where respiratory epithelium is replaced by squamous epithelium. The base of the epiglottis and areas around the ventral pouch are most susceptible to this change. It has also been described in the gallbladder of mice and dogs. In this case the alteration consists of hyaline eosinophilic cytoplasm. This lesion has been associated with administration of penicillin in mice.

Epithelioid macrophages are enlarged macrophages (monocytic phagocytic cells) with an increased amount of cytoplasm which often appears eosinophilic. These cells can be observed within areas of chronic inflammation. See **Granulomatous inflammation** for further information.

Epitheliotrophic lymphoma, see the preferred term **Lymphoma, epitheliotrophic (canine)**.

Epitheliotropic cutaneous lymphoma is a skin-associated lymphoma comprised of neoplastic T cells. Refer to **Hematopoietic System** in Appendix 2 for further information.

Epoxidation is the formation of epoxides during oxidative metabolism of olefins or aromatic compounds. Many epoxides are reactive metabolites as a consequence of their electrophilic nature and may react with cellular macromolecules such as proteins and nucleic acid resulting in cytotoxicity or genotoxicity. See **Drug metabolism** for further information.

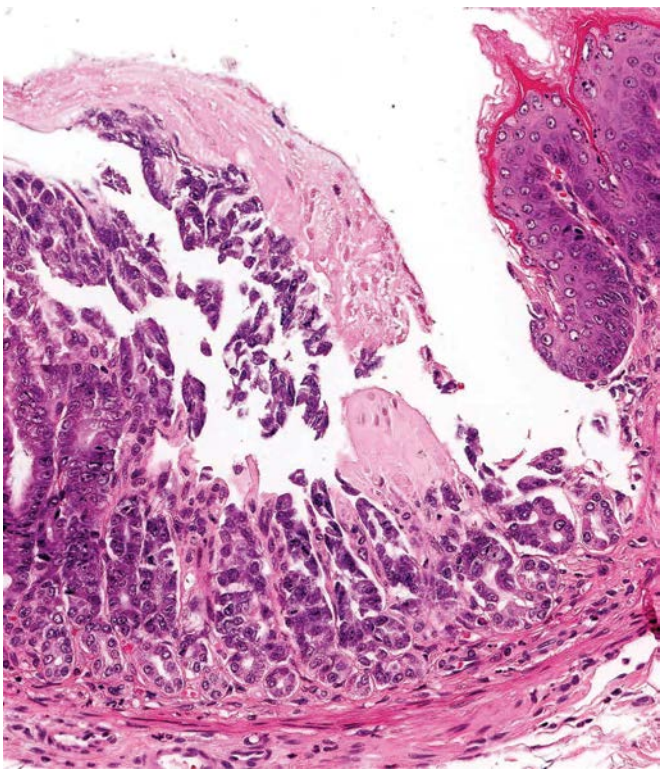
Epoxide hydrolase (hydratase) enzymes catalyze the hydrolysis of epoxides to the corresponding dihydrodiols. Both microsomal (EC 3.3.2.9) and cytosolic (EC 3.3.2.10) enzymes are known. The main function of epoxide hydrolase is the inactivation of potentially toxic epoxides formed during drug oxidation.

Epulis, acanthomatous, see the preferred term **Ameloblastoma, acanthomatous**.

Epulis, fibromatous of periodontal ligament origin is a benign oral neoplasm in dogs. This stromal neoplasm appears grossly as a gray mass adjacent to teeth commonly in the maxilla. It is composed of stellate to spindle-shaped fibroblasts and collagen resembling the periodontal ligament. Islands or cords of epithelial cells are commonly seen in these tumors but are considered a secondary feature derived from the cell rests of Malassez. Refer to **Bone, Muscle, and Tooth** in Appendix 2 for further information.

Equilibrium dialysis is a method of determining the noncovalent interaction between small molecules and macromolecules such as proteins. It is one of the methods used to determine the extent of binding of drugs and drug candidates to plasma proteins. In equilibrium dialysis, a small-molecular-weight ligand is placed on one side of a semipermeable membrane and the protein solution on the other side. The small molecule is then allowed to diffuse until an equilibrium is achieved. Under these conditions, if there is no interaction between the drug and the protein, then the concentration of the drug would be the same on both sides of the membrane. If the drug binds to the protein, then the free concentration of the drug will be the same on either side of the membrane but the total concentration (bound plus free concentration) will be higher on the side of the membrane with the protein solution. In this manner, the extent of binding of the drug to the protein may be determined. See **Plasma protein binding** for further information.

Erosion is complete or partial loss of the epidermis or epithelial mucosa of the skin, gastrointestinal tract, or urinary or respiratory organs. It affects only the superficial layers, with



Erosion of the stomach of a rat, H&E. There is focal loss of glandular epithelium in the mucosa of the stomach. (Reproduced with the permission of Germann, P. and Morawietz, G. (eds.) *Toxicopathology Case Collection CD-ROM*. European Society of Toxicologic Pathology.)

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the basement membrane remaining intact, and inflammation may be absent or only modest. In contrast, ulceration involves disruption of the basement membrane and therefore more significant inflammation.

Differential diagnosis: **Ulcer**.

Erythema is redness of the skin observed clinically caused by capillary congestion. It commonly accompanies inflammation or injury to the skin. Erythema is often visible in the living animal, but postmortem the congestion disappears and the erythema is no longer visible.

Erythema multiforme is single cell necrosis of multiple epidermal cells. The use of this term implies that either a toxic or immune-mediated mechanism has induced this change. Exposure to ultraviolet (UV) light will also cause single cell necrosis of multiple epidermal cells, which are commonly called sunburn cells. Erythema multiforme should not be used when the cause is UV exposure. Due to the implied cause of single cell necrosis resulting from the use of either term, especially if the cause is uncertain, the preferred term is single cell type epidermal necrosis with qualifiers. See **Epidermal necrosis** for further information.

Erythroblastic leukemia, see the preferred term **Erythroid leukemia**.

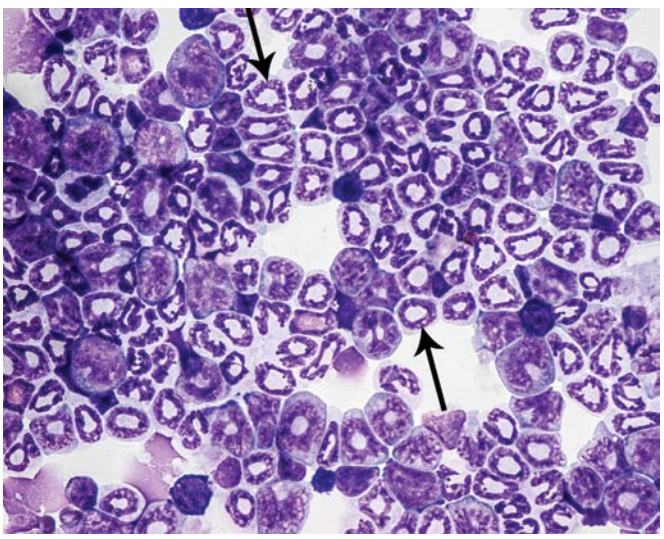
Erythrocyte is also called a red blood cell (RBC). RBCs are the most numerous of the formed elements in blood, and function to carry and deliver oxygen to body tissues. Mature erythrocytes are anucleate, are rich in cytoplasmic hemoglobin, and contain a lipid membrane. The red color of erythrocytes is due to the iron-rich hemoglobin. In humans, erythrocytes circulate for approximately 120 days before they are eliminated by macrophages. Circulation time for erythrocytes is species specific, and monkeys, dogs, rats, and mice have substantially shorter circulation times than humans. New erythrocytes are continually replaced by the bone marrow located primarily in flat bones or the ends of long bones. Maturation begins with nucleated erythroblasts, but the nucleus is extruded before the erythrocyte is released into peripheral blood. Since erythrocytes lack cellular organelles, they produce energy glycolysis of glucose and lactic acid fermentation on the resulting pyruvate. In addition, since they lack a nucleus, mature erythrocytes cannot divide and have very limited repair capabilities. Erythrocytes in most species are typically shaped like biconcave disks, with a flattened, compressed center; however, some species, such as pig, deer, or cattle, contain large numbers of abnormally shaped erythrocytes. The disk shape facilitates the flow properties through vasculature without damage. In addition, the phospholipid and cholesterol content of the erythrocyte membrane also contribute to the flexibility and deformability of the red blood cell. The size of erythrocytes is another parameter that is species specific, but typically ranges from approximately 6–8 μm.

Erythrocytosis, see the preferred term **Polycythemia**.

Erythrodysplasia, see the preferred term **Erythroid hematopoietic dysplasia**.

Erythroid is a general term that means relating to erythrocytes. All erythroid cells are derived from committed erythroid stem cells. Erythroid progenitor cells then develop in two phases: erythroid burst-forming units (BFU-E) followed by erythroid colony-forming units (CFU-E). Erythropoietin stimulates the conversion of BFU-E to CFU-E. Further differentiation of the CFU-E results in the production of erythroblasts.

Erythroid depletion refers to a decrease in nucleated erythroid precursors in bone marrow sections. It can also be termed erythroid hypocellularity or erythroid hypoplasia. When either an erythroid or myeloid is affected, the myeloid-to-erythroid (M:E) ratio will be altered. For example, the M:E ratio will be increased with erythroid depletion as long as myeloid numbers remain constant. Erythroid depletion can be observed in a non- or poorly regenerative anemia. Decreases in erythropoietic cells in the bone marrow have been reported due to the direct effect of estrogens, chloramphenicol, antiviral agents, and chemotherapeutics or to indirect effects such as tumor necrosis factor or cupric sulfate. A variety of other factors have also been associated with suppressed erythroid production, including chronic inflammation, neoplasia, inanition, hypothyroidism, hypoadrenocorticism, chronic renal disease, and chronic hepatic disorders. Lineage-specific erythroid depletion occurs more frequently than myeloid depletion.



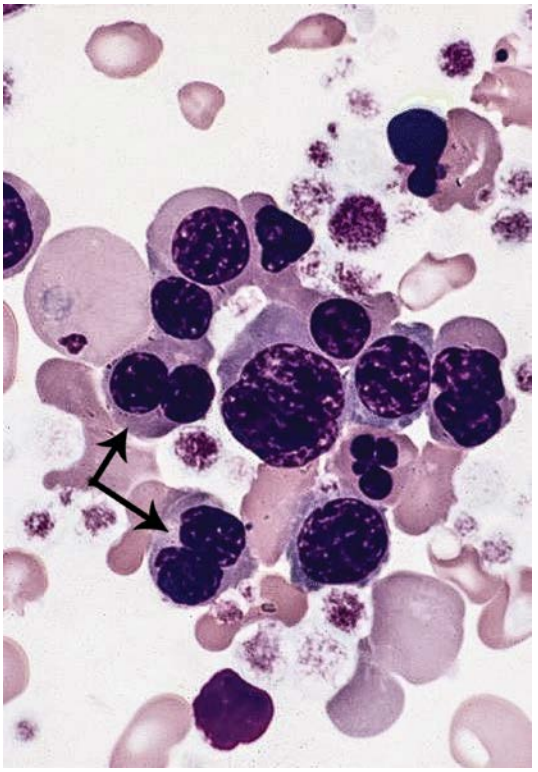
Erythroid depletion, drug induced, bone marrow, rat. Note the predominant cell type are ring form neutrophils (arrows) as erythroid cells are lacking.

Erythroid dysplasia is a condition in which immature erythroid cells in the bone marrow are abnormal. The abnormality can involve the size, shape, number, or organization of the cell. Chemotherapy and vitamin deficiency causing megaloblastic anemia are two primary causes of erythroid dysplasia.

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It can also occur with refractory anemia or myelodysplastic syndrome.

Synonym(s): **Erythrodysplasia**.



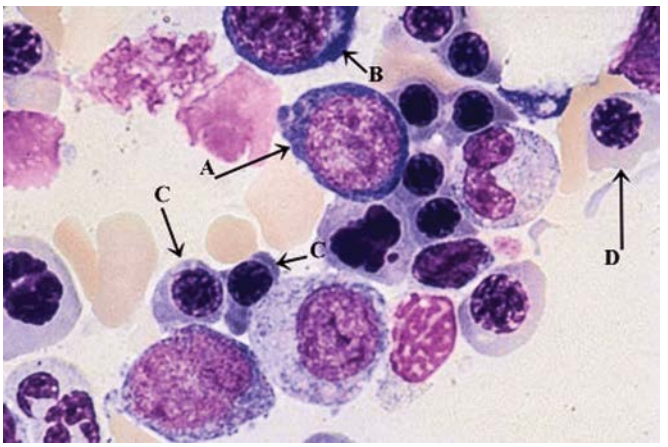
Erythroid dysplasia, bone marrow, human, associated with chemotherapy. Note the multinucleated erythroid cells (arrows).

Erythroid hematopoietic dysplasia is a condition in which immature erythroid cells in the bone marrow are abnormal. Refer to **Hematopoietic System** in Appendix 2 for further information.

Erythroid hyperplasia is an increase in the number of red blood cells in the hematopoietic tissues. Subsequently, the myeloid:erythroid ratio in the bone marrow is decreased. Refer to **Hematopoietic System** in Appendix 2 for further information.

Erythroid leukemia is a leukemic neoplasm of the erythroid cell lineage in the bone marrow or spleen characterized by excessive malignant proliferation of erythroblasts and normoblasts. Refer to **Hematopoietic System** in Appendix 2 for further information.

Erythroid maturation series in bone marrow. As bone marrow erythroid cells mature, they decrease in size, the nuclear chromatin becomes more coarse and condensed until it is extruded in the mature erythrocyte, and the color changes from deeply basophilic to gray to pink. (A) rubriblast (or prorubricyte), (B) basophilic rubricyte, (C) polychromatophilic rubricyte, (D) metarubricyte (see figure at the top of the right column).

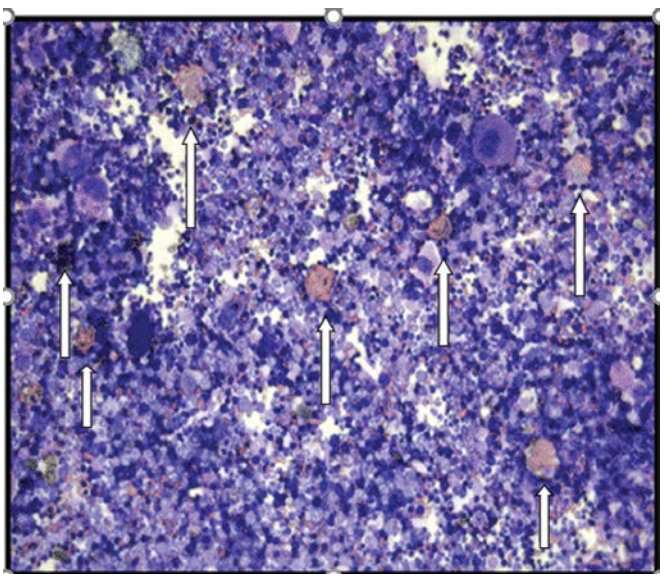


Erythroid maturation: (A) rubriblast (or prorubricyte), (B) basophilic rubricyte, (C) polychromatophilic rubricyte, (D) metarubricyte.

Erythroleukemia, see the preferred term **Erythroid leukemia**.

Erythron refers to the circulating erythrocytes in peripheral blood, precursor erythrocytes, and all the body elements required in erythrocyte production.

Erythrophagocytosis is the ingestion of red blood cells by macrophages or other phagocytes. It can be observed in liver, spleen, bone marrow, lung, peripheral blood, and occasionally in body fluids, such as lung effusions. The occurrence of erythrophagocytosis is rare but can be increased in the presence of hemolytic anemia, chronic infection, and chronic renal failure. Erythrophagocytosis is believed to be a mechanism of destruction for aged or damaged erythrocytes. Typically, senescent red cells demonstrate complement binding. The presence of complement and/or IgG allows binding of Fc receptors to macrophages. Phagocytosis of red blood cells allows a mechanism for recycle of iron and protein



Erythrophagocytosis (arrows).

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globin components. In animals, erythrophagocytosis is most commonly seen in the spleen, as this is the primary site for disposal of senescent red blood cells. The preceding figure demonstrates enhanced erythrophagocytosis in mouse bone marrow. White arrows indicate erythrophages at various stages of red cell destruction and accumulation of hemosiderin (iron-containing black pigment). Erythrophagocytosis in lymph nodes is a mechanism for removal of red cells from lymphatic drainage fluid that occurs with tissue hemorrhage distal to the lymph node. See **Hemosiderin accumulation** and **Hemosiderosis** for further information.

Differential diagnosis: **Emperipolesis**.

Erythropoiesis is the process of formation of erythrocytes (i.e., red blood cells [RBCs]), and is regulated by erythropoietin.

Erythropoietin (EPO) is the hormone responsible for red blood cell production. EPO production is stimulated by hypoxia. The primary site for EPO production is the kidney, although the liver also has some capacity to produce EPO. During fetal development, the liver is the primary site for EPO production. Recombinant EPO is used to stimulate erythropoiesis in cancer patients with anemia, those with end-stage renal disorders, and patients with acquired immunodeficiency syndrome. EPO receptors are found on marrow CD34 + stem cells and erythroid precursors. EPO acts as a survival factor and prevents apoptosis of erythroid cells. EPO acts on progenitor cells and induces transformation of erythroid-committed CFU-E to proerythroblasts, enhances proliferation of the BFU-E, increases the transition from proerythroblasts to basophilic erythroblasts, and stimulates the premature release of stress reticulocytes from the bone marrow. Stress reticulocytes refer to reticulocytes that are released prematurely from the bone marrow as an exaggerated regenerative response to anemia.

Esophageal dilation, see the preferred term **Esophageal dilatation**.

Esophageal distention, see the preferred term **Esophageal dilatation**.

Esophageal diverticulum is a rare congenital abnormality caused by mechanical or biochemical disruption of esophageal wall structures resulting in loss of extracellular matrix integrity and herniation of the squamous epithelial lining into the deeper layers. Diverticulum forms an irregular cyst-like extension of the mucosal lumen into or through the muscularis layer and may become impacted with food, become locally inflamed, ulcerate, and/or eventually perforate, leading to abscess formation.

Differential diagnosis: Esophageal cyst.

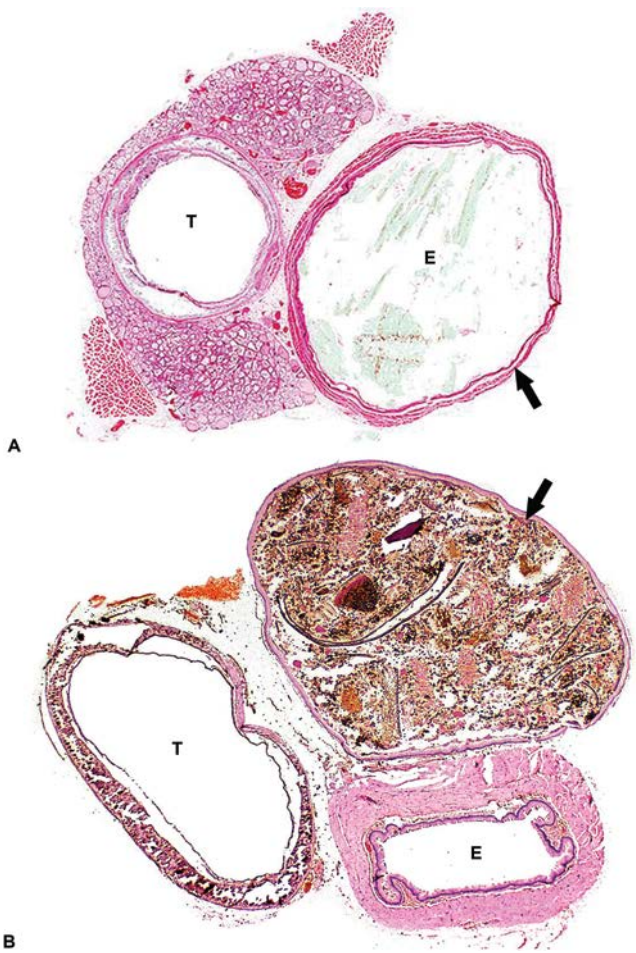
Synonym(s): **Pharyngoesophageal diverticulum**.

Esophageal impaction, see the preferred term **Esophageal dilatation**.

Esophagitis, see the preferred term **Esophagus inflammation**.

Esophagus dilatation (megaesophagus) is a spontaneous/idiopathic macroscopic finding in rats, mice, dogs, and humans due to food impaction but can also be secondary to an alteration of the esophageal neuromuscular function, decreased secretion of the salivary glands, or an altered swallowing reflex. Histologically, esophageal dilatation is characterized by enlargement of the esophageal lumen and thinning of the muscle and mucosal layers. Chronic esophageal dilatation may be associated with degeneration of the muscles and nerve cells in the wall of the esophagus. Esophageal dilation has been reported in female F344 rats and attributed to feeding a powdered food diet in National Toxicology Program (NTP) studies. Esophageal dilatation has also been reported as an induced finding in mice with intrauterine exposure to diethylnitrosamine, and in rats secondary to the effects of scopolamine on salivary secretion and the swallowing reflex. Dilatation of esophagus (megaesophagus) has been reported in several strains of rats and mice including transgenic [Pvrl3-Cre] rats, Cdb:BHE rat, and ICRC mice.

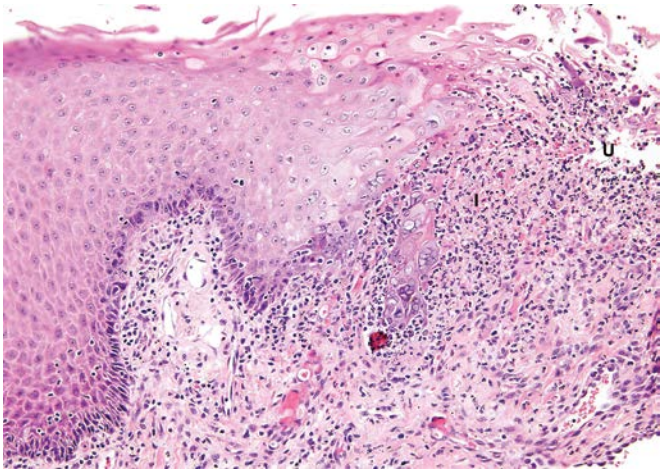
Synonym(s): **Esophageal distension**; **megaesophagus**; **esophageal dilation**; **esophageal impaction**.



Esophagus, mouse. H&E. (A) Dilatation. Arrow = dilated lumen. (B) Arrow = diverticulum and lumen distention with food material. T = trachea. E = esophagus. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

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Esophagus erosion/ulcers are more commonly associated with injury as a result of the gavage procedure, which can also result in perforation, periesophageal inflammation, and fibrosis. Inflammation, regeneration of the epithelium and myocytes, hyperkeratosis, and parakeratosis with increased thickness of keratinized squamous epithelial cell layers typically accompanies ulcerations.



Tongue, rat. H&E. U = ulcer, I = inflammation. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

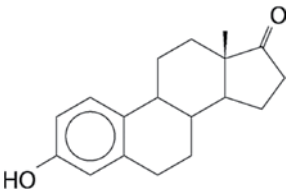
Esophagus inflammation is characterized by an infiltration of inflammatory cells (e.g., neutrophils, macrophages, and lymphocytes) and disruption of associated anatomy. It can be precipitated by a variety of stimuli, including mechanical, chemical, or fungal (see esophageal candidiasis).

Synonym(s): **Esophagitis**.

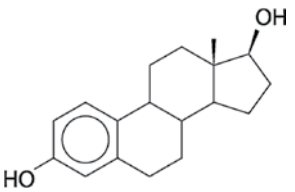


Esophageal candidiasis. Cynomolgus monkey. H&E. C (arrow) = Candida, I = inflammation and squames, E = epithelium, M = muscular wall.

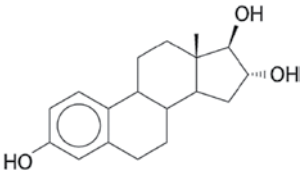
Estrogen is hormone synthesized from androgens and produced by the reproductive system that directs embryological female sex organ development and secondary sex characteristics in mammals. Estrogens include estrone (E1), estradiol (E2), estriol (E3), and estetrol (E4). Circulating levels of specific estrogens vary with age, function, and species. In most mammals, E2 is the primary estrogen of the reproductive years and E4 is primarily elevated during pregnancy. Although low in concentration, E2 is present in males and serves to modulate spermatogenesis, as well as other reproductive functions. Some estrogens are manufactured as pharmaceuticals, such as the stilbestrol estrogens, and others occur as contaminants in the environment or as products of fungi (xenoestrogens). There are three main estrogenic hormones: estrone, estradiol, which is the most potent, and estriol. See **Female reproductive hormones** for further information.



Estrone (E1)



Estradiol (E2)



Estriol (E3)

Structural formulas (from top to bottom) for the estrogens – estrone (E1), estradiol (E2) and estriol (E3).

Estrous cycle is the recurring physiologic and behavioral changes induced by reproductive hormones in most female mammals that bear live young; primates have menstrual cycles and typically are not considered to have estrous cycles. The start of estrous cyclicity signals reproductive maturity. The cycle is comprised of phases (i.e., proestrus, estrus, metestrus, and diestrus) driven by reproductive hormones during which time the follicles in the ovary mature, ovulate, and become corpora lutea. The length of the cycle varies with

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species and strain of animal: rats and mice have 4- to 5-day cycles, pigs have 21-day cycles, and dogs generally cycle 1–3 times per year, with long anestrus phases between each cycle.

Synonym(s): **Ovulatory cycle**; **ovarian cycle**; **reproductive cycle**.

Eukaryote is an organism wherein the cells possess nuclei. There is a very basic discriminator in biology, where organisms are divided into prokaryotes (no nucleus, e.g., bacteria) and eukaryotes.

Eukaryotic mutagenicity tests are mutagenicity assays using eukaryotic cells, in contrast to bacteria. In vitro eukaryotic cell assays include the mouse lymphoma L5178Y TK+/− gene mutation assay, which measures mutations at the thymidine kinase locus, or assays that measure mutations at the hypoxanthine guanine phosphoribosyl transferase (HPRT) locus. Cell lines used with this endpoint include CHO and V-79 cells. These in vitro cellular assays may be complemented by in vivo assays, for example, the Pig-a assay, which is primarily performed in rats, and measures mutations in the phosphatidylinositol *N*-acetylglucosaminyltransferase gene. Eukaryotic gene mutation assays of this type are not usually included in the standard genotoxicity battery for pharmaceuticals but may be used to further investigate unclear findings in the standard test battery.

European Medicines Agency (EMA) the body that oversees drug development and registration within the European Union (EU) and after assessment of the submitted documentation issues marketing approval in all EU member states.

Eustachian tube inflammation consists of focal, multifocal, or diffuse accumulations of inflammatory cells (neutrophils or heterophils [rabbit, chinchilla, and guinea pig], eosinophils, macrophages, lymphocytes, plasma cells, and multinucleated giant cells) within the lumen and the adjacent epithelium. Inflammation may be accompanied by hemorrhage, cellular debris, and Eustachian tube squamous cell metaplasia with chronic inflammation. Lymphocytes without other indicators of inflammation at the nasopharyngeal end of the tube are most likely acquired mucosa-associated lymphoid tissue. Inflammation is common with viral infections but may also occur with transtympanic injections of xenobiotics.

Differential diagnoses: **Eustachian tube inflammatory cell infiltrate; Eustachian tube mucosa-associated lymphoid tissue**.

Eustachian tube inflammatory cell infiltrate, see the preferred term **Eustachian tube mucosa-associated lymphoid tissue**.

Eustachian tube mucosa-associated lymphoid tissue (MALT) is acquired lymphoid tissue that varies from small, loose aggregates of submucosal lymphocytes to mature lymphoid nodules with germinal centers along the nasopharyngeal end of the eustachian tube (refer to Appendix 3 for further information). As with other MALT, the epithelium is frequently elevated into the lumen by lymphocytes, and the epithelium over the MALT will be differentiated into follicle-associated epithelium which lacks microvilli and goblet cells, and transepithelial migration of leukocytes is usually present in these specialized areas.

Differential diagnosis: **Eustachian tube inflammation**.

Eustachian tube squamous metaplasia consists of transformation of ciliated pseudostratified columnar epithelial cells into other epithelial types, particularly squamous cells, but also mucus-secreting goblet cells which may change the secretory and pressure equalizing capacity between the middle ear and the oropharynx (refer to Appendix 3 for further information).

Excision repair enzymes are DNA repair enzymes that work by excising parts of damaged DNA strands and resynthesizing the missing part. Both nucleotide and base excision repair systems are found.

Excitatory amino acids include aspartic and glutamic acid, both of which act on the voltage gated ion channels of cell membranes in the nervous system. These amino acids cause depolarization of cells and may also trigger cell death. They can be produced by plants and fungi leading to neurotoxicity. Glutamate is a major excitatory neurotransmitter in the brain. Glutamate abnormalities may be involved in a variety of neurodegenerative diseases (e.g., cerebral ischemia, Huntington's chorea, amyotrophic lateral sclerosis, epilepsy, spasticity, emesis, chronic pain, and schizophrenia). Excitatory amino acid receptor agonists and antagonists are therefore of interest as potential drugs for these disorders.

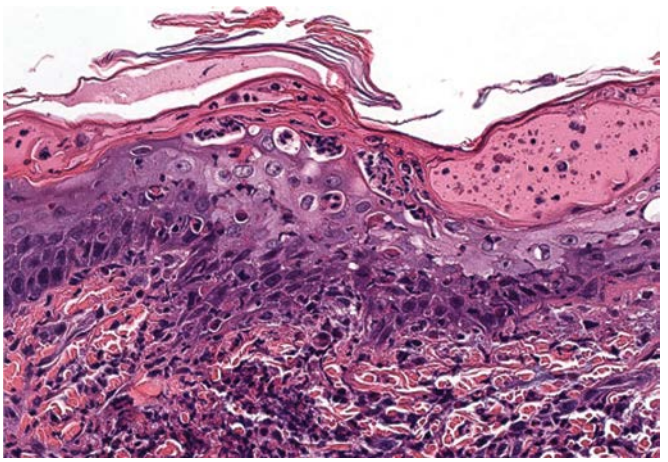
Excretion is the process by which a drug or foreign compound is irreversibly removed from the body. Excretion may occur as parent compound or metabolites. The major routes of excretion are via the kidney (renal excretion) or the bile (biliary excretion), although excretion may also occur via the lungs, the sweat glands, or by direct transport or diffusion across the intestinal epithelium. Biliary excretion or direct excretion across the intestinal epithelium results in the products being found in the feces. Following renal excretion, the products are found in the urine. See **Enterohepatic recirculation** for further information.

Exocrine pancreas is the largest portion of the pancreas. It produces and secretes digestive enzymes (e.g., amylase, lipase), or inactive proenzymes and zymogens of digestive enzymes (e.g., trypsinogen, chymotrypsinogen, proelastase, prophospholipase, carboxypeptidase) that help in the digestion of dietary proteins, triglycerides, and complex carbohydrates. The exocrine pancreas is a compound tubuloalveolar or compound acinar gland with pancreatic acini consisting of a single layer of pyramidal acinar cells arranged concentrically around a lumen. The base of the pyramidal acinar cells is basophilic due to the presence of abundant rough endoplasmic

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reticulum. These cells also contain one or two nuclei and intracytoplasmic eosinophilic zymogen granules. Pancreatic acini are surrounded by a thin basal lamina, scant reticular stroma, and pancreatic stellate cells. Acinar cells are lined by flattened, pale staining centroacinar cells at the luminal surface which are continuous with the intercalated, intralobular, interlobular, and main ducts. Ducts are lined by cuboidal to columnar (sometimes ciliated) epithelial cells with occasional goblet cells in the larger ducts. The exocrine pancreas is compartmentalized into peri- and tele-insular regions based on morphology and physiological functions. The peri-insular acinar cells are in close proximity to the islets of Langerhans, and are larger due to more abundant cytoplasm, larger zymogen granules, and nuclei that are larger than the tele-insular acinar cells that are away from the islets. The exocrine pancreas has great reserve capacity such that no clinical evidence of exocrine pancreatic insufficiency is noted with up to 90% destruction. Exocrine pancreatic function deficiency of more than 90% results in improper digestion of food and malabsorption of nutrients.

Exocytosis is the process by which large molecules are exported from cells via fusion of a secretory vesicle with the plasma membrane, releasing its contents into the extracellular milieu. It is also the process of inflammatory cells crossing an epithelial cell layer from the underlying tissue, most commonly the epidermis.



Exocytosis of inflammatory cells through the epidermis of a cat, H&E. There are also large areas of intra-epithelial edema as well as degenerating keratinocytes.

Exon is that part of a gene that is eventually transcribed into mRNA. In the DNA, exons are separated by the noncoding introns, which are removed during splicing.

Exposure assessment during toxicity studies with pharmaceutical products is generally performed by assessing the systemic exposure to a drug and (if appropriate) major circulating metabolites, via measurement of plasma, serum, or whole blood concentrations. On rare occasions when circulating blood levels cannot be assessed, or poorly represent systemic exposure, the exposure may be estimated from the amount of drug excreted in the urine or taken up by selected tissues. See **Bioanalytics** for further information.

Exposure route, or "route of administration," is the path by which substances enter the body. Typical routes in toxicology studies include oral, inhalation, dermal, intravenous, ocular, and subcutaneous, followed by more specialty routes often mimicking the intended clinical routes of administration. The intraperitoneal route is used more often in rodent discovery models than in drug or chemical toxicology studies.

External ear canal debris consists of cellular and secretory materials that accumulate within the ear canal and represents degenerating or fragmented exfoliated cells and leukocytes, lipid clefts (sebum), and amorphous eosinophilic (proteinaceous) material and other environmental contaminants. Such material may be a spontaneous finding, associated with abnormalities of the ear canal, or found after transtympanic injection of irritating material.

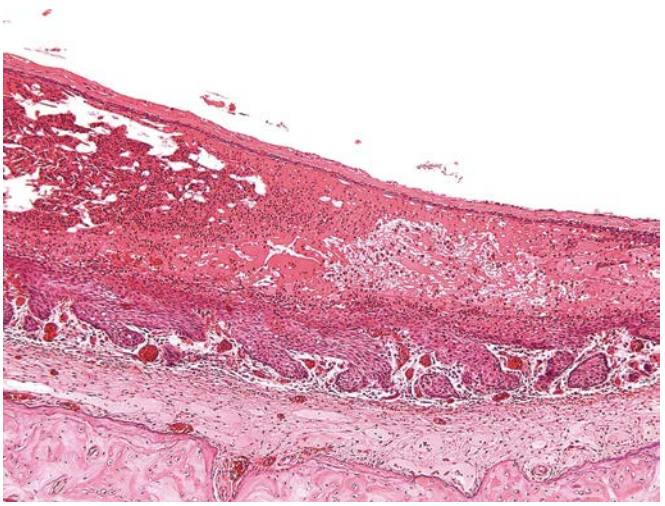
Differential diagnosis: **External ear canal inflammation**.

See **External ear canal inflammation** for illustration.

External ear canal inflammation consists of focal or diffuse accumulations of inflammatory cells (neutrophils or heterophils [rabbit, chinchilla, and guinea pig], eosinophils, macrophages, lymphocytes, plasma cells, and multinucleated giant cells) and involves inflammation of the epithelium or adnexa of the external ear canal, which may be a spontaneous change or related to local irritation from administration of test articles. Inflammation may be accompanied by epithelial or glandular hyperplasia, hemorrhage, and cellular debris. Many of the inflammatory changes of the external ear canal are similar to those of the outer ear (pinna) and skin and adnexa, with varying severity and cell types in the inflammatory response.

Differential diagnosis: **Auricular cartilage inflammation**.

Synonym(s): **Otitis externa**.



External ear canal inflammation with cellular debris, hemorrhage, and epithelial hyperplasia; bony canal of the external ear, rabbit, H&E. (Image courtesy of K. Schafer, Vet Path Services, Mason, Ohio.)

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Extracellular matrix (ECM) is the substance located outside of the cells of a tissue or organ whose function is to support (both physically and chemically) the cells of the tissue or organ. The ECM is secreted by at least some cells of the tissue and includes the basement membrane underlying the epithelia. Extracellular matrix components vary by tissue or organ and can compose the majority (as in bone or tendon) or minority (as in endocrine glands) of the tissue or organ. ECM components are often aggregated proteins such as collagen, elastin, fibronectin, and laminin admixed with polymers of heavily modified carbohydrates like glycosaminoglycans, heparin sulfate, chondroitin sulfate, keratin sulfate, and hyaluronic acid that can adsorb water, providing cushioning for mechanical and physiologic stressors. The ECM sequesters inactive growth factors, cytokines, and enzymes that are important in the tissue or organ's response to injury.

Extramedullary hematopoiesis (EMH) is a term used to describe the presence of hematopoiesis in tissues outside of the bone marrow. This can occur in many tissues (e.g., spleen, lymph nodes, liver, adrenals). An increase in EMH is generally a reaction to an increased demand due to blood loss, infections, tumors, or ulcerations. In some tissues like spleen and liver, EMH is normal depending on the age of the animal. Morphologically, EMH is characterized by the presence of multiple focal accumulations of hematopoietic cells of different lineages with normal differentiation. Depending on the stimulus, EMH may be more erythroid or myeloid. In contrast to a leukemia, increased EMH is not invasive, and follows normal anatomical boundaries.

Extramedullary neutrophilic hematopoiesis is a form of extramedullary hematopoiesis (EMH) in which myeloid cells dominate. Morphologically, it is characterized by an increased EMH of predominantly myeloid (granulocytic) lineage cells and their precursors, with a normal differentiation. Megakaryocytes and some erythroid cells are also often present. Extramedullary neutrophilic hematopoiesis may occur in reaction to an infection (e.g., ulcerated tumor) and bone marrow will exhibit an increased myeloid-to-erythroid (M:E) ratio. See **Extramedullary hematopoiesis** for further information.

Extravascular hemolysis is a condition in which red blood cells are phagocytized by the hepatosplenic monocyte phagocyte system (MPS). Accelerated extravascular hemolysis is associated with bound immunoglobulin or physical abnormalities that restrict erythrocyte deformability and antagonize egress through the spleen and liver. Splenic and hepatic macrophages remove only the damaged segment of red blood cell as the Fc receptors bind to attached immunoglobulin. The remainder of the erythrocyte rounds up producing microspherocytes in extravascular hemolysis. Heme is removed, degraded to bilirubin, and reused. Little hemoglobin escapes into the plasma, so haptoglobin is not decreased, and there is little evidence of free hemoglobin in plasma or urine.

Exudate is fluid in a tissue or body cavity that is often associated with an inflammatory process. As such, exudates will have higher protein content than transudates. For example, for pulmonary effusions, a fluid is classified as an exudate if it meets one or more of the following criteria: effusion protein/serum ratio greater than 0.5 and/or a lactate dehydrogenase (LDH) level greater than two-thirds the upper limit of the laboratory's reference range for serum LDH. See **Transudate** for further information.

Exudative glomerulonephritis is a stage in acute glomerulonephritis where neutrophils (polymorphonuclear cells [PMNs]) are present within the glomerulus.

Eye irritation tests are required for many products to determine safety in the facilities where they are made and formulated, and for safe use of many industrial products. In the pharmaceutical industry, they are required for drug substance and drug product for worker protection, and for any drug product intended for ocular or tropical application. In vitro and in vivo methods are used as described in OECD guidelines. In vitro methods include the bovine corneal opacity and permeability (BCOP) test (TG 437), the isolated chicken eye test (TG438), the fluorescein leakage test (TG460), and short time exposure test (TG491). Substances should only be tested in vivo on rabbit eyes (TG405) if they cannot be classified by in vitro methods and are non-irritating to rabbit skin. The in vivo test guidance recommends albino rabbit as the preferred species. The test substance is applied as a single dose into the conjunctival sac of one eye of each animal. The other eye, which remains untreated, serves as a control. Initially a single animal is used, and the dose is determined based on knowledge of the compound. An irritant or negative response is confirmed using up to two additional animals.

Eyelid infiltrate inflammatory cell foci consist of small numbers of leukocytes in the absence of obvious inflammation at the eyelid margin.

Differential diagnosis: **Eyelid inflammation**.

Eyelid inflammation consists of inflammatory cells or abscesses at the mucocutaneous junction with possible extension from or to the palpebral conjunctiva, outer haired surface or within the Meibomian glands and eyelashes. Sebum, keratin, and cellular debris often accumulate on the eyelid margin and eyelashes, and Meibomian glands may also become atrophic. External trauma and infections, and irritation caused by topical administration of test substances with secondary self-mutilation or infections can contribute to eyelid changes.

Synonym(s): **Blepharitis**; **blepharoconjunctivitis**.

Eyelid malformation, see the preferred term **Optic fissure malformation**.

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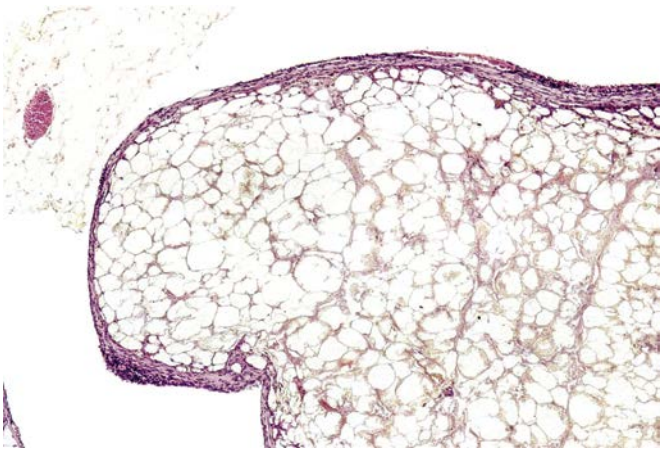
Fallopian tube, see the preferred term **Oviduct**.

Fanconi syndrome is typified by impaired renal proximal tubule reabsorption leading to urinary loss of sugar, amino acids, protein, bicarbonate, potassium, and phosphorus. The syndrome can be inherited in certain breeds of dogs such as Basenjis, border terriers, Norwegian elkhounds, whippets, Yorkshire terriers, Labrador retrievers, and Shetland sheepdogs, but may also be associated with chemical-induced toxicity.

Fast and slow acetylator phenotypes result from the polymorphic distribution of the enzymes *N*-acetyl transferase. See **Acetylation** for further information.

Fat atrophy, see the preferred terms **Adipose tissue atrophy** and **Mucoid or serous atrophy of adipose tissue**.

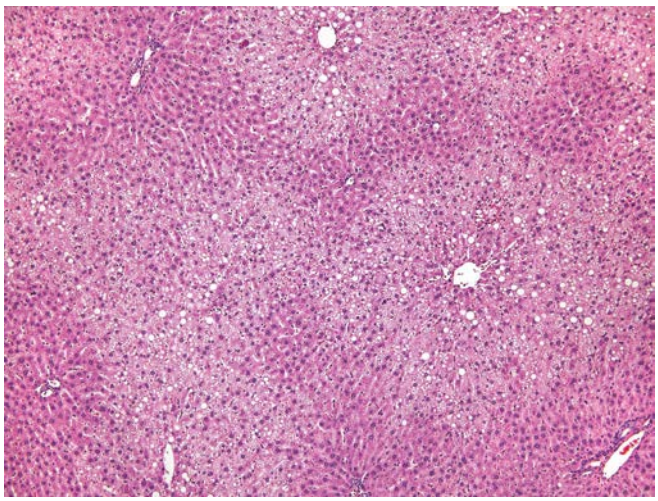
Fat necrosis refers to a cluster of irreversibly damaged adipocytes. These are often seen in the vicinity of degenerate adipocytes. Morphologically, adipocytes may swell, lose cellular membrane detail, and may include areas of basophilia due to deposition of calcium salts and/or extracellular matrix such as glycosaminoglycans. Necrotic adipocytes appear "ghosted" and are often demarcated from adjacent viable tissue by a rim of fibrous connective tissue.

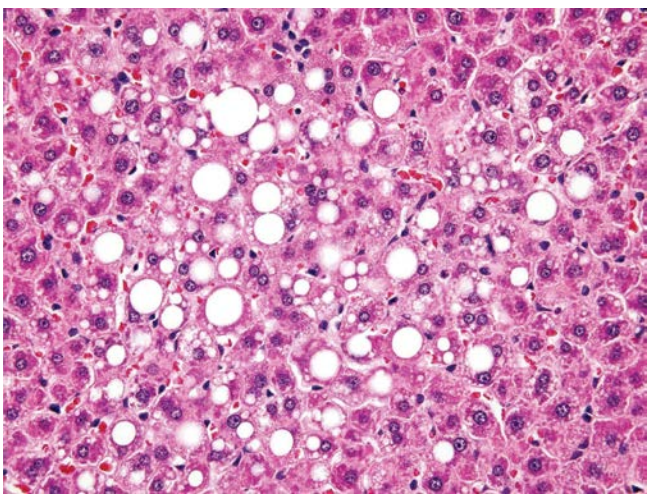


Fat necrosis in the mesentery of a mouse, H&E. Necrotic adipocytes are contained within a fibrous capsule. Necrotic adipocytes retain the outline of their cellular architecture but lack normal cellular detail and appear like "ghost" cells. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

Fatty change occurs in response to injury or alteration in metabolism and is manifested in the cell as an accumulation of small (microvesicular) to large (macrovesicular) vacuoles containing unmetabolized or untransported lipids in the cytoplasm. It occurs most often in tissues that are involved in lipid metabolism, especially the liver, but can also be seen in kidney and heart. The lipid in the vacuole is lost during routine tissue processing but can be demonstrated with special stains such as oil red O or Sudan Black on frozen sections. Generally, a descriptive diagnosis of vacuolation on a routine hematoxylin and eosin (H&E) section is the standard approach with a definitive diagnosis of fatty change based on special stains or a well-known mechanism of action of a xenobiotic.

Synonym(s): **Lipid accumulation**; **lipidosis**; **steatosis**.





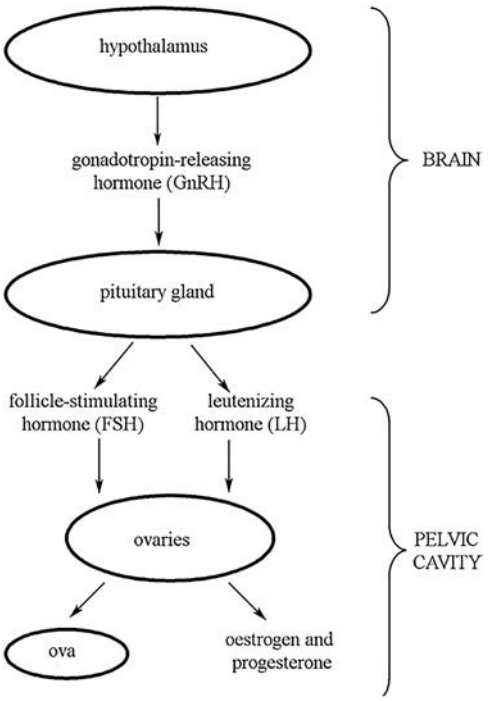
Fatty change in the liver of a rat, H&E. On low magnification, the staining pattern of the hepatic lobules varies with centrilobular areas appearing more pale than the adjacent hepatocytes. The pale appearance is the result of increased lipid content. On higher magnification, hepatocytes contain numerous variably sized, clear vacuoles containing lipid. The lipid is washed out during processing so vacuoles appear clear. (Images courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

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Fatty infiltration is defined as the abnormal accumulation of fat droplets within the cytoplasm of cells; it is not the same as adipocyte accumulation. See also **Adipocyte accumulation, lipomatous** for further information.

FDA is the acronym for the U.S. Food and Drug Administration.

Female reproductive hormones which control the female reproductive cycle are produced in the hypothalamus, pituitary gland, and ovary. Gonadotropin-releasing hormone (GnRH) is produced by the hypothalamus and stimulates the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the pituitary gland. FSH stimulates the development of ovarian follicles (primary follicle to ovulation), and the secretion of estrogen by the follicular cells. LH triggers ovulation and stimulates the secretion of progesterone by the corpora lutea. In conjunction with FSH, LH controls the secretion of estrogen from ovarian follicles.

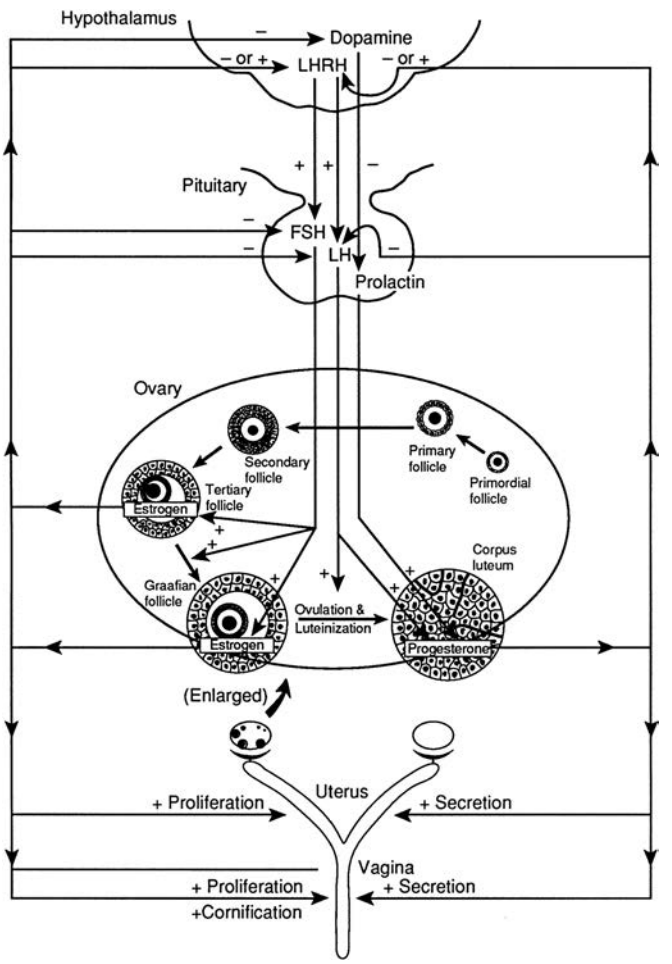


Hormonal control of the female reproductive cycle. (Open University.)

Female reproductive system consists of the organs needed to produce offspring: internal organs of ovary, oviduct, uterus, cervix and vagina, and external genitalia (i.e., vulva).

Female reproductive tract squamocolumnar junction (SCJ) is the region of transition from a columnar epithelial mucosa to a stratified squamous mucosa. In the female reproductive tract, the prepubertal SCJ is the junction between the endocervical and vaginal mucosa. The cervix expands and everts during puberty and pregnancy, forming the portio vaginalis, and the exposed cervical mucosa undergoes squamous metaplasia as an adaptive change to the vaginal environment, thus shifting the location of the SCJ. See **Uterine squamous metaplasia** for further information.

Female sex hormones consist of LH, FSH, estrogen, progesterone, prolactin, and testosterone. The glycoprotein gonadotropins (LH, FSH) are secreted from the anterior pituitary and stimulate the ovary (also the adrenal in the non-rodent). Both FSH and LH are necessary for ovarian follicular maturation and promote follicular steroidal hormone (estrogen, progesterone, and testosterone) production. In the rat, an LH surge results in ovulation with subsequent formation of the corpus luteum (CL). In primates and dogs, ovulation occurs spontaneously, and in rabbits and other induced ovulators the LH surge does not occur until cervical neurons are stimulated by mating. Under the influence of LH and prolactin, the latter also produced by the anterior pituitary, the CL secretes progesterone (also estrogen in the nonhuman primate) to maintain pregnancy. Prolactin stimulates mammary lobuloalveolar development, estrogen and androgen drive uterine and vaginal cell proliferation and maturation, and estrogens prime the uterus for its response to progesterone. The hypothalamic-pituitary-ovarian reproductive axis is tightly regulated. Decreased (or increased) circulating concentrations of ovarian steroidal hormones will stimulate (or suppress) the anterior pituitary's secretion of LH and FSH



Female hypothalmic-pituitary-ovarian hormonal axis. (Reproduced with permission of the Academic Press from Rudmann, D.G. and Foley, G.L. 2013. In: Haschek, W.M. et al. *Handbook of Toxicologic Pathology*, 3rd ed. Elsevier Inc., Academic Press, pp. 2599–2660.)

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through the function of factors (LHRH and GnRH) produced by the hypothalamus.

Female sex organs (uterus, oviduct, cervix, vagina), fibroma is a well-circumscribed, benign tumor composed of well differentiated fibroblasts. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Female sex organs (uterus, oviduct, cervix, vagina), fibrosarcoma is a locally invasive, malignant tumor composed of pleomorphic spindle cells. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

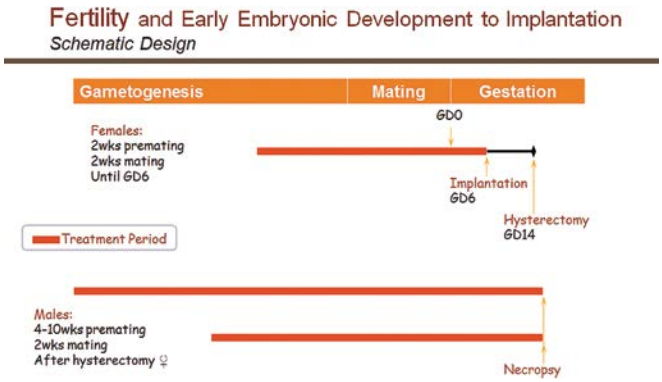
Female sex organs (uterus, oviduct, cervix, vagina), leiomyoma is a well-circumscribed, benign tumor of smooth muscle cells. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Female sex organs (uterus, oviduct, cervix, vagina), leiomyosarcoma is a poorly circumscribed, invasive, malignant tumor of smooth muscle cells. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Feminization is the normal induction or development of female sex characteristics in females. As a pathologic process, the induction or development of female sex characteristics or female tissue in a genotypic male, sometimes accompanied by atrophy of male reproductive tissues, can occur owing to a relative excess of estrogens relative to androgens. There are multiple causes that include exposure to estrogenic substances, inability to convert testosterone to (active) dihydrotestosterone, castration, and androgen resistance (testicular feminization). Because the rat mammary gland is sexually dimorphic, the mammary gland of the feminized male rat will have a tubuloalveolar appearance comparable to that observed in the normal female rat.

Fertility refers to the ability of an animal to reproduce and have offspring.

Fertility and early embryonic development (FEED) studies are usually performed in rodents to assess the effects of a substance on fertility and general reproductive performance. Male animals are treated for at least 28 days prior to mating and throughout the mating period; females are treated for at least 2 weeks before mating and until mid-pregnancy sacrifice. Fertility of the individual genders may be assessed by mating treated males with untreated females and vice versa. Parameters assessed include mating and fecundity performances (mating, fertility, pregnancy and gestation indexes, time to copulation [precoital interval], number of implantation sites, and live and dead offspring).



Fertility index (%) is calculated in fertility studies and represents the percentage of paired animals that become pregnant × 100 or number of pregnant animals/number of paired animals.

Fertilization is the union of male and female gametes: an egg/oocyte from a female with sperm of a male.

Fetal abnormalities are anatomical alterations of the development of a fetus that will adversely affect the morphology and/or functionality of organs. Based on the nature of the change, transient or permanent, and its adversity on survival or health, the abnormality is called a variation or a malformation.

Fetal abnormalities, malformation is a permanent developmental change that is likely to adversely affect survival, development, or function of the offspring. See **Teratogenesis** for further information.

Fetal abnormalities, variation is a specific anatomical abnormality that occurs with a relatively high frequency. It represent a retardation in development, a transitory alteration, or a permanent alteration not believed to adversely affect survival, growth, or functional competence of the offspring.

Fetal alcohol syndrome (FAS) is a condition found in an offspring born to an alcoholic mother. The common features of alcohol-related birth defects are intrauterine growth retardation (IUGR), mental retardation, small head, and facial defects (eye, nose). See also **Alcohol-related birth defects** for further information.

Fetal glomeruli are small, immature glomeruli present in both a fetus and neonate that are not yet fully expanded and functional. See **Neonatal kidney** for further information.

Fetotoxicity is a series of adverse events caused by a substance (e.g., chemical, drug), a pathogen (e.g., microorganism, virus), or any other agent (e.g., radiation) that can affect a fetus during the late stages of gestation.

Fetus is the stage of a developing organism between the embryo and birth. During this phase the organs formed during the

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embryonic period continue to grow and differentiate. In humans, it is from 9 weeks after fertilization to birth (~38 weeks after fertilization), in rats and mice from about day 14 of development until birth, and in rabbits from day 20 until birth.

FEV is an acronym for forced expiratory volume. See **Forced expiratory volume** for further information.

Fibrinoid necrosis occurs when blood vessel walls undergo necrosis accompanied by fibrin insudation, often due to immune complex deposition. The key microscopic feature is effacement of vessel wall architecture by hypereosinophilic, amorphous material.

Fibroma is a benign neoplasm of fibroblasts. Neoplasms are dense, space occupying, and typically contain abundant mature dense collagen matrix with low cellularity. Neoplastic fibroblasts are spindle-shaped and well differentiated without mitotic figures or pleomorphism. Neoplastic cells often form interlacing bundles; however, storiform or cartwheel-shaped patterns have been described. Nuclei are oval-shaped and vesicular to hyperchromatic. Refer to **Bone, Muscle, and Tooth** in Appendix 2 for further information.

Fibroma, cementifying/ossifying is a benign, well-demarcated neoplasm composed of spindle-shaped cells arising in the jaw often adjacent to the incisors. Neoplastic cells surround islands of woven bone or cementum, creating islands that can produce shapes reminiscent of the letters "Y" or "C." Neoplastic cells can transform into osteoblasts and cementoblasts forming these islands. Cementifying/ossifying fibromas have rarely been reported in mice and dogs. Refer to **Bone, Muscle, and Tooth** in Appendix 2 for further information.

Fibroma, odontogenic is a benign dental tumor arising from the periodontal ligament or dental papilla. These expansile, well-circumscribed masses have primitive mesenchymal cells admixed with collagen, undifferentiated dental epithelium, and cementum-like material. Nests of squamous epithelial cells have been observed. Refer to **Bone, Muscle, and Tooth** in Appendix 2 for further information.

Fibromatosis, retroperitoneal is a proliferation of fibrous tissue localized in the mesentery, and in monkeys, frequently at the junction of the ileum and cecum. The proliferation usually exhibits areas of florid fibroblastic proliferation organized in bundles and whorls associated with abundant blood vessels and inflammatory cells and/or less cellular areas rich in sclerotic fibrous tissue. The neoplastic masses can strangle and/or invade various portions of the gastrointestinal tract. This proliferation bears similarities with human Kaposi sarcoma. Refer to **Bone, Muscle, and Tooth** in Appendix 2 for further information.

Fibro-osseous lesion (FOL) is a distinct entity in mice characterized as a fibroproliferative lesion of bone that may invade and crowd the bone marrow. It is a common spontaneous lesion of B6C3F1 mice that preferentially affects up to 100% of aged female mice, with a much lower incidence in males. Osteoclastic resorption of bone is followed by fibrovascular stromal proliferation, osteoblast proliferation, and production of boney trabeculae that encroach upon the medullary space. The lesion may be seen as early as 32 weeks and can progress with age so that up to two-thirds of the medullary cavity may be occupied. FOL can occur in any bone but is most commonly observed in sternabrae, long bones, and vertebrae. The etiology is undetermined but the prevalence in female B6C3F1 mice and the occurrence of a similar change in other strains of mice treated with estrogens or prostaglandin suggests hormonal influences. Serum alkaline phosphatase may be elevated. In certain strains of mice concurrent lesions of the reproductive tract (ovarian atrophy and cervical dysplasia with hydrometra) are often observed.

Differential diagnosis: **Osteodystrophy, fibrous**.
Synonym(s): **Fibro-osseous proliferation**; **osteofibrosis**.

Fibro-osseous proliferation, see the preferred term **Fibro-osseous lesion**.

Fibrosarcoma is a malignant neoplasm of fibroblasts. Tumors are invasive and contain variable amounts of collagen matrix with or without necrosis and hemorrhage. Spindle-shaped neoplastic fibroblasts are arranged in interlacing bundles. Fibrosarcomas have been described in rats, mice, ferrets, and dogs. These tumors have been observed in rats administered peroxisome proliferator-activated receptor agonists and are often induced by implant materials or chemical injection. Refer to **Bone, Muscle, and Tooth** in Appendix 2 for further information.

Fibrosarcoma, pleomorphic is a malignant neoplasm in which the cell of origin is unknown. The two most widely accepted hypotheses are that this tumor arises from undifferentiated early (stem) mesenchymal cells or it is a collection of undifferentiated sarcomas that have morphological similarities. The subcutaneous tissue is a site where this tumor is frequently observed in mammalian species used in toxicology studies (mice, rats, dogs and monkey). Refer to **Bone, Muscle, and Tooth** in Appendix 2 for further information.

Synonym(s): **Histiocytoma, malignant fibrous** at the end of the description for **Fibrosarcoma, pleomorphic**.

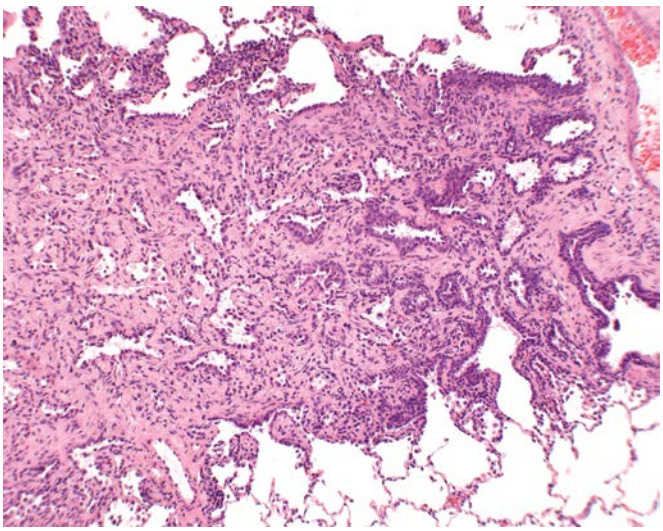
Fibrosing alveolitis is relatively common in laboratory beagles, but its etiology is unknown. It is characteristically located between the distal ends of respiratory bronchioles and the pleura, and often has a wedge-shaped appearance. The lesion has three basic components—interstitial fibrosis, bronchioloalveolar epithelial hyperplasia, and respiratory bronchiolar squamous metaplasia—which are present to varying degrees in individual lesions. The lesion appears to originate in the respiratory bronchiolar epithelium in a process that involves squamous metaplasia, followed by myofibroblast

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proliferation and gradual progression along the subsequent respiratory bronchiolar divisions and alveolar ducts and adjacent alveoli toward the pleura. The lesions are often associated with increased alveolar macrophages and pleural thickening, which is often recorded as a macroscopic abnormality. Subpleural/pleural fibrosis is also a common background finding in laboratory macaques.

Differential diagnosis: **Pulmonary fibrosis**.

Synonym(s): **Pulmonary segmental fibrosis**.



Fibrosing alveolitis, lung, dog, H&E.

Fibrosis is the transformation from normal parenchymal or interstitial tissue to abnormal fibrous tissue consisting of excess extracellular matrix, primarily collagen. The fibrous transformation is a form of nonfunctional repair at a site of injury where normal tissue is unable to regenerate. Whether a tissue regenerates or becomes fibrotic is determined by multiple factors, including tissue regenerative capacity and degree and/or persistence of the injurious stimulus. As fibrosis increasingly replaces normal tissue, there is reduced organ function and eventually organ failure. The fibrotic response is highly regulated through cellular components, their cytokine production, and cell-signaling pathways, including elements of the innate and adaptive immune system and organ-specific cell responses.

Fibrous hyperplasia is expansion of the gingiva in dogs appearing grossly as localized or widespread thickening. This non-neoplastic lesion is composed of dense stromal tissue and inflammatory cells with overlying hyperplastic epithelial cells. The mature fibroblastic stroma in this lesion has lower cellularity as compared to that in the tumor fibromatous epulis of periodontal ligament origin. Refer to **Bone, Muscle, and Tooth** in Appendix 2 for further information.

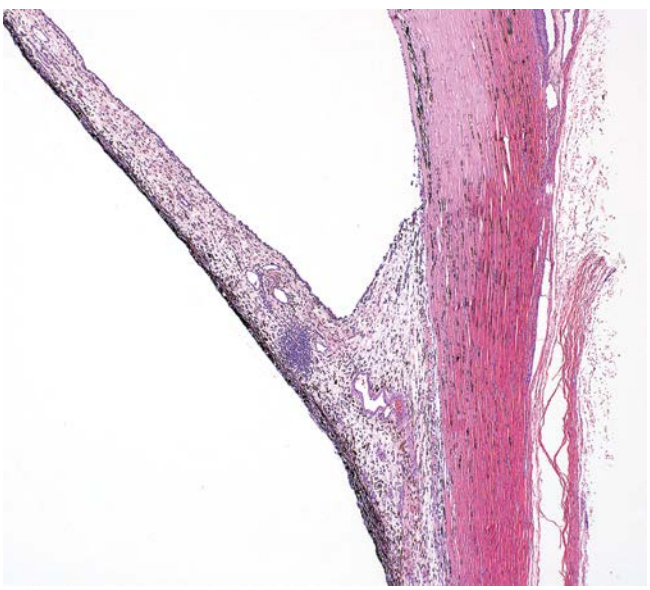
Fibrous metaplasia, see the preferred term **Subretinal fibroplasia**.

Filtration angle malformation is an abnormality that results in disorganization or absence of the trabecular meshwork, or abnormalities in the function of the filtration angle. In rodents, failure of the development of the spaces in the trabecular meshwork occurs, whereas in New Zealand white rabbits and beagle dogs, the malformation is inherited as an autosomal recessive trait that results in obstruction to aqueous fluid outflow despite a normal appearing or open filtration angle. Inflammation and a gradual increase in extracellular matrix or cellular debris and loss of the trabecular meshwork may also be seen. See **Filtration angle narrowed** and **Glaucoma** for further information.

Synonym(s): **Goniodysgenesis**; **pectinate ligament dysplasia**; **mesodermal dysgenesis**.

Filtration angle narrowed consists of an acquired reduction in angular acuity or collapse of the iridocorneal angle at the intersection of the base of the iris and the end of Descemet's membrane. Narrowing causes compression or collapse of the trabecular meshwork trabeculae, reduces spaces between trabeculae, results in loss of visible aqueous plexus, and interferes with aqueous humor fluid outflow. There is less trabecular meshwork and rare instances of collapse of the trabeculae in rodents compared to larger mammals. Narrowed filtration angle is a fundamental feature of closed-angle glaucoma, and occurs secondary to obstruction due to trauma, inflammation, cellular debris, lens dislocation, adhesions, or masses (neoplasia) in the anterior segment, neovascularization, implantation of intraocular materials, and by injection of viscous solutions or chemicals (alloxan, cresol and phenol) that destroy cells of the trabecular meshwork, and can be laser-induced. A normal filtration angle, but with trabecular cell degeneration and increased extracellular matrix or cellular debris that obstructs the drainage angle, may be age-related or a genetic abnormality. See **Filtration angle malformation, Lens dislocation**, and **Glaucoma** for further information.

Synonym(s): **Ocular trabecular meshwork collapse**; **ocular compaction of trabecular beams**.



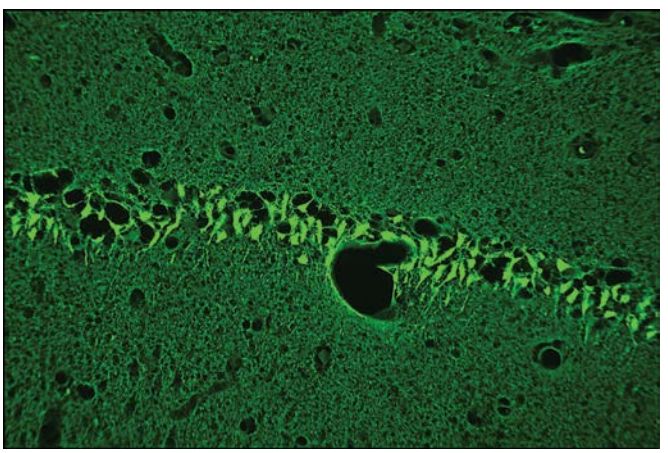
Filtration angle narrowed with destruction of the trabecular cell meshwork and Iris inflammation, rabbit, H&E. (Image courtesy of L. Teixeira, University of Wisconsin.)

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First-pass effect refers to the extensive metabolism of an orally administered drug during its first passage through the liver after absorption. Orally administered drugs are absorbed from the intestinal tract, reaching the liver via the hepatic portal vein, and thus must pass through the liver before reaching the systemic circulation. Some compounds are subject to extensive hepatic extraction, either through rapid metabolism in the liver or biliary excretion. In such cases, although the drug may be well absorbed from the intestinal tract, the bioavailability of parent drug in the systemic circulation may be very low. This extensive hepatic clearance resulting in low bioavailability is known as the "first-pass effect" or "first-pass metabolism." First-pass metabolic processes may be become saturated, whereby the bioavailability of the drug increases significantly at higher doses.

Flavin-containing monooxygenases (FMO) (EC 1.14.13.8) are flavoproteins that catalyze the oxidation of a variety of xenobiotic substrates, particularly amines and sulfur-containing compounds, using nicotinamide adenine dinucleotide phosphate-oxidase (NADPH) as a cofactor. Similar to other monooxygenases, the flavin-containing enzymes catalyze the reduction of oxygen, with one atom of molecular oxygen being incorporated into the oxidized reaction product and the other being reduced to water. The required electron transfer is facilitated through the flavin prosthetic group.

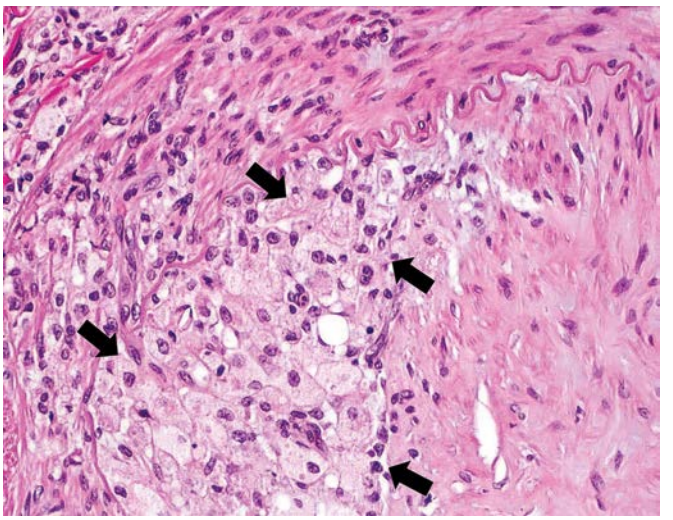
Fluoro-Jade is a fluorescent histologic stain for necrotic neurons. The original stain is rarely used. Fluoro-Jade B provides somewhat greater background staining that facilitates anatomic localization by allowing for visualization of unaffected cells as compared to the more specific labeling of Fluoro-Jade C. See **Neuronal necrosis** for further information.



Necrotic neurons highlighted by a Fluoro-Jade B stain. Hippocampus. Rat. Fluoro-Jade B.

Foam cell is a macrophage/histiocyte or vascular smooth muscle cell whose cytoplasm is distended by small vacuoles, generally containing lipid. Within the vasculature, foam cells signify hyperlipidemia, atherosclerosis, and decreased luminal diameter.

Synonym(s): **Foamy macrophage**.



Foam cells (as outlined with arrows) in an artery of a nonhuman primate with severe atherosclerosis, H&E. Note the intimal proliferation and foam cells within the wavy internal elastic lamina.

Foamy macrophage, see the preferred term **Foam cell**.

Focal is a modifier attached to a diagnostic term in order to indicate that the finding is limited to and/or originating from a single site within the tissue. For common test article–related findings such as degeneration, necrosis, and inflammation, modifiers such as focal or diffuse are helpful to communicate the likelihood that diagnostic terms are spontaneous or test article mediated.

Focal eosinophilic cellular change, see the preferred term **Eosinophilic focus of cellular alteration**.

Focal hepatocellular hyperplasia, see the preferred term **Hepatocellular hyperplasia, non-regenerative**.

Focal segmental glomerulosclerosis (FSGS) is scarring of only a portion of the glomerulus (segmental) in the kidney. Focal refers to only some, but not all, glomeruli being affected.

Follicle-associated epithelium (FAE) is a specialized epithelium covering mucosa-associated lymphoid tissue formed by membranous/microfold (M) cells that are frequently interspersed by leukocytes (lymphoepithelium) and rarely goblet cells. M cells lack apical microvilli and secretory capacity, and selectively sample antigens and particles that would normally be excluded by the mucosal barrier. Weak intercellular junctional complexes between M cells allow bidirectional leukocyte migration and selective transport of antigens to the underlying mucosa-associated lymphoid tissue (MALT) for lymphoid interactions. Mucous over the FAE is not attached to the epithelium and is cyclically removed and replenished to allow exposure to antigens. Immune responses to antigens can occur locally in the lymphoid follicle resulting in the production of protective immunoglobulins, particularly IgA secreted across the mucosal epithelium, and reactive leukocytes can migrate via high endothelial venules to regional lymphoid tissue and throughout the body as part of the interaction between

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mucosa-associated lymphoid tissue and the systemic immune system. Pathways used by antigens to pass through the FAE are also exploited by pathogens and potentially by xenobiotics.

Synonym(s): **Lymphoepithelium**.

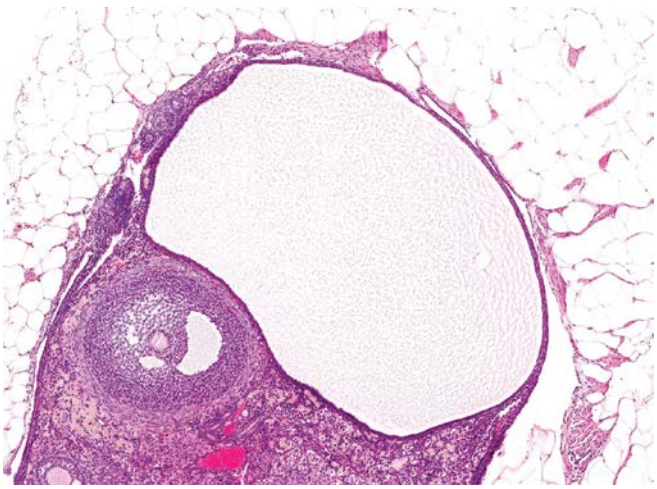
Follicle-stimulating hormone (FSH) is one of the gonadotropic hormones (i.e., FSH and LH). FSH is produced by the anterior pituitary gland. In females, FSH stimulates the development of ovarian follicles (primary follicle to ovulation) and the secretion of estrogen by the follicular cells. In males, FSH stimulates the initiation of spermatogenesis (primary spermatocytes to secondary spermatocytes), and enhances the activity of the Sertoli cells of the testes. See **Female reproductive hormones** for further information.

Follicular atresia, see the preferred term **Oocyte follicular degeneration**.

Follicular center cell lymphoma, see the preferred term **Pleomorphic lymphoma**.

Follicular cyst is a variably dilated ovarian follicle that may also be fluid-filled with blood, cell debris, degenerate oocytes, and/or foamy or hemosiderin-laden macrophages. The associated follicular epithelium may be atrophic or degenerate. Cysts may occur in any stage of follicular development, and are a common spontaneous finding in older rats. As a xenobiotic-induced change, cysts are more common in the antral follicle. Agents that disrupt the hypothalamic-pituitary-ovarian axis and cause imbalances of luteinizing hormone (LH), prolactin, thyroid hormone, and androgens may cause cyst formation.

Synonym(s): **Ovarian cystic follicle**.



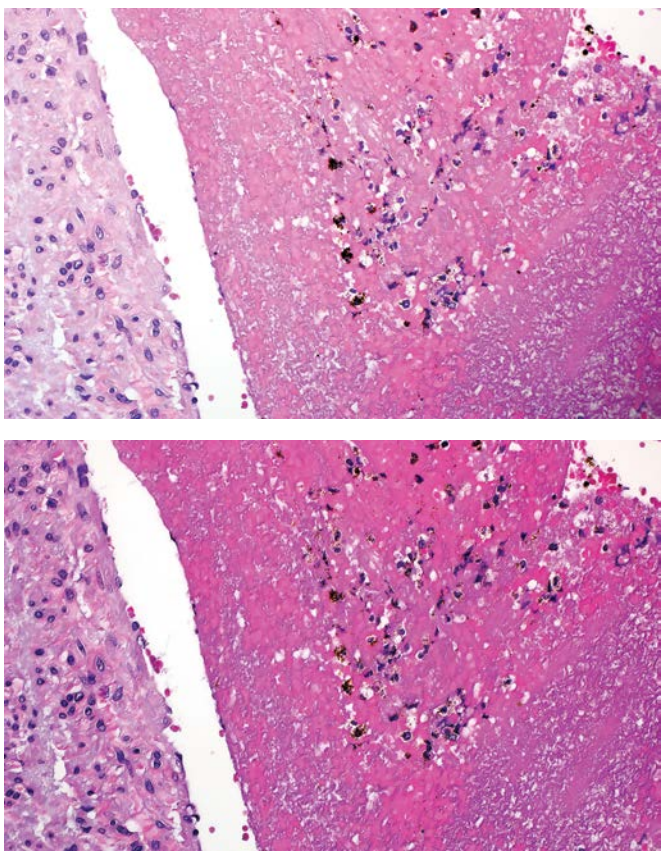
Follicular cyst, ovary, B6C3F1/N mouse, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

Forced expiratory volume (FEV) is a measure of the maximal volume of air that can be expired in a specific time. The subject takes a maximal inspiration and then blows as hard and fast as they can into a flow measuring device (e.g., spirometer). The measurement is cut off at the designated period of time (0.5, 1, 2, or 3 seconds). The result is converted into a percent of normal and used for evaluation of pulmonary function, for example in trials to assess the efficacy of drugs against chronic obstructive pulmonary disease (COPD) or asthma. In animal experiments plethysmography is used to assess the test article effect on pulmonary function.

Forced vital capacity (FVC) is the total maximum volume that can be expired rapidly after maximum inhalation. This is a pulmonary function test that is most useful when tracked over time (L/Min) to detect changes in lung capacity, for example in patients suffering from pulmonary fibrosis or chronic obstructive lung disease. In animal experiments pulmonary function is often assessed by plethysmography.

Fordyce granules, see the preferred term **Ectopic sebaceous gland in the oral cavity**.

Formalin pigment is amorphous black to brown granular pigment that may be encountered in histologic sections prepared from tissues fixed in formalin having a low pH. The pigment can appear similar to hemosiderin or pigment produced by certain parasites such as lung mites, or those that cause malaria or schistosomiasis. While formalin pigment can be differentiated from these other pigments since it appears slightly out of focus within the tissue, it is best to avoid its development as it may obscure critical tissue details. This can be accomplished by



Formalin pigment accumulated within the blood vessel lumen (top) and the same section as viewed under polarized light demonstrating birefringence of the crystals, cynomolgus monkey, H&E.

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using neutral buffered formalin and by replacing the formalin if the solution appears red-tinged from excessive blood.

Synonym(s): **Acid hematin**.

Forward mutation is a mutation that inactivates a gene.

Frameshift mutation is a type of mutation that leads to a shift in the reading frame when the DNA is transcribed. It occurs through insertion or deletion of a number of bases that are not three or multiples of three (i.e., 1, 2, 4, etc.), so that upon transcription, the codons downstream from the mutation site form an altered reading frame and may code for the wrong amino acids. Such mutations often result in a nonfunctional protein.

FSH is an acronym for **Follicle-stimulating hormone**. See **Follicle-stimulating hormone** and **Female reproductive hormones** for further information.

Fuchs endothelial corneal dystrophy is one form of clinically diagnosed genetic-based corneal dystrophies (see **Corneal dystrophy** for further information) that causes thickening of Descemet's membrane and loss of endothelial cells. This form of corneal dystrophy arises from multiple gene defects in humans, dogs, and genetically-altered mice.

Functional observational battery (FOB) is a set of observational parameters used to determine the effects of a compound on behavior and physiological function, particularly as related to the central nervous system. See **Irwin test** for further information.

Furunculosis is characterized by rupture of hair follicles with associated/resultant inflammation. See **Adnexal inflammation** for further information.

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Gallbladder adenocarcinoma is a rare spontaneous malignant neoplasm arising from epithelium of the gallbladder in aging laboratory animals. Neoplastic cells show disordered growth, with cellular atypia and mitotic figures, often invading the wall of the gallbladder or of the adjacent tissue. Refer to **Liver, Gallbladder, and Exocrine Pancreas** in Appendix 2 for further information.

Gallbladder adenoma is a rare, spontaneous, often solitary mass of well-differentiated gallbladder epithelial cells lining a papillary, fibrovascular stroma. The pattern of growth is disordered and papillary- or cauliflower-like with cellular atypia and mitotic figures. Refer to **Liver, Gallbladder, and Exocrine Pancreas** in Appendix 2 for further information.

Gallbladder calculi, sometimes referred to as gallstones or cholelithiasis, are extremely rare spontaneous findings in most animal species but may be experimentally induced by genetic manipulation and lithogenic diets. Calculi are grossly visible concretion(s) in the gallbladder of mice, and may be solid or soft, single or multiple, and of various colors including white and pigmented (yellow, gray). Depending on the etiology, the stone may be composed of a mixture of cholesterol, calcium salts, hemoglobin, and occasionally as a pure gallstone composed of just one of these substances. Gallbladder calculi must be differentiated from mineralization, gallbladder inflammation, parasites, and neoplasia (grossly). See **Calculi** for further information.

Synonym(s): **Gallstones**; **cholelithiasis**.

Gallbladder glandular metaplasia is a rare, spontaneous finding in aged rodents, and has been reported with chronic inflammation of the gallbladder, or as change associated with gallbladder proliferative lesions. It is characterized by focal or diffuse proliferation of tall columnar cells with uniform, homogeneous, bright eosinophilic cytoplasm, forming glandular structures in the lamina propria with lumen containing eosinophilic crystals. The epithelial cells may show hypertrophy and increased proliferation. Gallbladder glandular metaplasia is reported in LXR$\beta-/-$ female mice.

Gallbladder heterotopic hepatocytes are cells morphologically identical to mature hepatocytes that are present in the submucosa of the gallbladder. The lesion occurs as a developmental anomaly, or due to postnatal transdifferentiation of gallbladder epithelium.

Differential diagnoses: Hepatocellular adenocarcinoma (metastasis); Artifact.

Gallbladder hyalinosis is characterized by the presence of uniformly eosinophilic intracytoplasmic hyaline in epithelial cells which are also present extracellularly in the interstitial spaces and gallbladder lumen. Hyalinosis may be induced by inflammation and is often due to an unknown etiology in aging mice and dogs. It often may be found in tandem with the same change in the bile duct epithelium as well as stomach and lung epithelium. The protein is usually immunoreactive for Ym1/Ym2, known as Chi313, a chitinase-like protein. Spontaneous hyalinosis may occur in high incidence in 129, B6;129 mice, CYP1A2-Null B6,129 mice, but is rare in most strains of mice and rats.

Gallbladder hyperplasia is often a small lesion with a few single-layered, well-differentiated hyperplastic cells lining papillary folds and small papillary projections. Refer to **Liver, Gallbladder, and Exocrine Pancreas** in Appendix 2 for further information.

Gallbladder inflammation, see the preferred term **Cholecytitis**.

Gallbladder metaplasia, see the preferred term **Gallbladder glandular metaplasia**.

Gallbladder papillary adenoma, see the preferred term **Gallbladder adenoma**.

Gallstone, see the preferred term **Gallbladder calculi**.

Gallstones, see the preferred term **Gallbladder calculi**.

Gamete is a reproductive cell: sperm in the male and egg/ovum in the female.

Gametocyte is a cell in the male or female gonads that will develop to produce the gametes. See **Germ cell** for further information.

Gametogenesis is the process of formation of the gametes. The production of sperm (spermatogenesis) in the male and ovum (oogenesis) in the female. See **Spermatogenesis** for further information.

Ganglia are functionally related groups of neurons that reside within distinct anatomic clusters of neurons in the central or peripheral nervous system. Ganglia are also called "nuclei" in the central nervous system. Dorsal root ganglia along the spinal cord contain the cell bodies of sensory nerves responsible for receiving and transmitting sensory information between peripheral sensory receptors and the central nervous system. Peripheral autonomic ganglia are paravertebral or within the

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viscera and are important for coordinating movement and responses of the viscera, which are generally beyond conscious control. Refer to Appendix 3 for further information.

Ganglion cell tumor is a neoplasm of the peripheral nervous system, originating from ganglion cells and including both neural and glial elements. They include gangliogliomas, ganglioneuromas, gangliocytomas, and ganglioneuroblastomas. Refer to **Nervous System** in Appendix 2 for further information.

Gastric ectopic tissue is the presence of normal appearing pancreas or liver in the mucosa or submucosa of the stomach. Ectopic pancreas acini or hepatocytes are rare incidental findings in rats and mice.

Differential diagnosis: Gastric adenocarcinoma.

Gastric intraepithelial neoplasia, see the preferred term **Atypical gastric hyperplasia**.

Gastritis, see the preferred term **Stomach inflammation**.

Gastroesophageal reflux disease (GERD) is mainly relevant to humans, whereby there is passive reflux of gastric contents into the esophagus (and by extension nasal and oral cavities, and lung in some cases). Causes of such reflux are considered multifactorial and include impaired lower esophageal sphincter (LES) resting tone and/or intermittent sphincter relaxation as well as delayed gastric emptying and/or impaired esophageal clearance. Anatomical factors may also predispose to reflux events, including hiatal hernia and impaired mucosal resistance. These causes in turn relate to other factors that predispose to them, such as obesity and lifestyle pattern, with higher incidences in North America (10–40% of the population) than in other regions of the world (less than 5% in Asia). Reflux of gastric contents into the distal esophagus that overwhelms the normal clearance and mucosal defense barrier results in damage to the esophageal lining. Microscopic features of reflux-associated esophagitis are nonspecific, and at the early stage may include biopsy findings of basal papillary elongation and minimal hyperplasia of the basal squamous epithelium, with balloon cells in the superficial layers. With increasing severity, these changes yield to more obvious inflammation, erosion, and ulceration. Barrett's esophagus is a complication of chronic GERD whereby the normal stratified squamous epithelium of the esophagus becomes replaced by columnar epithelium containing acid mucin-containing goblet cells (intestinal metaplasia). This change is associated with a significant risk of progression to dysplastic epithelial changes, and ultimately neoplastic transformation. Esophageal adenocarcinoma occurs in 0.5% of the population diagnosed with Barrett's esophagus (representing a 30–50-fold increase in risk compared to the general population in North America). In veterinary species, the incidence of naturally occurring GERD is poorly documented. In preclinical toxicity testing, the majority of cases of reflux-associated esophagitis are most likely associated with drug effect (either mechanism based or secondary to contact with the mucosa) or due to gavage procedure for administration of the test article.

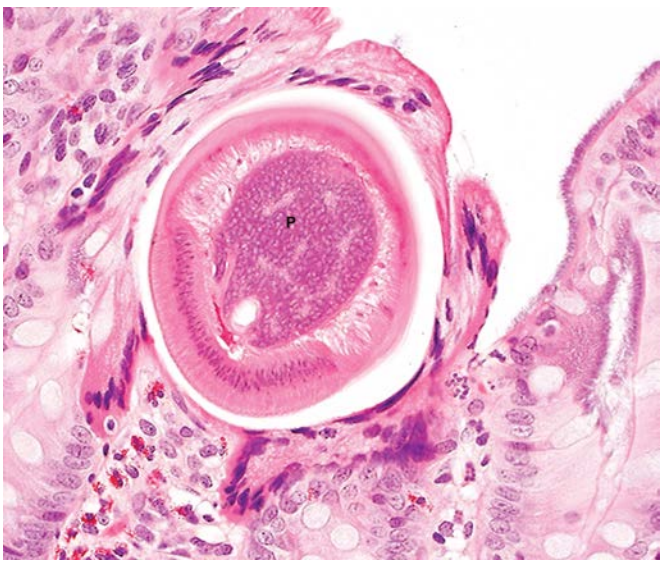
Gastrointestinal absorption is the process of physiological uptake from the gastrointestinal tract. Drugs may pass through the intestinal barrier by passive diffusion or by facilitated uptake. See **Drug transporters** for further information.

Gastrointestinal adenocarcinoma is a malignant, infiltrative neoplasm which may be exo- and/or endophytic, abandoning normal mucosal architecture, growing in a variety of patterns, which are used as descriptors (tubular, papillary, cystic, solid, scirrhous, mucinous, signet ring, undifferentiated). Refer to **Gastrointestinal Tract** in Appendix 2 for further information.

Gastrointestinal adenoma is a benign neoplasm characterized as an exophytic growth of distorted mucosal epithelium that maintains some normal architecture with glandular profiles and little cellular atypia. Adenomas may invade beyond the lamina propria but remain bounded by a basement membrane. Refer to **Gastrointestinal Tract** in Appendix 2 for further information.

Synonym(s): **Polyp**; **gastrointestinal adenomatous polyp**; **gastrointestinal polypoid adenoma**; **gastrointestinal exocrine adenoma**.

Gastrointestinal parasite is an organism that benefits by deriving nutrients from the host's gastrointestinal tract. More common types include protozoa (single-celled organisms) and helminths (nematodes/cestodes/trematodes: see whipworm (*Trichuris* spp.) in figure. While they may be present in different life stages throughout the body, most locate to the stomach or intestinal wall following exposure by ingestion of undercooked meat, drinking infected water, or migration through the skin. Intestinal parasitism can cause local pathologic changes but can also result in a variety of clinical diseases (e.g., malaria and schistosomiasis).



Colon, cynomolgus monkey. H&E. Mucosal parasite (P). *Trichuris* spp.

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Gastrointestinal reflux is the backward or retro-flow of lumenal material, and there are specific examples in the gastrointestinal tract. Biliary reflux**,** bile reflux, or duodenogastric reflux are conditions that occur when bile flows upward from duodenum into the stomach or esophagus. Biliary reflux, however, can be confused with acid reflux; see GERD. While bile reflux involves fluid from the small intestine flowing into the stomach and esophagus, acid reflux is backflow of stomach acid into the esophagus. These conditions are often related, and differentiating between the two can be difficult.

Gastrointestinal stromal tumor (GIST) are benign or malignant tumors derived from the specialized smooth muscle cells (i.e., interstitial cells of Cajal) in the tunica muscularis or myenteric plexus. Refer to **Gastrointestinal Tract** in Appendix 2 for further information.

Differential diagnoses: **Leiomyoma**; **Leiomyosarcoma**; **Schwannoma**.

Synonym(s): **Interstitial Cajal cell tumor, benign**; **gastrointestinal pacemaker cell tumor, benign/malignant**.

Gastrointestinal tract, Anatomy and Histology, see Appendix 3 for further information.

Gastrointestinal tract hyperkeratosis is an increased production and/or retention of keratin by squamous epithelium, occurring in the upper digestive tract of preclinical species and in the nonglandular stomach of rodents. Hyperkeratosis may be either parakeratotic (suggesting abnormal hyperkeratotic maturation) or orthokeratotic (suggesting normal maturation). It may occur as a single feature or as a consequence of hyperplasia of the underlying squamous epithelium. Hyperkeratosis (orthohyperkeratosis) of the nonglandular stomach in rodents has been associated with a lack of mechanical abrasion in the context of decreased food intake. Hyperkeratosis can also occur due to local irritation of orally administered test articles. In nonhuman primates and humans, oral and/or esophageal yeast infection by *Candida albicans*, often secondary to immunosuppression and/or stress, sometimes in association with retroviral infection and/or antibiotic therapy, results in raised plaques containing yeast organisms with pseudohyphae throughout the hyperkeratotic keratin. In rodents, a variety of dietary regimes (acidified drinking water, decreased protein intake with no calorie restriction, zinc deficiency) and compounds (alloxan, vitamins) have resulted in hyperkeratosis.

Gastrointestinal tract mucinous metaplasia (mucous cell metaplasia) is a reversible replacement of one mature, differentiated cell type with another mature, differentiated cell type that is producing mucin (i.e., a glycoprotein constituent of mucus). The change from one type of cell to another may generally be a part of the normal maturation process or caused by an abnormal stimulus. The original cells are not best adapted to withstand the new environment, and so they change into another cell type more suited to that new environment. If the stimulus that caused metaplasia is removed or ceases, tissues return to their normal pattern of differentiation. Metaplasia is not synonymous with dysplasia and is not considered proliferative or preneoplastic.

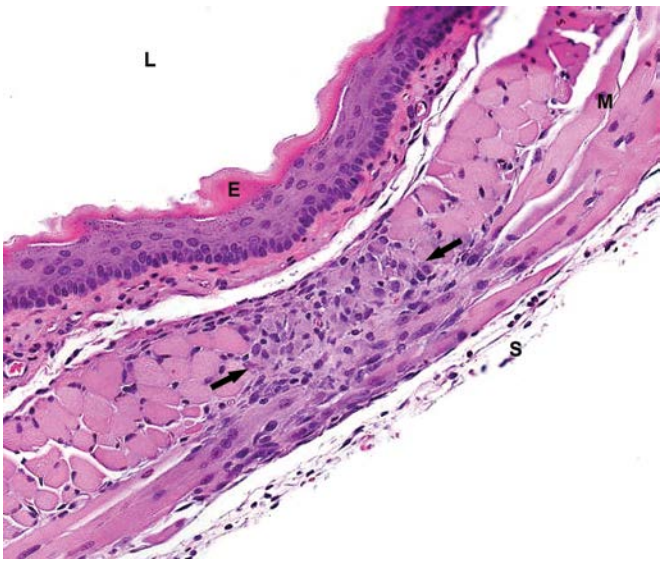
Gastrointestinal tract muscle degeneration/necrosis is usually a focal change of minimal severity in muscle fibers of the tongue or esophagus, and to a lesser degree in the stomach and small intestine. Muscle fiber degeneration is typically characterized by the presence of both swollen and contracted hyperchromatic to pale eosinophilic degenerative fibers with loss of striations, and mineralization. The necrotic (coagulative necrosis) fibers show nuclear pyknosis and/or lysis. The presence of amphophilic muscle fibers is consistent with a regenerative response. Very minor physical effects from the gavage procedure can result in damage to the muscular wall of the esophagus, resulting in muscle degeneration/regeneration, inflammation, and/or necrosis (see **Gavage**). Degeneration/necrosis of muscle fibers is often an incidental finding but can potentially be test article related. Degeneration/necrosis of esophageal muscle fibers is reported in transgenic (Pvrl3-Cre) rats with megaesophagus at 3–4 months of age and with spontaneous esophageal impaction observed in Cdb:BHE Rat, a model for non-insulin-dependent, non-obese diabetes mellitus.

Gastrointestinal tract (GIT) squamous cysts occur as down growths of invaginated/entrapped surface mucosa, or a dilated salivary duct. Cysts may be seen as incidental, congenital background lesions in the oral cavity/pharynx, tongue, or esophagus. The lumen of this cyst is lined by well-differentiated, keratinized squamous epithelium, and may contain sebaceous secretion or keratin debris. Inflammation may be observed in association with larger and/or ruptured cysts.

Differential diagnosis: **Esophageal diverticulum**.

Gavage is a method by which liquid material is administered directly into the stomach via soft tube or by rigid cannula. It is used to ensure that a measured dose of test-article or control material is reliably administered to the stomach, most typically in the development of compounds intended to be taken orally. Although nasogastric tubes may be used in some instances for large animal species, oral gavage is by far the most commonly used approach. The decision to administer by this route is considered during protocol design, taking into consideration the intended route of administration in humans, as well as compound factors (such as viscosity or pH) that may limit delivery by this route in a particular species. Inadvertent administration into the lung, perforation of the esophagus (in rodents), or reflux and/or emesis with subsequent aspiration are risk factors associated with this technique. Complications can be minimized by using trained personnel, limiting the frequency of dosing, using correctly sized gavage tubes, and employing standardized volume limits according to the species and weight of the treated animals. Such limits are usually defined within animal use and care guidelines.

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Esophagus, rat. H&E. Arrows = focus of muscle degeneration/regeneration associated with gavage procedure. L = lumen, E = epithelium (squamous), M = muscular wall, S = serosa.

Gavage-related reflux and aspiration is the result of aspiration of a dose of the experimental formulation or material into the respiratory tract and can be responsible for a range of clinical signs ranging from increased salivation through respiratory distress to death. Findings may be seen throughout the respiratory tract and in the lungs, and refluxed material may often be visible within the posterior nasal cavity. Microscopically, ulceration, necrosis, and neutrophilic inflammation may be seen in the acute phase, progressing to metaplastic epithelial changes in the larynx and, in more chronic cases, macrophage aggregation and fibrosis in the lung. Risk factors include non-fasting in animals prior to dosing, administering high volumes, high viscosity, irritant formulation, and/or effects of the test article on gastroesophageal function. The viscosity of the test article and vehicle combined may be greater than the viscosity of the vehicle alone, which can lead to test article–related distribution of findings. Alternative dosing routes (e.g., intravenous) may be used to differentiate between irritancy related to reflux and a systemic, direct effect of the test article on the respiratory tract. This condition must be differentiated from pulmonary inflammation from other causes.

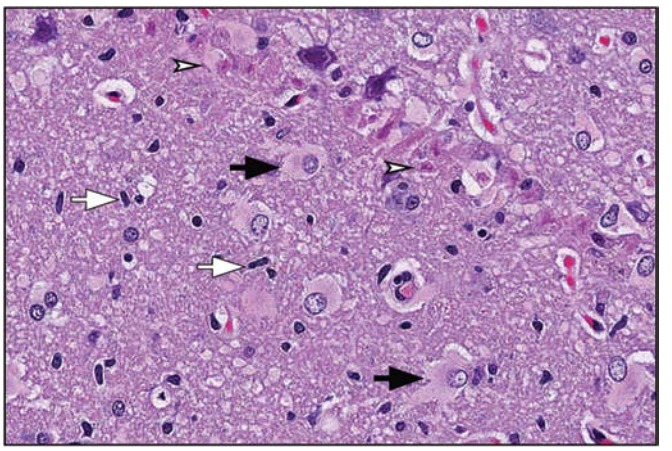
Synonym(s): **Regurgitation**.

GCP is an acronym for good clinical practice. See **Good clinical practice** for further information.

Gelatinous transformation is a condition in bone marrow characterized by atrophy of fat cells, loss of hematopoietic cells, and extracellular deposition of gelatinous material that is high in mucopolysaccharides and hyaluronic acid. The pathogenesis is undetermined but is often associated with severe malnourishment.

Synonym(s): **Serous atrophy of fat**.

Gemistocytic astrocytes are reactive astrocytes with abundant pale cytoplasm and eccentric nuclei. Gemistocytic astrocytosis and gemistocytosis are synonyms for a particular category of astrocytosis/gliosis that is characterized by the presence of gemistocytic astrocytes. See **Astrocytosis** for further information.



Gemistocytic astrocytes (black arrows) are markedly hypertrophied astrocytes with abundant eosinophilic cytoplasm and an enlarged pale nucleus. Present also in this field are acutely necrotic neurons (white arrowheads) and increased microglial cells (white arrows). Brain, rat. H&E.

Gene expression is the functionalization of the DNA to form proteins. It consists of transcription (mRNA synthesis from the DNA sequence) and translation (formation of the protein strand). Gene expression is highly regulated by epigenetic modifications, microRNAs, suppressors, and activator proteins.

Gene expression system is a cellular (often bacterial) system that produces gene products (proteins) from specific DNA sequences, which are normally introduced by appropriate vectors.

Gene mutation test is the term used in genetic toxicology to describe test systems that use individual gene functions as the genetic endpoint. See **Eukaryotic mutagenicity tests** for further information.

Genomics is the discipline that studies the function and structure of the genome. It is generally a term used for gene expression profiling to investigate the effects of a xenobiotic compound on cellular processes that may be assessed in cell culture, or in various organs and tissues after treatment of an animal. Genomic profiling may be unbiased, using whole genome arrays or directed, using selected arrays to investigate specific endpoints. Such gene expression profiling is often used in studies to investigate mechanisms of toxicity.

Genotoxic carcinogen is an agent that induces tumors via interaction with DNA. Such agents are generally positive in the Ames test. See **Ames test** for further information.

Genotoxicity is the ability of a compound or agent such as ionizing radiation to induce damage to genetic material, generally manifested as mutations, chromosome aberrations, or DNA damage.

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Germ cell is a male or female gonadal cell that will develop to produce the gametes. See **Gametocyte** for further information.

Germ cell toxicity is adverse events caused by a substance (e.g., chemical, drug), a pathogen (e.g., microorganism, virus) or any other agent (e.g., radiation) that could affect the male or female germ cells.

Germinoma, see the preferred term **Seminoma, benign** or **Seminoma, malignant**.

Gestation is the period between fertilization and birth during which the embryo, and later the fetus, develop.

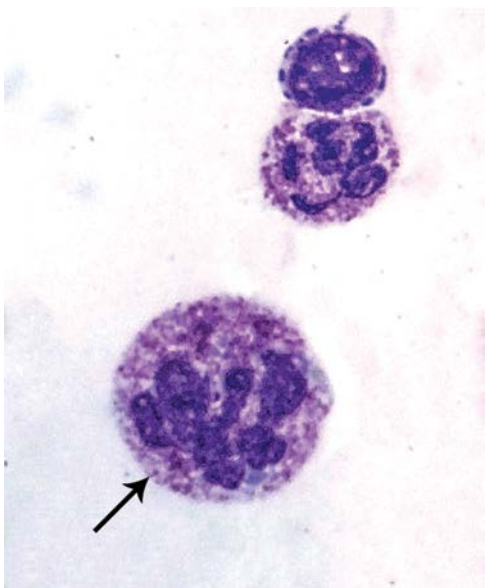
Gestation index (%) is the percentage of pregnant animals with live litters or number of females with live litters/number pregnant × 100.

GFAP, see **Glial fibrillary acidic protein**.

GFR is an acronym for glomerular filtration rate. See **Glomerular filtration rate** for further information.

Giant hypertrophic gastritis, see the preferred term **Hypertrophic gastritis**.

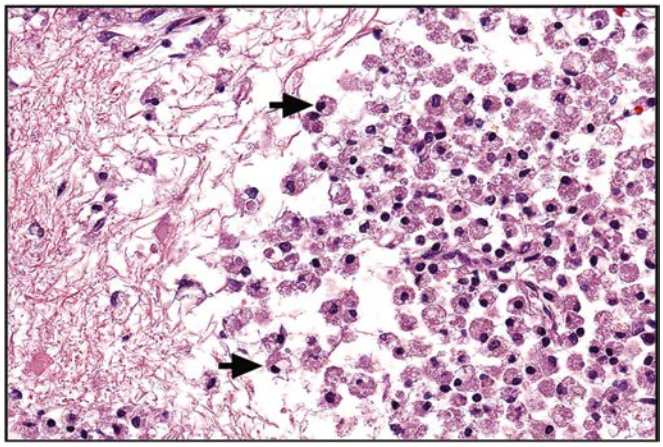
Giant neutrophils dysplastic neutrophils that can be observed in the bone marrow and/or peripheral blood. Giant neutrophils may occur with inflammatory disease or dysgranulopoiesis and may exhibit normal nuclear morphology. They are often associated with other neutrophilic toxic changes including Döhle bodies, cytoplasmic basophilia, and vacuolation. They have also been reported with myelodysplastic syndrome and acute myeloid leukemia.



Giant neutrophil (arrow), bone marrow, monkey.

Gigantism, see the preferred term **Acromegaly**.

Gitter cells are microglia that have become actively phagocytic in response to injury in the nervous system and contain numerous cytoplasmic vacuoles. See **Microgliosis** for further information.



Gitter cells (arrows) are macrophages with ample microvacuolated cytoplasm, which become prominent when removal of myelin-rich necrotic debris is actively ongoing. Brain, dog. H&E.

Glandular secretory depletion is the absence or decrease of secretory material within the lumen of a gland or associated secretory cell and is typically characterized by the presence of smaller cells that have lost granules/cytoplasm (e.g., salivary gland or pancreas). This may be related to administration of a test article or can occur as a secondary finding in moribund animals.

Glandular stomach adenocarcinoma is a spontaneous neoplasm in rodents is but more common in several knockout and transgenic mouse strains. Neoplasms may exhibit tubular, papillary, cystic, solid, scirrhous, mucinous, and signet ring phenotypes with exophytic or endophytic growth patterns. Invasion of nests and cords of neoplastic cells into the lamina propria or deeper layers and loss of basement membrane integrity may occur. A fibrous/scirrhous reaction with inflammation may also be present. Refer to **Gastrointestinal Tract** in Appendix 2 for further information.

Differential diagnoses: **Glandular stomach mucosal hyperplasia**; **Glandular stomach atypical mucosal hyperplasia**; **Glandular stomach diverticulum**; **Glandular stomach adenoma**; **Neuroendocrine cell tumor, malignant**.

Synonym(s): **Glandular stomach carcinoma**.

Glandular stomach adenoma is a spontaneously occurring neoplasm in rodents that is common in several knockout and transgenic mouse strains. Rodents administered the synthetic progestin cyproterone acetate, diethylnitrosamine (DEN), and *N*-nitrosamine compounds develop adenoma (and adenocarcinoma) that typically arise in the antral or pyloric mucosa of the glandular stomach. Neoplastic cells are basophilic with little atypia. Growth patterns may be polypoid, sessile, or papillary in nature with or without a fibrovascular stalk. Refer to **Gastrointestinal Tract** in Appendix 2 for further information.

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Differential diagnoses: **Glandular stomach mucosa hyperplasia**; **Glandular stomach adenocarcinoma**; **Neuroendocrine cell tumor, benign**.

Synonym(s): **Glandular stomach polyp**; **glandular stomach adenomatous polyp**; **glandular stomach polypoid adenoma**; **glandular stomach exocrine adenoma**.

Glandular stomach amyloid is an extracellular deposit of polypeptide fragments of a chemically diverse group of glycoproteins in glandular stomach mucosa. An increase in incidence has been reported in association with fighting among group-housed male mice, and with ectoparasitism.

Synonym(s): **glandular stomach amyloidosis**; **glandular stomach amyloid deposition**.

Glandular stomach amyloid deposition, see the preferred term **Glandular stomach amyloid**.

Glandular stomach atypical herniation, see the preferred term **Glandular stomach diverticulum**.

Glandular stomach atypical mucosal hyperplasia is a focal proliferation of acinar or tubular epithelium with multiple layers and cellular atypia; most importantly, without invasion of surrounding tissue. Refer to **Gastrointestinal Tract** in Appendix 2 for further information.

Glandular stomach calcification, see the preferred term **Glandular stomach mineralization**.

Glandular stomach carcinoma is a synonym for glandular stomach adenocarcinoma. See the preferred term **Glandular stomach adenocarcinoma**.

Glandular stomach dilatation of glands is a common observation in the basal to mid-portion of the gastric glands in the rat stomach, and the incidence and/or severity may be affected by treatment. The presence of dilated gastric glands is often increased with age in rodents. Dilated glands are lined by well-differentiated, cuboidal to flattened epithelial cells without cellular atypia, and the lumen may contain clear fluid, mucus, or cellular debris.

Differential diagnoses: **Stomach glandular cyst**; Glandular stomach cystic or atypical diverticulum; **Glandular stomach mucosal atrophy**.

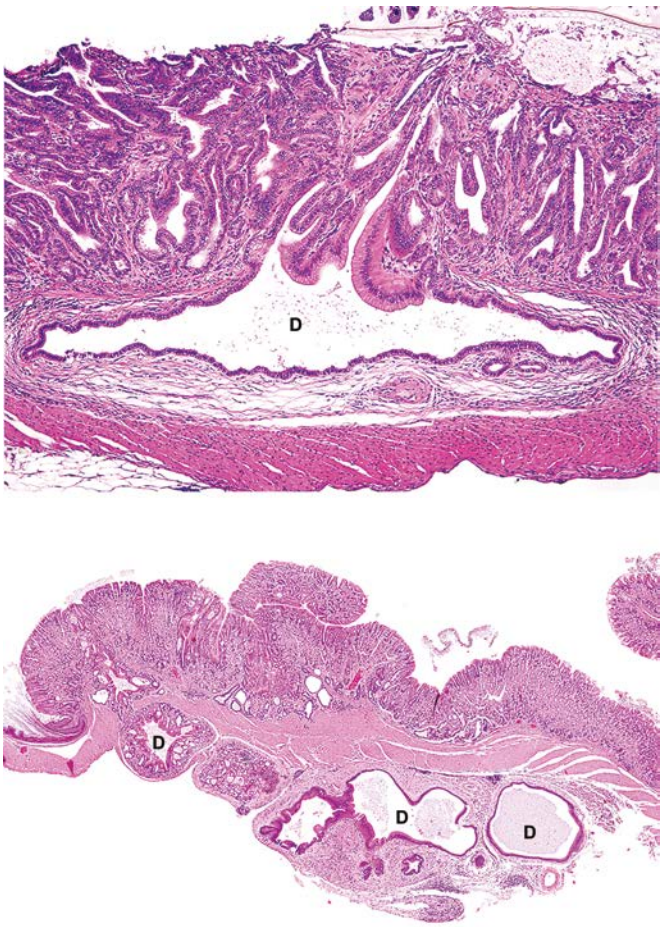
Synonym(s): **Glandular stomach dilation of glands**.

Glandular stomach dilation of glands, see the preferred term **Glandular stomach dilatation of glands**.

Glandular stomach diverticulosis, see the preferred term **Glandular stomach diverticulum**.

Glandular stomach diverticulum is often a congenital finding but may also be caused by mechanical or chemical (metabolic) disruption of stomach wall structures. It is characterized by loss of extracellular matrix integrity and extension of gastric glands through the muscularis mucosae into the submucosa, and further in some cases, without loss of basement membrane integrity. The morphology of the lining of the diverticulum can be variable, ranging from a single layer of cuboidal or columnar epithelial cells to complete mucosa. Epithelium of the diverticulum may have features of regeneration including increased basophilia, increased nucleus-to-cytoplasm ratio, loss of polarity, and minimal atypia. Diverticula of the glandular stomach are often seen in the antrum of mice, especially in genetically engineered mice, in chronic experimental gastric infections in mice, and may be associated with focal areas of post-ulcerative repair. Diverticula may contain ingesta, hair, or other foreign material, accompanied by inflammation. The cystic type of a diverticulum may contain cystic structures filled with mucus, lined by atrophic epithelium. Atypical diverticula may contain hyperplastic atypical (dysplastic) epithelial cells forming cystic glands that appear to be dissecting through the outer layers of the stomach but are not considered a neoplastic change.

Differential diagnoses: **Glandular stomach adenoma**; **Glandular stomach adenocarcinoma**.



Glandular stomach, mouse. H&E. Diverticulum (D). Downward distention of glands through the muscularis mucosa; glands lined by well-differentiated single-layered epithelium with maintained basement membrane integrity. (Image reproduced with permission of the Japanese Society of Toxicologic Pathology from Nolte et al., 2016.)

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Synonym(s): **Glandular stomach cystic adenomatous hyperplasia**; **glandular stomach diverticulosis**; **glandular stomach atypical cystic hyperplasia**; **glandular stomach cystic hyperplasia with growth into the gastric wall**; **glandular stomach cystic adenomatous hyperplasia**; **glandular stomach atypical "pseudoinvasion"**; **glandular stomach atypical hamartoma**.

Glandular stomach eosinophilic change, see the preferred term **Glandular stomach eosinophilic globules**.

Glandular stomach eosinophilic chief cells, see the preferred term **Glandular stomach eosinophilic globules**.

Glandular stomach eosinophilic droplets, see the preferred term **Glandular stomach eosinophilic globules**.

Glandular stomach eosinophilic globules is the presence of intensely pink-red staining cytoplasmic droplets and/or crystals in the surface epithelium or mucous neck cells of the glandular stomach. This occurs occasionally in rodents either as a spontaneous change or associated with another lesion such as inflammation (involving eosinophils) or lymphoma infiltration and is most often observed adjacent to the limiting ridge; it may extend into and/or replace the fundic glands. A high incidence of eosinophilic globules in various epithelia, including glandular stomach, respiratory tract, bile duct, gallbladder, and pancreatic duct has been reported in aging C57BL/6, 129, and B6,129 mouse strains. Treatment-related transformation of any glandular epithelial cell to produce hyaline cytoplasm is reported following the administration of gastric antisecretory agents, and by a range of chemicals and biologically active compounds, including loxtidine, oxmetidine, and omeprazole. The affected cells are usually hypertrophic. Crystals, if present, may be intracellular or extracellular. The use of the term "hyalinosis" for this lesion can potentially cause confusion in safety assessment studies, as the same term may also be used for a distinctly different clinical disorder in humans and can also be used to describe vascular and renal glomerular changes.

Synonym(s): **Glandular stomach hyalinosis**; **glandular stomach eosinophilic chief cells**; **glandular stomach eosinophilic change**; **glandular stomach eosinophilic droplets**.

Glandular stomach erosion/ulcer is characterized by focal or multifocal loss of the superficial mucosa with preservation of the muscularis mucosa (erosion) or, with extension through the muscularis mucosa (ulcer), as a result of changes in mucosal blood flow, mucosal cell kinetics, mucus or acid/bicarbonate secretion, or maintenance of the mucus barrier by physical trauma (e.g., gavage accident). Ulceration is often associated with bacterial infections, inflammation, hemorrhage, and reactive hyperplasia of adjacent epithelium. In more severe cases, ulceration and/or inflammation may extend into the tunica muscularis and serosa.

Erosions and ulcers in rodents are some of the most common lesions in the gastrointestinal tract that can occur under a variety of conditions such as administration of a hyperosmolar solution, following stress, due to increased bile reflux, due to changes in acid secretion, and under hypoxic conditions. They are usually associated with oral administration of xenobiotics but occasionally occur via the systemic administration of nonsteroidal anti-inflammatory (NSAIDs) drugs and ethyl alcohol. Ulcers can also reflect systemic disease; for example, they may be associated with uremia. Perforation followed by peritonitis and intestinal adhesions may occur in rodents as a sequel to ulceration of glandular stomach. NSAIDs are the most common cause of erosion/ulcers in humans and laboratory species including dog, rat, guinea pig, mouse, and monkeys, with some evidence of species differences. The dog and rat are more susceptible than the guinea pig or mouse, with monkeys being the least sensitive. This lesion is typically diagnosed under the single combined term of erosion/ulcer with an appropriate severity grade in most instances.

Differential diagnoses: **Glandular stomach adenocarcinoma**; Artifact; **Autolysis**.

Glandular stomach hyalinosis, see the preferred term **Glandular stomach eosinophilic globules**.

Glandular stomach mineralization is deposition of an acellular, basophilic-staining material in the muscle layers, blood vessels, basement membranes, and/or in the interstitium of the mucosa and submucosa secondary to necrosis (dystrophic mineralization) or hypercalcemia (metastatic mineralization). Mineralization of the interstitium of the mucosa occurs predominantly in a band paralleling the parietal cell-rich region of the corpus mucosa. Diffuse mineralization of the corpus mucosa may be accompanied by degenerative changes, mucous cell hyperplasia, or cystic dilatation of the neighboring glands. Multifocal or diffuse mineralization occurs secondary to chronic progressive renal disease, altered calcium-phosphorus metabolism induced by vitamin D analogues, gadolinium III, inhibitors of the FGFR/MEK/ERK pathway, and hyperparathyroidism. Mineralization also occurs in uremic gastropathy due to chronic renal disease in rodents and dogs. Mineralization secondary to necrosis (dystrophic mineralization) can be observed in combination with inflammation and neoplasia. Mucosal mineralization limited to occasional small focal deposits may be noted as an age-related background lesion in laboratory animals. The presence of mineral can be confirmed with Von Kossa or Alizarin red stains, but these are rarely needed to make this diagnosis.

Differential diagnoses: Hematoxylin stain precipitate artifact; Bacterial colonies (*Helicobacter* spp.).

Synonym(s): **Glandular stomach calcification**.

Glandular stomach mucosal atrophy is characterized by reduced mucosal thickness of the glandular mucosa due to a decreased number and/or size of one or more cell types. In most instances, chief cells are most affected with dilatation of atrophic glands. Atrophy affecting all cell types of the gastric mucosa can be produced by food deprivation, unilateral/bilateral vagotomy, antrectomy, hypophysectomy, cytotoxic and cytostatic anticancer agents, or due to a lack of trophic stimulation of gastrin. *Helicobacter* infection, chronic inflammation, histamine H2 antagonists, cholecystokinin-B/gastrin receptor antagonist (CI-988), proton pump inhibitors, and gastric acid

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secretion inhibitors can cause loss of specific cell types. Focal mucosal atrophy may result from ulceration, inflammation, mineralization, vascular occlusion, or infarction with reparative epithelial hyperplasia. Focal or diffuse atrophy of the mucosa can occur with age in rodents resulting in a decrease of mucosal height and increase in fibrous connective tissue.

Differential diagnoses: **Glandular stomach mucus secretory depletion**; Artifact.

Glandular stomach mucosal hyperplasia is characterized by proliferation of mucosal epithelium but no evidence of cellular atypia or invasion. Refer to **Gastrointestinal Tract** in Appendix 2 for further information.

Glandular stomach mucus secretory depletion is reduced mucus content of glandular stomach mucous cells with loss of clear cytoplasm or increased cytoplasmic basophilia and may be associated with reduction in PAS-positive staining of surface mucus. Mucus depletion may be xenobiotic induced or secondary to inflammatory changes. Administration of histamine H2 receptor antagonists, proton pump inhibitors, anti-inflammatory agents, and adrenocortical steroids is associated with reduction in mucus.

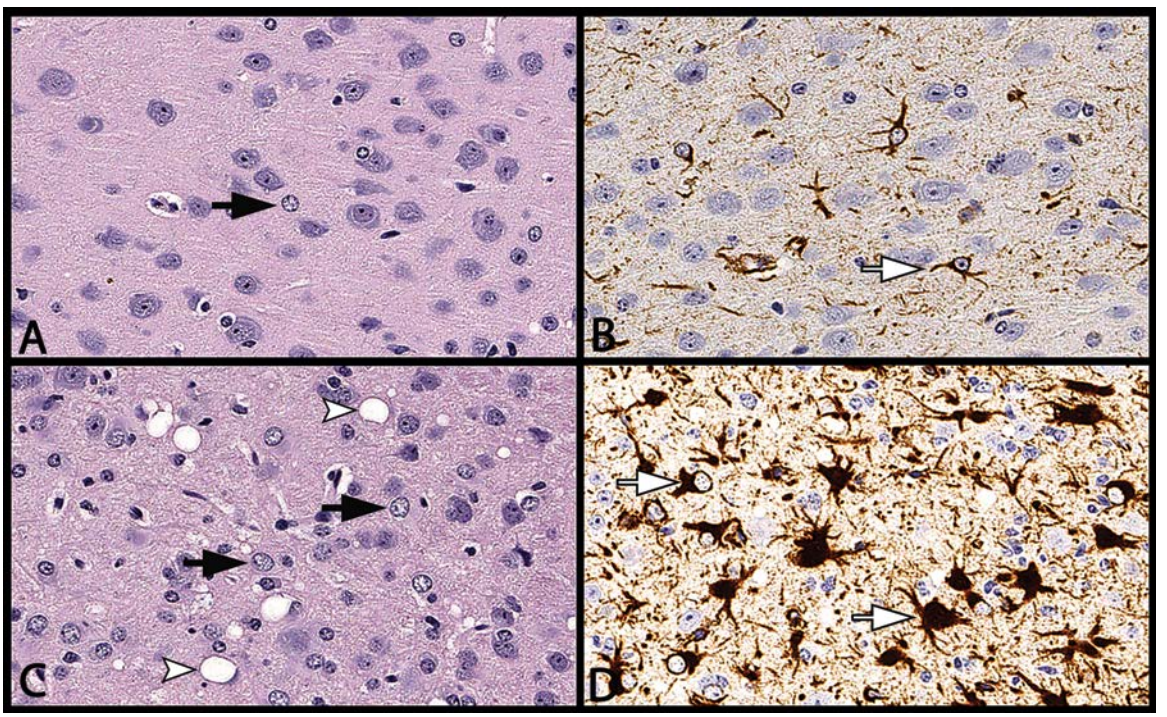
Differential diagnoses: Glandular stomach epithelial degeneration; Glandular stomach mucus cell atrophy.

Glandular stomach polyp is a synonym for glandular stomach adenoma. See the preferred term **Glandular stomach adenoma**.

Glaucoma is a genetic or acquired clinical condition of a sustained increase in intraocular pressure with an increase in the globe size (buphthalmos) that correlates histologically to one or more degenerative changes and abnormalities of the cornea, lens, iris, ciliary body, vitreous, retina, and sclera. Glaucoma may be categorized as primary (congenital) or secondary to another abnormality and may be open angle (normal appearing filtration angle) or closed angle (collapse or loss of trabeculae in the filtration angle). See **Filtration angle narrowed**; **Filtration angle malformation**; **Retinal atrophy and detachment** for further information.

Glia is the collective name for the support cells of the central nervous system, including astrocytes, oligodendroglia, and microglia.

Glial fibrillary acidic protein (GFAP) is a protein that is encoded by the GFAP gene in humans and represents an intermediate filament (IF) protein that is expressed by numerous cell types of the central nervous system (CNS) including astrocytes and ependymal cells. Anti-GFAP antibodies are used in an immunohistochemical label for upregulated GFAP which, when combined with cell features such as cell shape, size, and regional increases in astrocytes containing the GFAP, differentiates reactive astrocytes from quiescent astrocytes in the CNS. See **Astrocytosis** and **Type II astrocyte** for further information (see figure below).



Immunohistochemical labeling for glial fibrillary acidic protein (GFAP), an astrocyte marker. (A) normal cerebral cortex. Mouse. H&E. (B) GFAP immunolabeling of normal astrocytes. Mouse. (C) Reactive, hypertrophic astrocytes with H&E staining are characterized by increased numbers of astrocytes with an enlarged pale nucleus (black arrows) and variably evident increased eosinophilic cytoplasm (not readily evident at this magnification). Neuropil vacuolation (white arrowheads) is also present in this field. Mouse. H&E. (D) Increased numbers and increased GFAP immunolabeling of cytoplasm and cellular processes in reactive, hypertrophic astrocytes. Mouse.

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Glial scar, see the preferred term **Retinal atrophy, global**.

Glia syndrome, see the preferred term **Astrocytic swelling/vacuolation**.

Glioblastoma multiforme (GBM) is a malignant glial neoplasm and a diagnostic category used in human neuro-oncology. In veterinary and toxicologic pathology, the malignant mixed (anaplastic) glioma in rodents shares some histological features with the human tumor termed glioblastoma multiforme. Refer to **Nervous System** in Appendix 2 for further information.

Glioma is a CNS tumor composed of one or more of the glial cell subtypes. When possible, glioma should be further classified according to the neoplastic glial cell subtype components: glioma, astrocytic (preferred term astrocytoma); glioma, oligodendrocytic (preferred term oligodendroglioma), or glioma, mixed (composed of both neoplastic astrocytes and neoplastic oligodendrocytes). Refer to **Nervous System** in Appendix 2 for further information.

Glioma, mixed, malignant (high grade) is a mixed glial neoplasm of astrocytic and oligodendrocytic origin arising from the neuroectoderm. High-grade malignant mixed gliomas are diffusely infiltrative with indistinct borders and multifocal within the CNS. Cellular atypia and pleomorphism is common, and tumor giant cells may occasionally be present. In rodents the anaplastic features of high-grade mixed gliomas are similar to the human lesion termed glioblastoma multiforme. Refer to **Nervous System** in Appendix 2 for further information.

Glioma, mixed, malignant (low grade) is a mixed glial neoplasm of both astrocytic and oligodendrocytic origin. Low-grade malignant mixed gliomas are often well delineated and focal within the CNS and consist of neoplastic oligodendrocytes and astrocytes in either an intermingled mix or occurring in large domains of each cell type abutting the other. Refer to **Nervous System** in Appendix 2 for further information.

Gliosis (not otherwise specified [NOS]) is a nonspecific term denoting increased size (hypertrophy) and/or number (hyperplasia) of astrocytes, microglia, and/or oligodendroglia within the central nervous system (CNS) occurring in response to tissue (especially neuronal) injury. Where possible it is preferred to identify the reactive glial cell type(s) more precisely with terms such as "astrocytosis," "microgliosis," or "oligodendrocyte satellitosis." Refer to **Nervous System** in Appendix 2 for further information.

Gliovascular lesion/syndrome, see the preferred terms **Astrocytic swelling** or **Astrocytic vacuolation**.

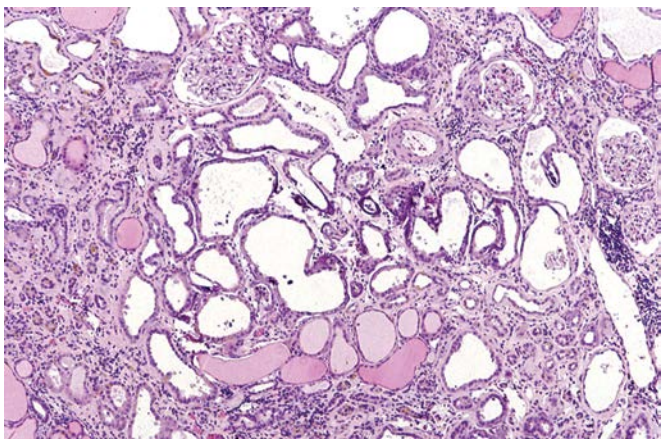
Glomerular amyloidosis, see the preferred term **Renal amyloidosis**.

Glomerular atrophy is shrinkage of the renal glomerular tuft to less than normal size for its stage in development.

Glomerular filtration rate (GFR) describes the rate of flow of fluid through the kidney.

Glomerulonephrosis is any noninflammatory disease of the kidney involving both the glomeruli and tubules. See the preferred term **Chronic progressive nephropathy**.

Glomerulosclerosis is a scarring of the renal glomerulus characterized mainly by increasing effacement of the normal glomerular structure by collagen deposition. It can represent the final glomerular change of glomerular disease and is most commonly seen in the aging laboratory rat in chronic progressive nephropathy (CPN), where, as the disease progresses, more glomeruli become sclerotic. Histologically, the glomerulus becomes devoid of internal structure as it is replaced with amorphous hyaline material. The basement membrane of the encircling Bowman's capsule also becomes thickened. Experimentally, glomerulosclerosis can occur as the end-stage of the glomerular injury induced by puromycin aminonucleoside.



Glomerulosclerosis as part of CPN, rat kidney, H&E.

Glossitis, see the preferred term **Tongue inflammation**.

GLP is an acronym for good laboratory practice. See **Good laboratory practice** for further information.

Glucocorticoid is a steroid hormone produced by the zona fasciculata in the adrenal gland. Glucocorticoids have a complex interrelationship with many organs, and serve to regulate homeostasis of mental, metabolic, cardiac, and immune function as well as fluid balance via specific cell receptors. Gluconeogenesis is greatly dependent on the modulatory effects of glucocorticoids. During embryogenesis, glucocorticoids serve to mediate pulmonary development, among other functions. Glucocorticoids may act on the central nervous system, particularly within the hippocampus, amygdala, and frontal lobes, to mediate memory. The "stress response" is a well-documented phenomenon of

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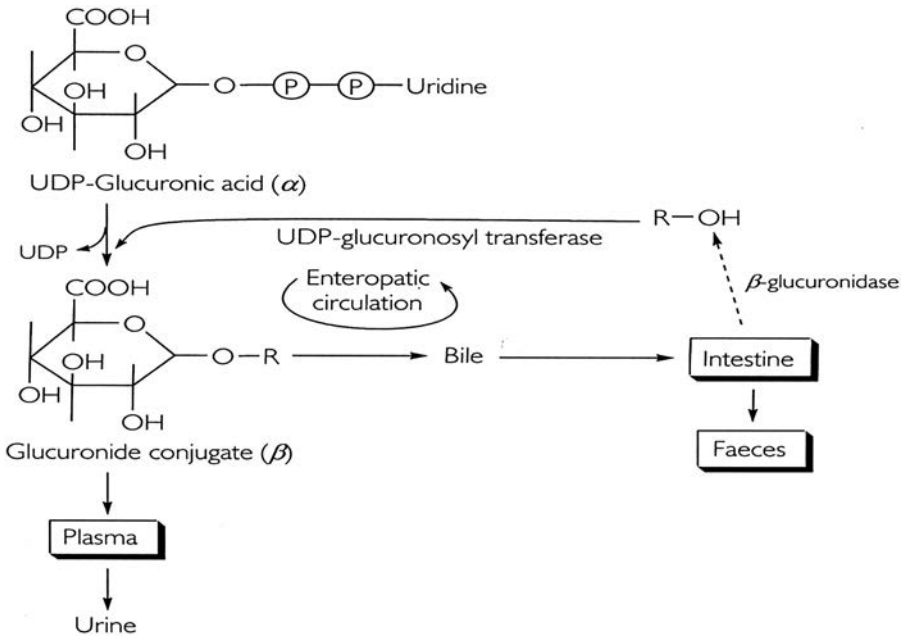
glucocorticoid synthesis and secretion under chronic stressful conditions that mammals encounter, resulting in immune suppression and increased risk of infection. The primary glucocorticoid is cortisol. Cortisol is manufactured for medical use as hydrocortisone (cortisone), and its use is primarily for down-regulation of immune-mediated responses during pathological conditions.

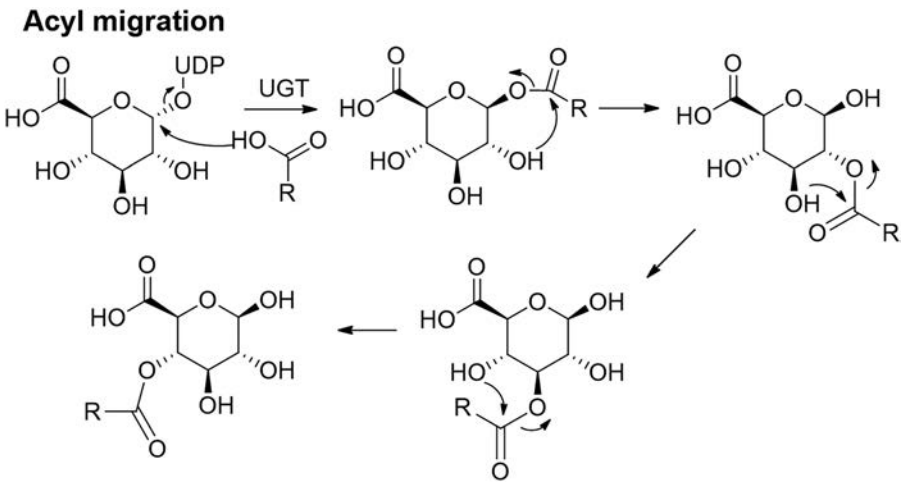
Synonym(s): **Glucocorticosteroid**; **corticosteroid**; **corticosterone**; **cortisol**; **cortisone**; **hydrocortisone**.

Glucocorticosteroid, see the preferred term **Glucocorticoid**.

Glucuronidation is catalyzed by UDP-glucuronosyl transferases and involves the transfer of a glucuronic acid group from UPD-glucuronic acid to the substrate. It is an important pathway of Phase 2 metabolism, accounting for over 30% of drug conjugations. Compounds containing alcohols, nitrogen atoms, or carboxylic acid groups may be directly glucuronidated forming *O*-glucuronides, *N*-glucuronides, and acyl glucuronides, respectively. Many alcohols and phenols formed by oxidation of the parent molecule are also further transformed to *O*-glucuronides. Many glucuronides are excreted into the intestine via the bile, where they may be hydrolyzed by bacterial β-glucosidases and reabsorbed, resulting in enterohepatic recirculation (see figure below).

Most glucuronides are pharmacologically inactive and rapidly excreted, although morphine glucuronide has been reported to retain pharmacological activity. Acyl glucuronides have also been a cause for concern, since they can be reactive metabolites. Reactive glucuronides have a propensity to rearrange through a process of acyl migration in which the ester bond migrates to different hydroxyl groups on the sugar. See **Enterohepatic recirculation** and **UDP-glucuronosyl transferases** for further information (see figure below).





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Glucuronosyltransferase, see **UDP-glucuronsyl transferase** for further information.

Glutathione (GSH) is a tripeptide containing γ-glutamylcyteinylglycine, in which the γ-carboxyl group of glutamine forms a peptide bond with the amine of the cysteine, and the carboxyl group of the cysteine forms a peptide bond with the amine group of glycine. Glutathione is found in all cell types, usually at very high (mM) concentrations. GSH is a very strong nucleophile which interacts with and inactivates electrophilic reactive metabolites, preventing or reducing toxicity. It is also a strong antioxidant which may be oxidized to the disulfide form glutathione disulfide (GSSG). During oxidative stress, cysteine groups within peptide chains may be oxidized to form disulfides (i.e., they are reduced by GSH and converted to GSSG). The GSSG may then be converted back to GSH by glutathione reductase using nicotinamide adenine dinucleotide phosphate-oxidase (NADPH) as a coenzyme. The ratio of GSH to GSSG is a measure of the level of oxidative stress; under normal conditions GSH predominates by about 10:1. Glutathione is also involved in the inactivation of reactive oxygen species; for example, hydrogen peroxide is reduced to water by GSH, and the enzyme glutathione peroxidase, the glutathione oxidized in the process, may be converted back to GSH by glutathione reductase.

$$2GSH + H_2O_2 \rightarrow GSSG + 2H_2O$$

See **Glutathione reductase** and **Glutathione peroxidase** for further information.

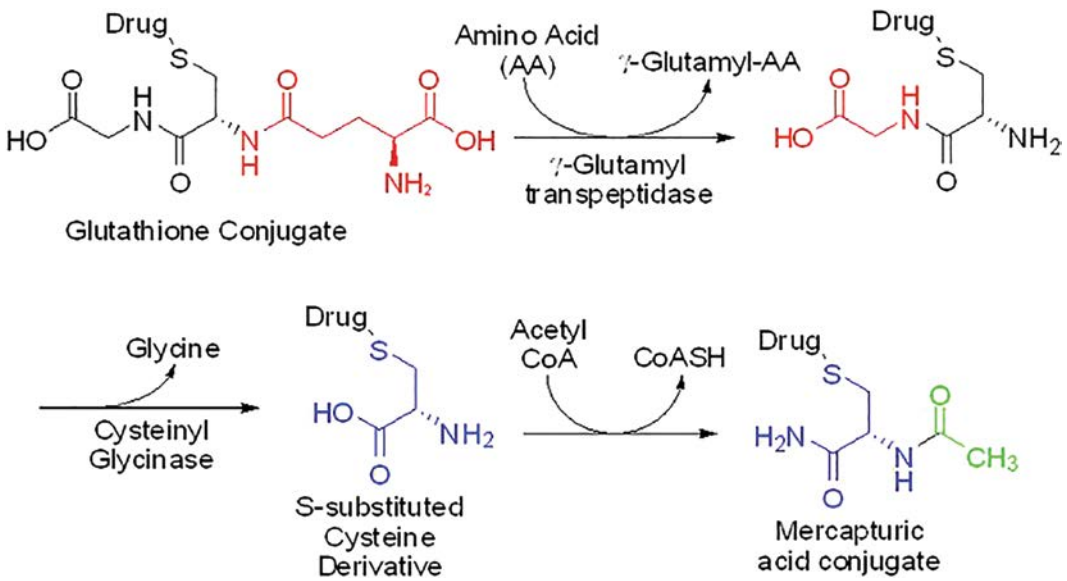
Glutathione peroxidase (EC 1.11.1.9) is a family of selenium-containing enzymes that catalyze the reduction of hydrogen peroxide to water with the concomitant oxidation of glutathione. They also catalyze the reduction of lipid peroxides.

$$2GSH + H_2O_2 \rightarrow GSSG + 2H_2O$$

There are several isoenzymes with differing locations, the most prominent being glutathione peroxidase 1. Glutathione peroxidase not only reduces hydrogen peroxide but also provides protection of cell membranes from oxidative damage.

Glutathione reductase (EC 1.8.1.7) is a flavoprotein containing flavin adenine dinucleotide (FAD), which reduces glutathione disulfide (GSSG) formed during the reduction of peroxides back to glutathione (GSH) using nicotinamide adenine dinucleotide phosphate-oxidase (NADPH) as a cofactor. This reduction of oxidized glutathione is essential for maintaining the redox balance within a cell and preventing oxidative stress.

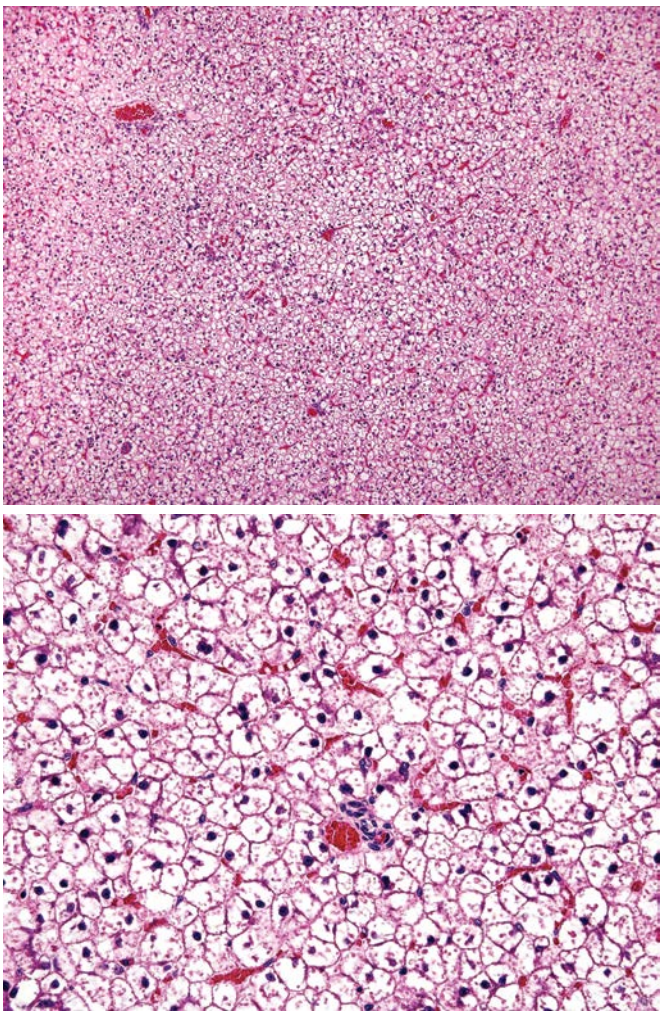
Glutathione S-transferases (GST) (EC 2.5.1.18) is a family of enzymes that facilitate the conjugation of xenobiotic intermediates with reduced glutathione. There are cytosolic, microsomal, and mitochondrial GST families. Thirteen classes of cytosolic glutathione transferases have been identified, known as alpha, beta, delta, epsilon, zeta, theta, nu, mu, pi, sigma, tau, phi, and omega, seven of which (alpha, theta, zeta, mu, pi, sigma, omega) are found in the human. The nomenclature to identify the individual isoenzymes uses a lowercase letter for the species followed by GST and an uppercase letter for the family, followed by a number for the subunit; thus the human GST alpha subunit 1 would be hGSTA1. The cytosolic and mitochondrial forms are found as dimers, with monomer molecular weights of around 25 kDa. Glutathione transferases catalyze the conjugation of a wide variety of electrophiles with reduced glutathione, after which the peptide of the glutathione conjugate may be further metabolized to a mercapturic acid through hydrolysis of the peptide bonds and acetylation of the remaining cysteine conjugate. As the name suggests, mercapturic acids are excreted in the urine (see figure below).



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Glycine conjugation, see **Amino acid conjugation** for further information.

Glycogen accumulation occurs in multiple organs as a stored energy supply. Changes in energy demand result in increased conversion of glucose to glycogen (glycogenesis) or degradation of glycogen (glycogenolysis) to release glucose. The primary sites of glycogen storage in mammals are liver and muscle. Glycogen accumulation can be visualized microscopically as clear cytoplasmic microvacuoles that are rose-pink when stained by the periodic-acid Schiff (PAS) reaction. Abnormal accumulation of glycogen occurs in several genetic disorders (glycogenoses) that produce defective enzymes within the glycogen synthetic or degradation pathway. Glycogenoses generally result in the inefficient conversion of glycogen to glucose with resultant hypoglycemia, secondary adverse biochemical changes, and eventual cellular functional failure.



Glycogen accumulation in the liver of a dog, H&E. Hepatocytes are diffusely pale on low magnification. On higher magnification, hepatocytes have mostly clear or faintly pink cytoplasm (glycogen). Glycogen is washed out during processing giving an empty appearance to the cells. (Images courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

Glymphatic is a controversial term that has been proposed as a macroscopic waste clearance system that utilizes perivascular tunnels formed by astrocytes (astroglia) to promote elimination of soluble proteins and metabolites from the central nervous system.

GMP is an acronym for good manufacturing practices. See **Good manufacturing practices** for further information.

GnRH is an acronym for **Gonadotropin-releasing hormone**. See **Gonadotropin-releasing hormone** for further information.

Gonad is the sexual or reproductive gland where gametes are produced. In the male it is the testes, and in the female it is the ovaries.

Gonadal stromal tumor, see the preferred term **Sertoli cell tumor, benign**.

Gonadal toxicology is the study of adverse events caused by a substance (e.g., chemical, drug), a pathogen (e.g., microorganism, virus) or any other agent (e.g., radiation) that could affect the male (testes) or the female (ovaries) gonads.

Gonadocorticoid is the sex hormone dehydroepiandrosterone (DHEA), but also includes its sulfonated metabolite (DHEA-sulfate), and androstenedione. These gonadocorticoids originate primarily from the zona reticularis of the adrenal cortex. DHEA and androstenedione are synthesized from serum cholesterol. Once released into the circulation, DHEA and androstenedione are converted to other sex steroids (e.g., estrogen, testosterone) by the ovaries and testes. Secretion of DHEA and androstenedione is regulated via a feedback loop involving adrenocorticotropic hormone (ACTH) secretion from the anterior pituitary gland, and corticotropin-releasing hormone (CRH) secretion from the hypothalamus.

Gonadotroph, see the preferred term **Pituitary basophil cell**.

Gonadotropin-releasing hormone (GnRH) is a hypothalamic hormone that mediates central control of reproduction by stimulating the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary gland. GnRH triggers sexual development at the onset of puberty and is essential for normal sexual physiology in both males and females. It constitutes the first step in the hypothalamic-pituitary-gonadal axis. Congenital deficiency of GnRH can cause hypogonadism.

Goniodysgenesis, see the preferred term **Filtration angle narrowed**.

Good clinical practice (GCP) encompasses a group of federal regulations promulgated and administered by the health authorities (e.g., FDA) as standards by which clinical studies

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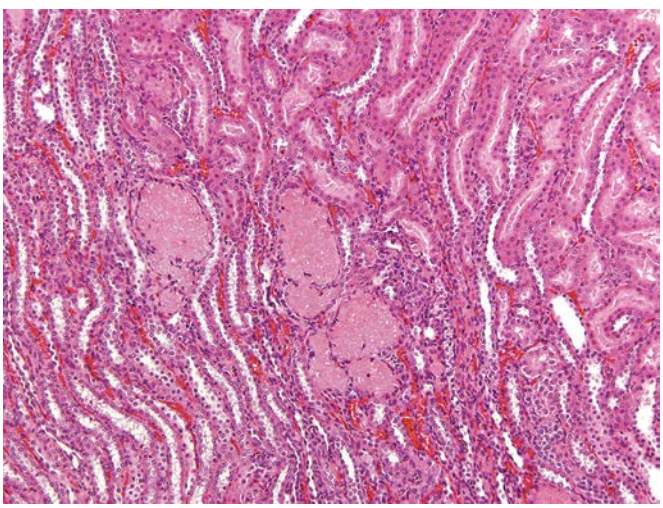
are designed, implemented, and reported so that the rights, integrity, and confidentiality of the subjects are protected, and there is public assurance that the data are credible.

Good laboratory practice (GLP) is a group of federal regulations established and administered by the health authorities (e.g., FDA) for conducting nonclinical laboratory studies that support, or are intended to support, applications for research or marketing permits for regulated products. They are designed to ensure the integrity of the data and were initially introduced to prevent fraud.

Good manufacturing practices (GMP) are regulations promulgated and administered by the health authorities (e.g., FDA, EU) that set the minimum standards for drug manufacturers to assure that drug products meet established requirements for identity, strength, quality, and purity which they purport or are represented to possess.

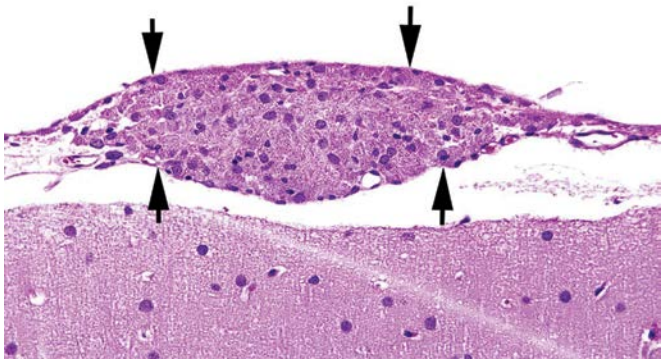
G proteins (guanine nucleotide–binding proteins) are transmembrane receptors of hormones or other ligands, which also bind guanine nucleotides (GDP and GTP) as part of their cellular function. Their activity is regulated by factors that control their ability to hydrolyze guanosine triphosphate (GTP) to guanosine diphosphate (GDP). The inactive G protein has a GDP in its binding site. Binding of the ligand to the receptor causes a change in the conformation that releases GDP, which is replaced with GTP. G-protein together with G-protein–coupled receptors transmit signals for many hormones and neurotransmitters.

Granular cast is a focal dilation of a renal tubule containing granular cell debris. The most common example is a hallmark of alpha 2u-globulin (α-2u-g) nephropathy, where granular casts form at the junction of the S3 tubule and thin descending limb of Henle. The formation of large granular casts is preceded by progressive accumulation of precursors in the form of cell debris in the distal end of the S3 tubule.



Granular casts, rat kidney.

Granular cell aggregate is a collection of cells of uncertain origin (possibly related to Schwann cells or primitive meningeal arachnoid cells) containing granular cytoplasm. This finding most often occurs in the uterus, vagina, or meninges of the brain. In the cervix or vagina, there are low numbers of scattered cells that form small clusters within the wall or adventitia. There is no disturbance of the surrounding tissue architecture. In the brain, small numbers of polygonal cells with abundant eosinophilic granules form as aggregates. There is no compression of the adjacent neural tissue. Intracytoplasmic granules in the uterus and vagina are weakly periodic acid-Schiff (PAS)-positive, but in the brain, they are strongly PAS-positive.



Granular cell aggregate in the brain of a rat, H&E. Arrows indicate the aggregate of cells with granular cytoplasm in the meninges. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

Granular cell aggregate is a collection of cells containing granular cytoplasm that are of uncertain origin, possibly related to Schwann cells in the peripheral organs and primitive meningeal arachnoid/ neural crest cells in the central nervous system. This finding most often occurs in the uterus, vagina, or meninges of the brain. In the cervix or vagina, there are low numbers of scattered cells that form small clusters within the wall or adventitia. There is no disturbance of the surrounding tissue architecture. In the brain, small numbers of polygonal cells with abundant eosinophilic granules form as aggregates, most commonly in the leptomeninges There is no compression of the adjacent neural tissue. Intracytoplasmic granules in the uterus and vagina are weakly periodic acid-Schiff (PAS)-positive, but in the brain, they are strongly PAS-positive. Unlike granular cell neoplasms, granular cell aggregates do not compress or invade tissues. Refer to **Nervous System** in Appendix 2 for further information.

Granular cell tumor is a soft tissue neoplasm generally thought to be of Schwann cell origin in the peripheral organs that can occasionally be observed in the gastrointestinal tract and female reproductive tract. Tumor cells are oval to polygonal, variably sized, with abundant, pale eosinophilic cytoplasm containing distinct intracytoplasmic granules. Refer to **Gastrointestinal Tract and Reproductive Tract (Female)** in Appendix 2 for further information. Granular cell tumors can also arise in the central nervous system. The origin of this tumor in that location is uncertain but thought to originate from the neural crest. The latter tumors are benign

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and confined to the meninges. Refer to **Nervous System** in Appendix 2 for further information.

Granular cell tumor, malignant is a compressive micronodular meningeal mass that can invade the adjacent brain. The neoplasm, composed of a relatively homogenous population of polygonal cells with cytoplasmic eosinophilic granules, exhibits mild to moderate anisocytosis and occasional megakaryocytosis. The neoplastic granular cells are of uncertain origin but thought to originate from the neural crest. Refer to **Nervous System** in Appendix 2 for further information.

Granulocytic hematopoietic dysplasia has asynchrony maturation or evidence of arrest at a stage of differentiation of the granulocytic (white blood cell) lineages. Refer to **Hematopoietic System** in Appendix 2 for further information.

Granulocytic leukemia, see the preferred term **Myeloid leukemia**.

Granulocytic sarcoma, see the preferred term **Myeloid leukemia**.

Granuloma, see **Granulomatous inflammation** for further information.

Granulomatous dacryoadenitis, see the preferred term **Lacrimal gland granulomatous inflammation**.

Granulomatous inflammation is a variant of chronic inflammation in which the predominant cell type is the macrophage, often induced by T lymphocytes. This reaction occurs as a response to contain a foreign object or microorganisms that are difficult to remove. Some macrophages become large, with abundant eosinophilic cytoplasm, and are referred to as epithelioid macrophages. Some macrophages may fuse to become multinucleate giant cells. A localized collection of these inflammatory cells is referred to as a granuloma.

GRAS (generally recognized as safe) is defined as the U.S. FDA designation that a chemical or substance added to food or as an excipient to a drug product is considered safe, and is exempted from the Federal Food, Drug, and Cosmetic Act requirements.

Growth hormone (GH) is a hormone and anabolic steroid primarily produced by the anterior pituitary gland. GH stimulates cell growth and reproduction and is required for normal maturation of mammals from infant to adult. GH also plays a role in glucose and fatty acid metabolism. In the immune system, GH helps regulate thymopoiesis and T-cell development. Abnormalities of GH production may lead to pronounced physical alterations of growth, including dwarfism (hyposecretion of GH) and acromegaly (hypersecretion of GH).

Synonym(s): **Somatotropin**.

Growth hormone–inhibiting hormone (GHIH) is a hormone produced in low amounts by the hypothalamus (and other organs, including pancreas and the major producer, the intestine). GHIH is synthesized in the hypothalamus and is transported via the portal vessels in the pituitary stalk to the GH- and TSH-secreting cells to inhibit the production and release of growth hormone (GH) and thyroid stimulation hormone (TSH) from the anterior pituitary gland. Additionally, GHIH has multiple organ effects, including inhibition of gastric secretion. Synthetic GHIH is used to treat acromegaly and other disturbances of growth due to overproduction of GH.

Synonym(s): **Somatostatin**.

Growth hormone–releasing hormone (GHRH) is a hypothalamic peptide that stimulates both the synthesis and secretion of growth hormone. GHRH secretion can be blocked by growth hormone or somatostatin. GHRH secretion is blocked by a powerful hypothalamic neurohormone called growth hormone–inhibiting hormone (GHIH). In addition, growth hormone feeds back to inhibit GHRH secretion. Hypersecretion of GHRH can cause acromegaly.

Growth plate closed occurs at the cessation of longitudinal bone growth. In a fully mature skeleton, the only indicator of where the growth plate was may be a linear irregularity of trabecular bone at the junction of the epiphysis with the metaphysis. In large animals, growth plate closure occurs earlier in females than in males. The timing of growth plate closure is site specific. In rodents, irregular cartilage remnants of the growth plate may remain throughout their lifespan so that additional bone growth is possible, albeit slow. Indian hedgehog (IHH) regulators may cause premature growth plate closure.

Synonym(s): **Age-dependent or premature physeal closure**.

Guide for the Care and Use of Laboratory Animals is a set of guidelines to assist in the care and usage of animals in the highest scientific, humane, and ethical way. These guidelines were first published in 1963, and the most recent (eighth) edition was published in 2011.

Gut-associated lymphoid tissue (GALT) consists of Peyer's patches, loose lymphoid cells, isolated lymphoid follicles, cryptopatches, and lymphoglandular complexes. Except for the Peyer's patches, GALT develops postnatally after antigenic exposure. Loose aggregates of lymphocytes may be found in the lamina propria throughout the gastrointestinal tract. Isolated lymphoid follicles found along the antimesenteric border of the small intestine in rodents, rabbits, and guinea pigs are smaller and consist of 1–2 follicles but are otherwise similar to Peyer's patches. Isolated lymphoid follicles may also be identified in the esophagus, stomach, and cecum in all species. Cryptopatches are clusters of primarily T- and dendritic-cells in the intercryptal lamina propria of the small intestine. Lymphoglandular complexes in the colon (and occasionally the rectum) are similar to but often smaller than Peyer's patches, except that lymphoglandular complexes often have crypts lined by follicle-associated epithelium within the submucosal lymphoid follicles. See Appendix 3 and **Mucosa-associated lymphoid tissue (MALT)** for further information.

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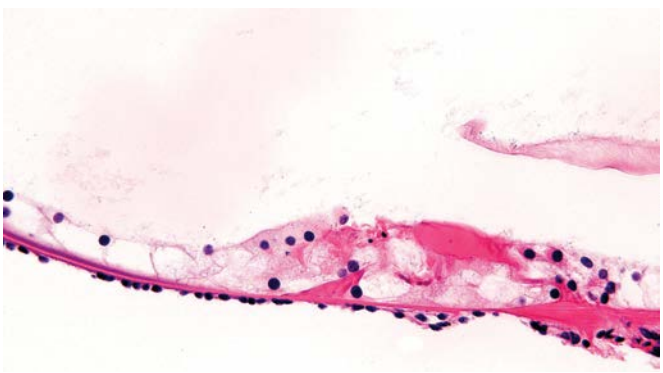
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Hair cell degeneration consists of disorganized, vacuolated or pyknotic inner or outer hair cells of the organ of Corti in the cochlea (auditory hair cells), or the hair cells of the maculae and crista ampullares (vestibular hair cells) in the semicircular canals of the vestibular system of the inner ear (refer to Appendix 3 for further information). Degeneration and necrosis of the hair cells may occur together, and is commonly found following exposure to toxins, particularly macrolide antibiotics (gentamycin). See **Hair cell numbers decreased** for illustration.

Differential diagnosis: **Hair cell necrosis**.

Hair cell necrosis consists of shrunken cells with hypereosinophilic cytoplasm and pyknotic, karyorrhectic, or karyolytic nuclei of the inner or outer hair cells of the organ of Corti in the cochlea (auditory hair cells), or the hair cells of the maculae and crista ampullares (vestibular hair cells) in the semicircular canals of the vestibular system of the inner ear (refer to Appendix 3 for further information). Degeneration and necrosis of the hair cells may occur together, and necrosis may occur rapidly with little residual evidence or inflammation following exposure to toxins, particularly macrolide antibiotics (gentamycin).

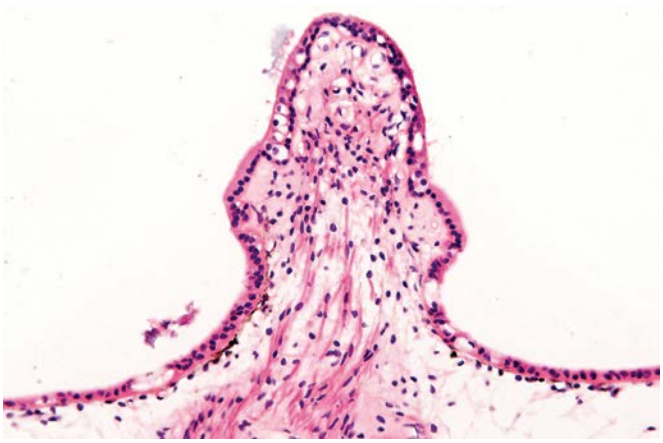
Differential diagnosis: **Hair cell numbers decreased**.



Hair cell necrosis with hair cell numbers decreased and disorganized, organ of Corti, inner ear, chinchilla, H&E. See **Hair cell numbers decreased** for an additional illustration. (Image courtesy of K. Schafer, Vet Path Services, Mason, Ohio.)

Hair cell numbers decreased consists of nondescript, swollen cells replacing the inner or outer hair cells of the organ of Corti in the cochlea (auditory hair cells), or the hair cells of the maculae and crista ampullares (vestibular hair cells) in the semicircular canals of the vestibular system of the inner ear (refer to Appendix 3 for further information). In the organ of Corti, these large cells may become low cuboidal cells lining the scala media.

Differential diagnosis: **Hair cell degeneration**.



Hair cell numbers decreased with hair cell degeneration and vacuolation due to macrolide antibiotic, vestibular organ crista ampullaris, vestibular system, chinchilla, H&E. See **Hair cell necrosis** for an additional illustration. (Image courtesy of K. Schafer, Vet Path Services, Mason, Ohio.)

Hair cell or supporting cell vacuolation is characterized by the loss of staining and development of clear spaces (hydropic change, or vacuolation) of the outer or inner hair cells and/or supporting cells of the organ of Corti in the cochlea (refer to Appendix 3 for further information). Outer hair cells regenerate, but non-regenerating inner hair cells may be replaced by vacuolated supporting cells. This finding may occur following exposure to toxins and physical injury. See **Hair cell numbers decreased** for illustration.

Differential diagnoses: **Hair cell degeneration**; **Hair cell necrosis**; **Hair cell numbers decreased**; Artifact (processing).

Hair follicle dystrophy, see the preferred term **Adnexal necrosis**.

Hair follicle growth cycle is shown as a schematic in Appendix 3 under **Skin**.

Hair follicle hyperplasia, see the preferred term **Adnexal hyperplasia**.

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Hair follicle tumor, benign is a well-demarcated, multilobular, benign neoplasm derived from hair follicle epithelium. Each lobule exhibits some degree of hair follicle differentiation with one or multiple cysts. Mitoses are rare, and there is no invasion into the surrounding tissues. Refer to **Skin** in Appendix 2 for further information.

Hair follicle tumor, malignant has not been described in rodents. In dogs, malignant pilomatricomas have been described in a few isolated diagnostic cases, but not in toxicologic studies. Malignant hair follicle tumors in dogs are locally aggressive, and often invade and/or metastasize to bone. Refer to **Skin** in Appendix 2 for further information.

Half-life ($T_{1/2}$) of a drug is the time it takes the plasma concentration of the drug to fall by 50%. The half-life is an intrinsic property of a drug and is a function of the volume of distribution (V_D) and the clearance (Cl):

$$T_{1/2} = 0.693 V_D / Cl$$

Hamartoma is an area of abnormal development within a tissue that appears as an atypical composition or organization of cells that are normally located in the organ.

Haploid is an organism or cell with one copy of the genome. In animals only germ cells are haploid; all other cells are diploid, possessing two copies of the genome.

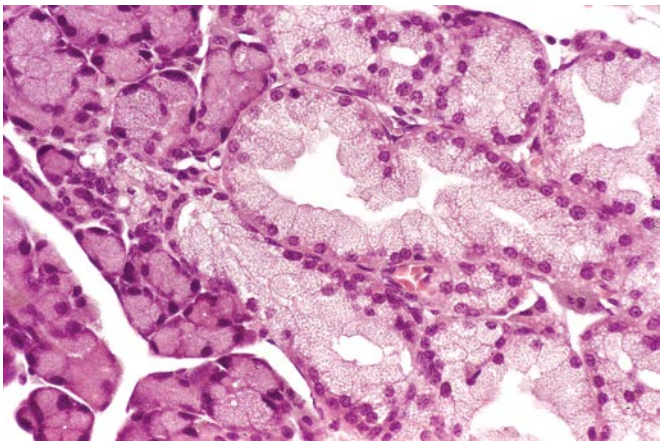
Harderian gland acinar hyperplasia consists of well-demarcated, noncompressive, and tinctorially distinct foci of alveoli that contain increased numbers of cells that are sometimes hypertrophied with variable cytoplasmic staining, contain enlarged nuclei, and are pseudostratified, often with papillary projections. Refer to **Special Senses** in Appendix 2 for further information.

Harderian gland adenocarcinoma is similar to Harderian gland adenoma, but consists of an expansive, distorted and invasive mass of variably differentiated cuboidal or columnar acinar cells with anisokaryosis and little to no normal secretions or glandular architecture. Refer to **Special Senses** in Appendix 2 for further information.

Harderian gland adenoma in rodents is characterized by a well-demarcated, expansive mass of enlarged acinar cells, often with enlarged nuclei, and acini may be cystic or pseudostratified with papillary growth into acinar lumina. Refer to **Special Senses** in Appendix 2 for further information.

Harderian gland alteration consists of clusters of normal appearing Harderian gland acini (cuboidal to columnar cells with pale foamy cytoplasm around acini) in the lacrimal gland of rabbits and rodents. This change increases with age, and is more frequent in male rats (androgen-dependent) and female mice. This change may arise from undifferentiated basal cells, or may be a degenerative or metaplastic change, but is not considered ectopic tissue.

Synonym(s): **Harderization**; **ectopic Harderian gland**; **lacrimal gland Harderian metaplasia**.



Harderian gland alteration, lacrimal gland, B6C3F1 mouse, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

Harderian gland atrophy consists of a focal, multifocal, or diffuse decrease in the size of acini or ducts, often with flattened epithelium lacking secretory differentiation. Lobules may be irregular, acinar luminal size may be increased or decreased, and stromal fibrosis may be present. Atrophy may occur in association with retroorbital bleeding, inflammation, infectious diseases, genetic mutations, and nutritional deficiencies. Age-related atrophy is usually multifocal and more frequent in rats than mice.

Harderian gland granulomatous inflammation consists of focal or diffuse accumulations of epithelioid macrophages, multinucleated giant cells, lymphocytes, and plasma cells involving alveoli, ducts, and interstitial stroma. Exogenous (hair shafts from retroorbital bleeding) or endogenous (escaped porphyrin accretions) foreign bodies may or may not be identified as the inciting agent. Granulomatous inflammation increases in frequency with age, particularly in rats.

Synonym(s): **Foreign body inflammation**; **porphyrin granuloma**.

Harderian gland increased porphyrin consists of more than normal yellow-brown porphyrin pigment in the acini or ducts or laminated brown concretions in atrophic acini. This occurs as a spontaneous change in aging rodents, particularly in females, as part of lacrimal gland inflammation with rat coronavirus infection, and may be a treatment-related finding associated with chemical and xenobiotic administration (phosphodiesterase inhibitors). Chromodacryorrhea (red tears) may be present on the skin due to hypersecretion of porphyrin.

Harderian gland inflammation consists of focal or diffuse accumulations of inflammatory cells (granulocytes or heterophils [rabbit], macrophages, lymphocytes, and plasma cells) in and

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around the acini, ducts, and interstitial stroma accompanied by other inflammatory indicators including interstitial edema, congestion, hemorrhage, and necrosis or cellular debris. Meibomian gland atrophy, squamous metaplasia of the acini, hyperkeratinization of duct epithelium, and interstitial inflammation may occur in chronic inflammation. Hemorrhage is usually found with inflammation associated with retrobulbar blood sampling, and diffuse inflammation is associated with infectious diseases.

Differential diagnoses: **Duct-associated lymphoid tissue**; **Meibomian gland inflammatory cell infiltrate**; **Meibomian gland granulomatous inflammation**.

Synonym(s): **Dacryoadenitis**.

Harderian gland inflammatory cell infiltrate consist of small numbers of leukocytes associated with acini, ducts or interstitium, in the absence of obvious inflammation. Spontaneous lymphocytic infiltrates are more frequent. Infiltrates around ducts may be difficult to differentiate from duct-associated lymphoid tissue.

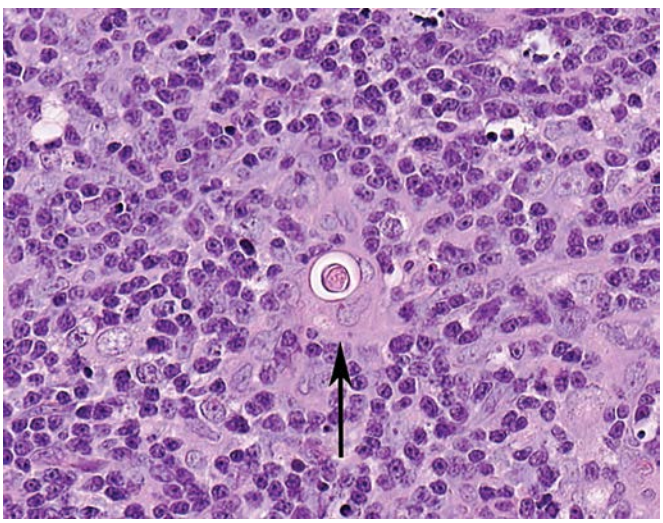
Differential diagnoses: **Duct-associated lymphoid tissue**; **Meibomian gland inflammation**.

Harderian gland tumors, see the preferred terms **Harderian gland adenoma** and **Harderian gland adenocarcinoma**.

Harderization, see the preferred term **Harderian gland alteration**.

Harmartoma, lipomatous is a benign focal malformation characterized by adipose tissue growing as a disorganized but nonneoplastic mass. Refer to **Nervous System** in Appendix 2 for further information.

Hassall's corpuscles are remnants of the epithelial tubes that grow out from the third branchial pouches of the embryo to form the thymus. They are composed of concentric or lamellated type IV reticular epithelial cells, and can sometimes show keratinization and contain cellular debris. These structures appear in fetal life and will increase with age or in tandem with cell degeneration/necrosis. Some exogenous treatments, such as sodium valproate, have been shown to cause an increase in numbers of Hassall's corpuscles. Although their function is unclear, they are thought to be involved in the removal of apoptotic thymocytes and the maturation of developing thymocytes. One study in human thymus has shown that they express thymic stromal lymphopoietin (TSLP) that instructs dendritic cells in to induce $CD4^+$ regulatory T-cell development.

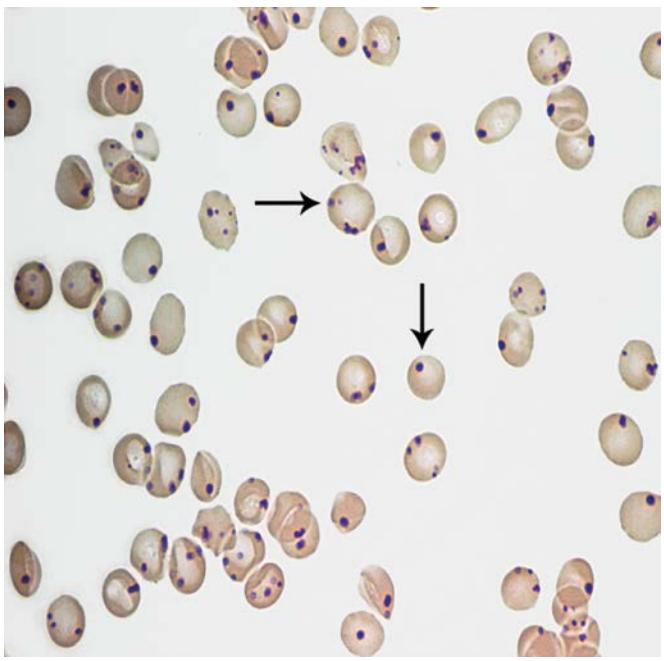


Example of a Hassall's corpuscle (arrow) in the medullary region of a rat thymus with increased cell death (apoptosis). There is a central area of keratinization surrounded by epithelioid cells.

Hazard is defined as a potential source of harm or adverse health effect on a person or persons.

Hazard identification in pharmaceutical safety assessment is the process of determining whether certain toxicological properties, specific organ toxicities, genotoxicity, or reproductive toxicity is associated with the agent, without consideration of the associated exposure. Consideration of the exposure parameters permits the risk associated with the therapeutic use to be estimated, since the extent and duration of exposure determines the risk associated with hazards empiric to the drug candidate.

Heinz body is a small red blood cell inclusion that represents oxidative damage to the erythrocyte, reflecting hemoglobin degradation. Heinz bodies can be observed with supravital stains but cannot be seen in Romanowsky stains. They are often seen close to the red blood cell membrane edge. Splenic pitting by macrophages can remove Heinz bodies leaving a cell that is termed a "bite cell." Any disorder that causes oxidative damage to the cell is capable of producing Heinz bodies. Because it is the role of red blood cells to carry oxygen, they are particularly



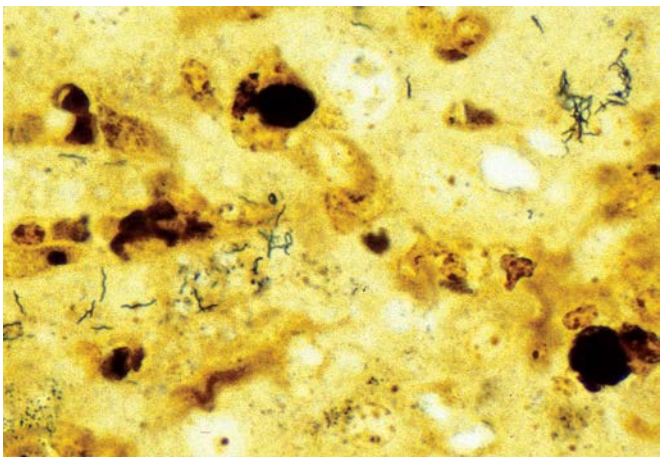
Heinz body formation (black arrows), blood smear, rat (stained with the supravital stain methylene blue following administration of phenylhydrazine as an oxidant damaging agent).

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prone to oxidative damage. Erythrocytes are physiologically protected from oxidative damage with glutathione enzymes and membrane thiols. Individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency are at high risk of oxidative damage to their red blood cells. Heinz bodies are also observed in chronic liver disease. In veterinary practice, Heinz body anemia has been reported in cats, dogs, and some primates following the ingestion of acetaminophen or onions. Propylene glycol used to be a common ingredient in moist cat food but it has been recently prohibited as it was also found to produce decreased red blood cell survival due to Heinz body formation.

Helicobacter is a genus of bacteria first described in the 1980s, and now comprised of 32 species, most of which inhabit the stomach or intestines in animals. They are helical, curved or straight, Gram negative organisms which can be broadly divided into three groups: species that colonize the stomachs of humans and animals and produce a urease that effectively allows them to survive by neutralizing gastric acid in the vicinity of the cell; enterohepatic species that inhabit the intestinal and hepatobiliary tracts of various mammal and bird hosts; and a third group that in some aspects resembles *Campylobacter* species. Most species are asymptomatic; however, some species have been associated with both inflammatory as well as neoplastic disease under certain circumstances. Restricting discussion to species relevant to preclinical toxicity testing, immunocompetent rodents are most significantly infected by *H. bilis* and *H. hepaticus*. These species do not colonize the stomach, but rather in the large intestine, where they may cause typhlocolitis, diarrhea, and rectal prolapse. In some mouse strains, *H. hepaticus* infection has been associated with hepatitis, and liver and colon cancer. In laboratory beagles, *Helicobacter* sp. can be isolated from the stomach of asymptomatic animals with an unproven association to natural disease, although the beagle can be used experimentally as a model for *H. pylori* gastritis. In monkeys, subacute lymphoplasmacytic gastritis is frequently encountered. The role of *Helicobacter* species in these lesions is unproven, but some case reports have implicated the presence of *H. pylori* with lesion formation in the stomach of adolescent animals. In humans, *H. pylori* has received the most scrutiny, and while mostly asymptomatic, *H. pylori* has been associated with an increased risk of stomach ulcer formation, colorectal polyps, and gastric and colorectal carcinoma. The *H. pylori* genome was sequenced from the stomach cavity of Ötzi, the 5300-year-old ice mummy discovered in the Tyrolean Alps in Italy.

Helicobacter hepaticus is a gram-negative, curved or helical-shaped bacterium associated with acute and chronic infection of the liver in susceptible strains of mice (some strains are considered resistant). Infection is generally characterized by areas of necrosis that may be accompanied by inflammatory cell accumulations including lymphocytes, macrophages, and neutrophils. In chronic stages, infection may also be associated with hepatocytomegaly, oval cell hyperplasia, and cholangitis. In experimental settings, *Helicobacter* infections may increase the formation of neoplasms of the liver and colon in conjunction with administration of carcinogenic substances. *Helicobacter* may be observed in the liver of infected mice via histochemical stains such as the Warthin-Starry, as the bacterium is present between hepatocytes within or adjacent to areas of inflammation. Definitive diagnosis is best performed by PCR testing of DNA extracted from suspected tissues, using genus- and species-specific probes for *Helicobacter* species. In addition to *H. hepaticus*, *H. bilis* may also cause hepatic inflammatory lesions, albeit of milder severity.



Helicobacter, mouse liver, silver stain. (Reproduced with permission of the Society of Toxicologic Pathology from Thoolen, B. et al. 2010. *Toxicol Pathol* 38(7 Suppl):5S–81S.)

Hemangioendothelial hyperplasia describes the proliferation of normal to hypertrophied endothelial cells lining dilated capillaries that variably contain proteinaceous fluid, red blood cells, and/or lymphoid cells. Refer to **Cardiovascular System** in Appendix 2 for further information.

Hemangioendothelioma, benign, see the preferred term **Hemangioma**.

Hemangioendothelioma, malignant, see the preferred term **Hemangiosarcoma**.

Hemangioma is a benign tumor of vascular endothelial cells that is usually well-defined and demarcated from the normal parenchyma. Morphologically, the vascular channels are lined by a single layer of well-differentiated endothelial cells, and thrombi sometimes develop within larger cavities, especially in the murine ovary and uterus. Refer to **Cardiovascular System** in Appendix 2 for further information.

Hemangioma, intramuscular, see the preferred term **Angioma, intramuscular**.

Hemangioma, mixed intramuscular, see the preferred term **Angioma, intramuscular**.

Hemangiomatous hyperplasia, see the preferred term **Angiomatous hyperplasia**.

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Hemangiosarcoma is an invasive malignant tumor arising from the vascular endothelium or from pluripotential mesenchymal stem cells. The endothelial cells are large, poorly differentiated, and can be anaplastic in appearance. Mitoses are common, and the capillary to cavernous spaces are supported by varying amounts of fibrous stroma. Refer to **Cardiovascular System** in Appendix 2 for further information.

Hematemesis is vomit containing blood which is usually the result of bleeding in the upper gastrointestinal (GI) tract. In toxicity studies it may be a consequence of gastric irritation by the test compound.

Hematocyst, see the preferred term **Valvular angiectasis**.

Hematology (as applied in toxicology studies) determines the effect of the test article on blood components. A standard hematology assessment is incorporated into all repeat-dose toxicity studies. the parameters routinely assessed are shown in the table below.

Hematology Parameters Routinely Assessed in Repeat-Dose Toxicity Studies

White blood cells	Differential leukocyte count (absolute):
Red blood cells	Neutrophils absolute
Hemoglobin	Lymphocytes absolute
Hematocrit	Monocytes absolute
Mean corpuscular volume	Eosinophils absolute
Mean corpuscular hemoglobin	Basophils absolute
Mean corpuscular hemoglobin concentration	Large unstained cells (LUC)
Red cell distribution width	Reticulocyte percent
Platelets	Reticulocyte absolute count
Mean platelet volume	

Hematoma is a well-demarcated accumulation of extravascular blood within a tissue compartment. Hematomas are grossly visible as confined, blood-filled spaces within a tissue.

Hematopoiesis is a process that produces new blood cells controlled by the number of red blood cells, leukocytes, and platelets in the peripheral circulation, as well as external stimuli in response to environmental stress. Hematopoiesis occurs primarily in the bone marrow, but also in the liver, lymph nodes, and lungs depending on the stimuli initiating the process. Hematopoietic cells collectively refer to all the cells involved in that process. Nonhematopoietic elements of bone marrow consist of mineralized bone, bone marrow stroma, and fat.

Hematopoietic cell proliferation is another term for hematopoiesis representing a hypercellular bone marrow with increases in all blood cell lineages in response to an external event.

Hematopoietic cells, hypercellularity is characterized by greater than normal numbers of hematopoietic cells in the bone marrow. Cells of one or more lineages may be affected and should be identified if possible. Refer to **Hematopoietic System** in Appendix 2 for further information.

Hematopoietic cells, increased is characterized by greater than normal numbers of hematopoietic cells within the medullary cavity, and a reduced amount of adipose tissue. Refer to **Hematopoietic System** in Appendix 2 for further information.

Hematopoietic dysplasia is a hyperplasia of the bone marrow with an abnormal shift in maturation or abnormal cellular phenotype of one or more bone marrow cell lineages. The recognized subtypes are erythroid, myeloid (granulocytic, monocytic), megakaryocytic, lymphocytic, and not otherwise specified (NOS). Bone marrow dysplasia is an abnormal maturation of one or more lineages of resident marrow cells and is often but not always considered a preneoplastic lesion. Refer to **Hematopoietic System** in Appendix 2 for further information.

Hematopoietic granulocytic dysplasia has asynchrony maturation or evidence of arrest at a stage of differentiation of the granulocytic lineages.

Hematopoietic megakaryocytic dysplasia has asynchronous maturation or evidence of arrest of the megakaryocytic lineages. It is observed in myelodysplastic syndrome, which affects mostly the megakaryocytic lineage, and is mainly characterized by thrombocytopenia. Giant platelets with abnormal granulations (hyper- or hypogranulation) are often observed in blood smears. Bone marrow appears normal to hypercellular, and megakaryocytes exhibit atypical features. Micromegakaryocytes, large mononuclear megakaryotic forms, or megakaryocytes with multiple small nuclei or abnormal granulations are observed. The other lineages, mostly erythroid, are also affected by dysplastic changes.

Synonym(s): **Thrombodysplasia**.

Hematopoietic stem cells are the progenitor cells that divide and mature into the erythroid, myeloid, megakaryocytic, or lymphoid series in a process called hematopoiesis toward the end of maintaining blood homeostasis.

Hematopoietic system, Anatomy and Histology, see Appendix 3 for further information.

Hematuria is the presence of red blood cells (i.e., erythrocytes, RBCs) in the urine, apparent from the red/brown color of the urine.

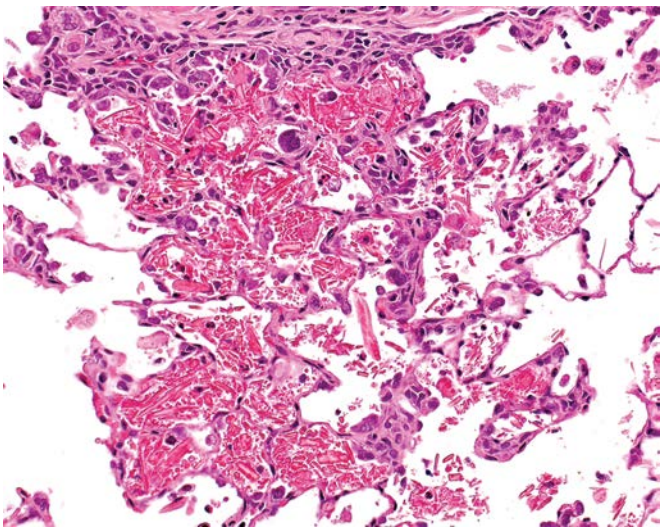
Heme consists of an iron ion coordinated to a porphyrin ring. Proteins with heme as the prosthetic group are known as hemoproteins. The iron in the heme group can bind to oxygen. The most common hemoprotein is hemoglobin. Other important hemoproteins include myoglobin, cytochromes, and catalase.

Hemocyst, see the preferred term **Valvular angiectasis**.

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Hemoglobin (Hb or Hgb) is a hemeprotein formed in red blood cells. It is responsible for carrying oxygen in the blood. Blood hemoglobin levels are monitored as part of the hematology panel in most repeat-dose toxicity studies.

Hemoglobin crystal alveolitis is specific to rats and related to the increased susceptibility of rat hemoglobin to crystallization. The elongate, eosinophilic crystals form within the alveolar capillaries, presumably causing mechanical rupture and consequent release into the alveolar spaces, where they initiate a neutrophil and macrophage phagocytic response.



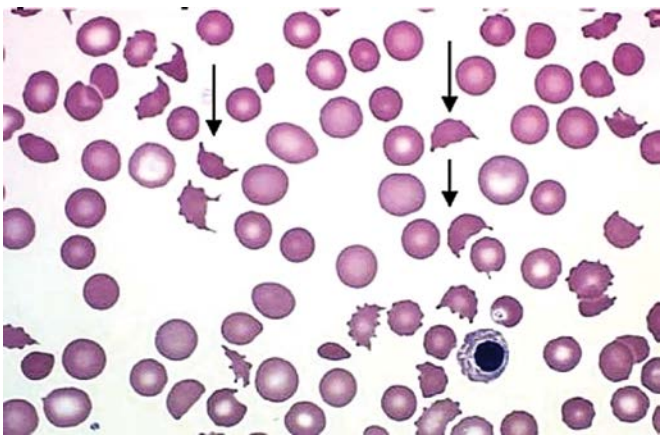
Hemoglobin crystal alveolitis, lung rat, H&E.

Hemoglobin distribution width (HDW) is an acronym that stands for hemoglobin distribution width. It is a red cell index that is provided on Siemens Advia automated hematology analyzers. It is calculated by determining the standard deviation of the RBC HC (hemoglobin concentration) histogram and is a measure of the red cell hemoglobin concentration variability. The HDW is not typically reported with routine CBC results. However, it can be a valuable parameter in the investigation of mechanistic issues. For example, it has proven useful in sickle cell anemia or hereditary spherocytosis subjects to provide an automated and objective estimate of changes in more densely hemoglobinated erythrocytes with abnormal morphology.

Hemoglobinuria is the presence of the protein hemoglobin in the urine, often associated with increased hyaline droplets (as renal proximal convoluted tubule cells reabsorb this protein) and hyaline cast formation.

Hemolysis is the lysis of red blood cells such that the hemoglobin is released. This may occur in vitro or in vivo. Agents causing hemolysis may result in anemia and iron accumulation during repeat-dose toxicity studies. In vitro hemolysis is a complicating factor in plasma preparation and may interfere in the accurate assessment of clinical pathology parameters and bioanalysis of parent drug and metabolites.

Hemolytic anemia is an anemia that results from an increase in the rate of red blood cell destruction. Erythroid hyperplasia and anatomical extension of the bone marrow may provide various levels of compensation so that increases in red cell destruction can be very elevated before anemia develops. Hemolytic anemia can occur as the consequence of intravascular hemolysis (the accelerated destruction of erythrocytes in circulation) or extravascular hemolysis (increased erythrocyte destruction through the hepatosplenic monocyte phagocyte system [MPS]). Chronic hemolytic anemias are often associated with extravascular hemolysis and increased splenic removal of red blood cells. In contrast, intravascular hemolysis is more typically abrupt in nature and occurs within the circulation. Refer to intravascular hemolysis and extravascular hemolysis for more details.



Schistocytes (arrows), blood smear, cynomolgus monkeys. (Fragmented red blood cells are a hallmark of intravascular hemolytic anemia.)

Hemolytic uremic syndrome is any condition (e.g., hemolytic anemia) resulting in hemolysis and platelet activation leading to a microangiopathy, involving the glomerular tuft, reduced renal blood flow, and renal failure. It can be initiated by bacterial toxins or an autoimmune phenomenon. It is the most common cause of acquired renal failure in juveniles.

Hemoprotein is a heme-containing protein (e.g., hemoglobin, cytochromes).

Hemorrhage is the extravasation of blood from blood vessels into the surrounding tissue or out of the body into the surrounding environment.

Hemosiderin accumulation is an increase in this endogenous pigment intracellularly. Hemosiderin is an iron-containing granular or globular pigment derived from ferritin. Collections of ferritin micelles form hemosiderin and are visible on hematoxylin and eosin (H&E)-stained histologic sections as golden-brown granules. Most hemosiderin is located in macrophages, primarily in tissues actively engaged in the turnover of red blood cells, such as the bone marrow, spleen, and liver. An increase in the amount of hemosiderin can occur locally

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following hemorrhage and/or necrosis in a tissue, or systemically due to iron overload.

Hemosiderin pigment is a golden-yellow to golden-brown globular or granular material which may be present intracellularly or extracellularly in tissues. Hemosiderin can be confirmed by the Prussian blue stain, where this iron-containing pigment will appear blue. Hemosiderin pigment often accumulates within macrophages of the spleen, lymph nodes, liver, and lung. Its origin is often increased turnover of red blood cells, so it is more common in organs involved in blood turnover (spleen, lymph nodes, liver) and also becomes increasingly common with age. In cases of left-sided heart failure, hemosiderin pigment accumulates within pulmonary alveolar macrophages, whose numbers are also increased (hyperplasia), giving rise to their colloquial description as "heart failure cells." See **Hemosiderin accumulation** for further information.

Differential diagnoses: **Ceroid pigment**; Lipofuscin pigment; **Wear-and-tear pigment**.

Hemosiderosis is an abnormal accumulation of the iron-containing pigment hemosiderin in tissue that is without tissue damage. Hemosiderin forms due to extravascular red blood cells or heme degradation by macrophages. The etiologies resulting in hemosiderosis are variable, including repetitive transfusions, hypertension, intravascular hemolysis, or chronic microhemorrhage. See **Hemosiderin accumulation** for further information.

Hemothorax is characterized by the presence of a bloody exudate in the thoracic cavity and may be seen as a consequence of anticoagulant administration, trauma, or secondary to neoplasia. The exudate contains hemosiderin-laden macrophages (as a consequence of erythrophagocytosis), and there is often an associated mesothelial proliferation together with inflammation.

Differential diagnoses: **Hydrothorax**; **Chylothorax**; **Pyothorax**.

Hepatic adenocarcinoma, see the preferred term **Hepatocellular carcinoma**.

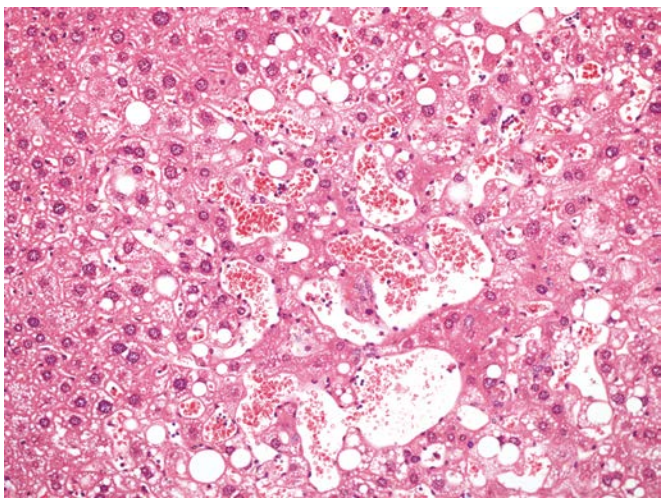
Hepatic adenofibrosis, see the preferred term **Cholangiofibrosis**.

Hepatic adenoma, see the preferred term **Hepatocellular adenoma**.

Hepatic amyloidosis is an extracellular deposit of polypeptide fragments of a chemically diverse group of glycoproteins in perisinusoidal and/or periportal liver locations or involving blood vessel walls, leading to dilatation or degeneration of bile ducts and blood vessels. The spontaneous incidence of systemic amyloid deposits is rare in BALB/c, C3H, and B6C3F1 mice, but common in CD-1, C57B6, albino, Swiss Webster, SJL mice, and Syrian hamsters, and extremely rare in rats. A number of factors including sex, diet, housing conditions, stress, endocrine status, and microbiological/parasitic status are reported to influence the occurrence of amyloid in susceptible strains of mice. The incidence of amyloid also increases with age. Histologically, amyloid appears as pale, amorphous, homogenous eosinophilic material with hematoxylin and eosin (H&E) stain and shows anomalous, often green birefringence under polarized light when stained with Congo red. Drug-induced amyloidosis is extremely rare in nonclinical species and humans. Amyloid can be induced in susceptible strains of mice with casein, silver nitrate, and following lipopolysaccharide administration. Rats tend to be resistant to xenobiotic-induced amyloid deposition.

Hepatic angiectasis (also known as telangiectasis, sinusoidal dilation, or peliosis hepatis) is a nonneoplastic lesion characterized by more or less defined areas of liver parenchyma with variably expanded sinusoidal lumens. Some controversy exists as to whether the endothelial lining of affected sinusoids is preserved, or whether the sinusoidal blood actually becomes continuous with the space of Disse. Hepatic angiectasis has been observed as a spontaneous aging lesion in mice but has also been associated with treatments and conditions that involve circulatory disturbances or hepatocellular injury. Two types of angiectasis, a cystic ("phlebectatic") type and a cavernous ("parenchymal") type, have been described. The cystic type is characterized by focal or multifocal dilation (distension) of endothelial-lined channels. The cystic spaces are lined by a single layer of endothelium filled with blood, separated from one another by cords of liver parenchyma. The cavernous type cysts mostly lack endothelial lining in the space of Disse, while the blood comes in direct contact with the neighboring parenchymal cells leading to focal necrosis. Some restrict use of the term "peliosis hepatis" for the cavernous type of hepatic angiectasis.

Synonym(s): **Hepatic telangiectasis**; **hepatic sinusoidal dilation**; **peliosis hepatis**.



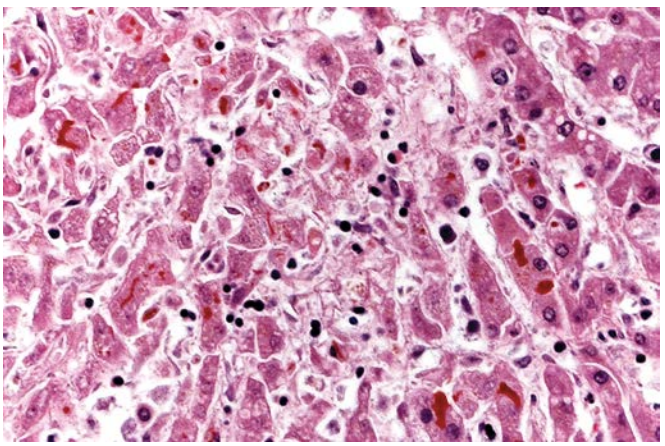
Hepatic angiectasis, mouse liver, H&E. (Figure courtesy of R. Cattley, Auburn University.)

Hepatic bile duct adenomatosis, see the preferred term **Cholangiofibrosis**.

Hepatic cell carcinoma, see the preferred term **Hepatocellular carcinoma**.

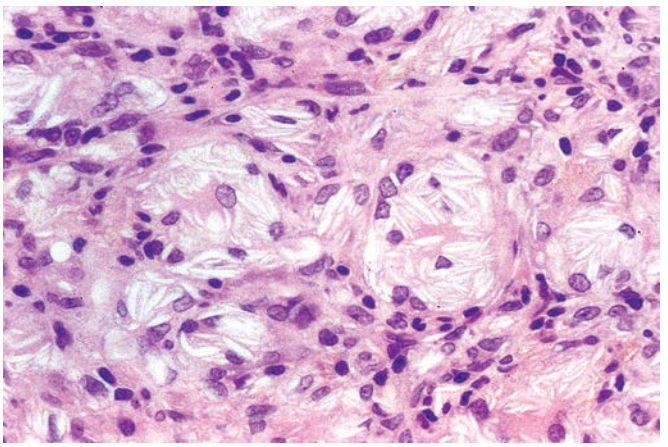
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Hepatic cholestasis is not a common xenobiotic induced finding in rodents and is more common in humans, dogs, and monkeys. Bile pigment is a common finding when there is cholestasis secondary to obstruction of bile flow, or when there is perturbation in bile metabolism. Circulatory alkaline phosphatase and gamma glutamyl transaminase are good biomarkers of both intrahepatic and extrahepatic cholestasis. Serum total bilirubin concentration is a relatively less sensitive indicator of cholestasis in laboratory animals. Bile pigment appears as elongated, pale green-brown plugs within the bile caniculi, stains green with Hall's method, and can appear as finely granular pigment within hepatocytes. Intrahepatic cholestasis is caused in laboratory animals by high dose of many NSAIDs (e.g., phenacetin, flurbiprofen, sulindac, flufenamic acid, nimesulide, indomethacin, diclofenac, and ibuprofen), flutamide, disulfiram, methapyrilene, piperonyl butoxide, bromobenzene, butylated hydroxytoluene, naltrexone, 2-acetamidoflourene, hydrazine, tannic acid, dipyridamole, ketoconazole, cyproterone acetate, and methylene dianiline. Several models of cholestasis are well-studied, and established in rats or mice, including biliary ligation, which mimics bile duct obstruction; alpha-naphthylisothicaynate (ANIT), which damages/destroys biliary epithelium; lipopolysaccharide (LPS), which down-regulates much of the hepatic metabolism including most transporters; and glucuronidated ethinyl estradiol–induced cholestasis by inhibition of the bile salt export pump (BSEP). Cholestasis is reported in abcb4 (mdr2), abcb11 (BSEP), and Cyp 7 knockout mice.



Hepatic cholestasis, dog liver, H&E. (Reproduced with permission of Elsevier from Cattley, R. and Cullen, J. 2013. In: Haschek, W., Rousseux, C., Wallig, B., Bolon, R.O. (eds.) *Handbook of Toxicologic Pathology*, 3rd ed. Academic Press, Elsevier, San Diego, CA, pp. 1509–1566.)

Hepatic cholesterol granuloma is a chronic (granulomatous) inflammatory focus surrounding clear, acicular cholesterol crystals which are birefringent under polarized light. Cholesterol crystals may form in hyperlipidemia but may or may not be surrounded by inflammatory cells. Alternatively, in foci of granulomatous inflammation (characterized by epithelioid macrophages and/or multinucleate giant cells, sometimes with lymphocytes), lipid and cholesterol may accumulate at the center of the lesion.



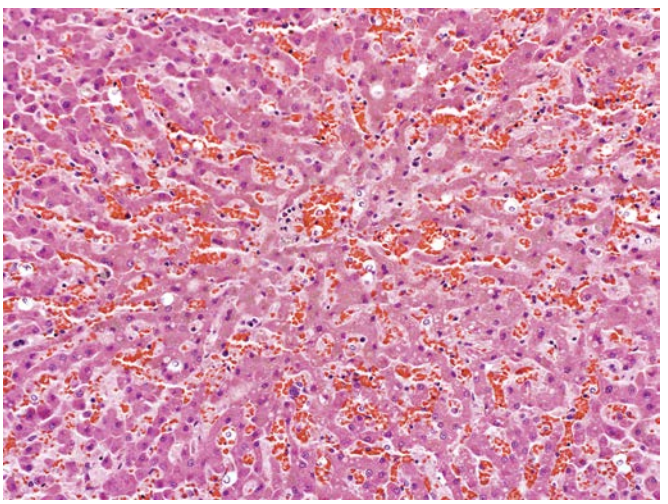
Hepatic cholesterol granuloma, rat liver, H&E. (Reproduced with permission of the Society of Toxicologic Pathology from Thoolen, B. et al. 2010. *Toxicol Pathol* 38(7 Suppl):5S–81S.)

Hepatic clearance results from drug metabolism within the liver and excretion into the bile. It is the volume of blood perfusing the liver which is cleared of drug in a unit of time. It may be defined by Roland's equation:

$$Cl(h) = Q\,[(f \times Cl_{int})/(Q + f \times Cl_{int})]$$

where Q = hepatic blood flow, f = fraction of free drug (not plasma protein bound), Cl_{int} = intrinsic capacity of the hepatocytes to metabolize the drug.

Hepatic congestion refers to the increased presence of blood elements within blood vessels. In the liver, congestion is visualized mostly in the sinusoids. Congestion is often not considered to be a pathologic condition. The exception is chronic passive congestion which infers impairment of blood to the heart due conditions such as narrowing of the vena cava lumen, right-sided cardiac valvular insufficiency, and compromised cardiac contractility. Chronic passive congestion is often accompanied by sinusoidal dilatation (also known as angiectasis), and central lobular atrophy with loss of hepatocytes.



Hepatic congestion, dog liver, H&E. (Figure courtesy of R. Cattley, Auburn University.)

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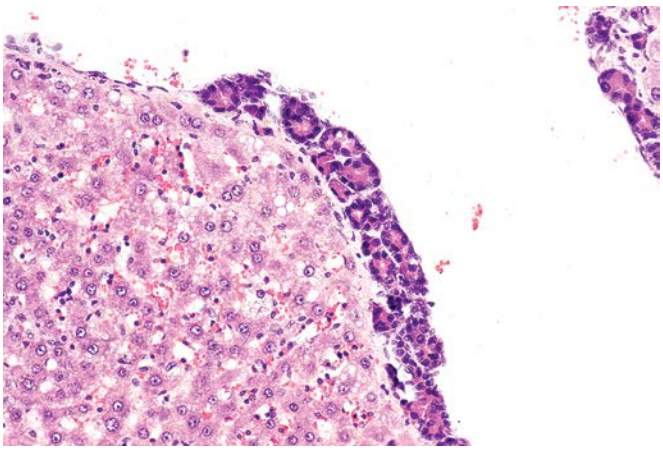
Hepatic crystals occur in the liver in two common forms, cholesterol and eosinophilic crystals. For hepatic cholesterol crystals, see **Hepatic cholesterol granuloma** for further information. For eosinophilic crystals, see **Gallbladder hyalinosis** for further information.

Hepatic cystic degeneration, see the preferred term **Spongiosis hepatis**.

Hepatic cysts, see the preferred term **Biliary cysts**.

Hepatic cytoplasmic inclusions, see the preferred term **Intrahepatocellular erythrocytes**.

Hepatic ectopic pancreatic acinar tissue is a collection of pancreatic tissue adjacent to but not integrated within hepatic parenchyma.



Hepatic ectopic pancreatic acinar tissue, rat liver, H&E. (Reproduced with permission of the Society of Toxicologic Pathology from Thoolen, B. et al. 2010. *Toxicol Pathol* 38(7 Suppl):5S–81S.)

Hepatic endothelial cell hypertrophy/karyomegaly refers to an increased size of the endothelial cells that line the parenchymal sinusoids of the liver. The cells and nuclei are both enlarged. Since it is difficult to distinguish sinusoidal endothelial cells from Kupffer cells, immunohistochemical methods may be needed to confirm the types of cells that are enlarged. It may occur due to xenobiotic-induced increased DNA synthesis, cell cycle arrest of endothelial cells secondary to cell damage, and/or obstruction of the sinusoids leading to local ischemia. Diagnosis requires confirmation of endothelial cells using immunohistochemical recognition of CD31 or transmission electron microscopy as it is difficult to identify specific sinusoidal cell types when evaluated by hematoxylin and eosin (H&E) stain in routine microscopic sections. Endothelial hypertrophy may be accompanied by degeneration and necrosis of endothelial cells. Endothelial hypertrophy has been associated with toxicity of pyrrolizidine alkaloids (e.g., riddelliine and monocrotaline).

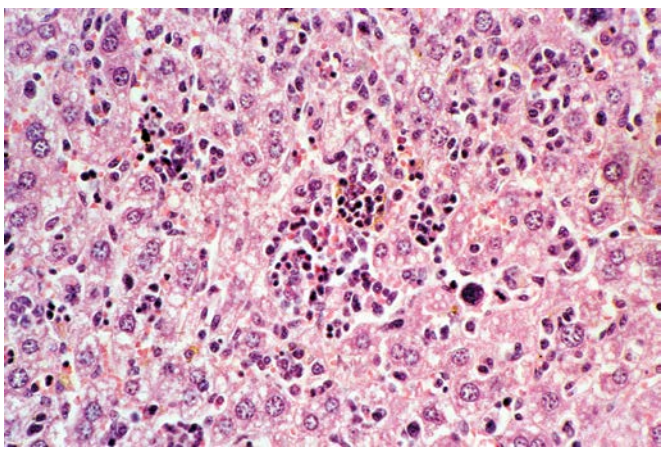
Hepatic endothelial hyperplasia refers to a focal increase in numbers of endothelial cells within or near one or more portal areas in the liver, sometimes forming blood-filled channels, and lacking underlying connective tissue. Confirmation of this diagnosis depends on co-location of the endothelial cell (CD31) and proliferation (Ki67) markers in the cells comprising the lesion.

Hepatic erythrophagocytosis, see the preferred term **Intrahepatocellular erythrocytes**.

Hepatic erythropoiesis, see the preferred term **Hepatic extramedullary hematopoiesis**.

Hepatic extramedullary hematopoiesis is the proliferation of blood cells outside of the bone marrow that is commonly observed in laboratory animals, especially rats, in response to increased hematopoietic demand, and is a rare finding in human liver. Hematopoiesis is normally found in the embryonic liver where embryonic hematopoiesis dramatically expands at mid-gestation but decreases after birth. Anemia, stress, xenobiotic bone marrow toxicity, infection, neoplasia (e.g., histiocytic sarcoma), and pregnancy are frequent predisposing factors. Extramedullary erythropoiesis is used when the erythroid precursors predominate over other cell types. Histologically, small aggregates of hematopoietic cells can be found randomly distributed in the hepatic sinusoids as well as around central veins and in portal areas. Both erythroid and granulocytic cells may be present in the aggregates; megakaryocytes are rarely present in the absence of inflammatory cells. Extramedullary hematopoiesis must be differentiated from mononuclear cell infiltrations and focal inflammation.

Synonym(s): **Hepatic hematopoietic cell proliferation**; **hepatic myelopoiesis**; **hepatic erythropoiesis**.



Hepatic extramedullary hematopoiesis, mouse liver, H&E. (Reproduced with permission of Elsevier from Cattley, R. and Cullen, J. 2013. In: Haschek, W., Rousseux, C., Wallig, B. Bolon, R.O. (eds.) *Handbook of Toxicologic Pathology*, 3rd ed. Academic Press, Elsevier, San Diego, CA, pp. 1509–1566.)

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Hepatic fatty change, see the preferred term **Hepatocellular lipidosis**.

Hepatic fibrosis is characterized by loss of liver architecture due to formation of fibrous connective tissue. It is sometimes referred to as cirrhosis when it is accompanied by regeneration and bile duct proliferation. It is often the result of repeated, ongoing injury, and has diverse and grave consequences on liver function.

Hepatic hemangioma is a benign neoplasm of endothelial cells originating from blood vessels and sinusoids in the liver. Refer to **Liver**, **Gallbladder**, **and Exocrine Pancreas** in Appendix 2 for further information.

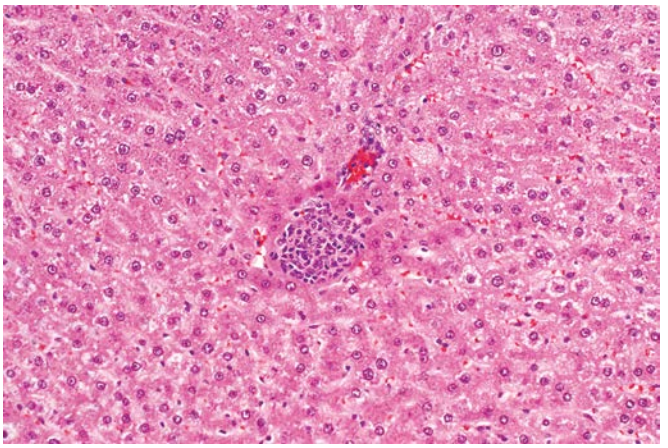
Hepatic hemangiosarcoma is a malignant neoplasm of the endothelial cells lining blood vessels and sinusoids in the liver. Refer to **Liver, Gallbladder, and Exocrine Pancreas** in Appendix 2 for further information.

Hepatic hematopoietic cell proliferation, see the preferred term **Hepatic extramedullary hematopoiesis**.

Hepatic histiocytic sarcoma is a neoplasm of the monocyte/macrophage lineage (histiocytes). In the liver, it can arise from resident Kupffer cells as well as circulating histiocytes. Refer to **Liver**, **Gallbladder**, **and Exocrine Pancreas** in Appendix 2 for further information.

Hepatic inflammation is a diagnosis that is only applied when there is generalized and severe involvement of the liver by infiltration of inflammatory cells combined with degenerative, necrotic, postnecrotic, and/or architectural changes in liver parenchyma. Ideally this term would be accompanied by modifiers that define the nature of inflammation (e.g., suppurative, lymphocytic), distribution (multifocal, diffuse, or specific to the part of acinus, if discernible), and duration (e.g., chronicity). The diagnosis of hepatic inflammation is rarely applicable in toxicology studies.

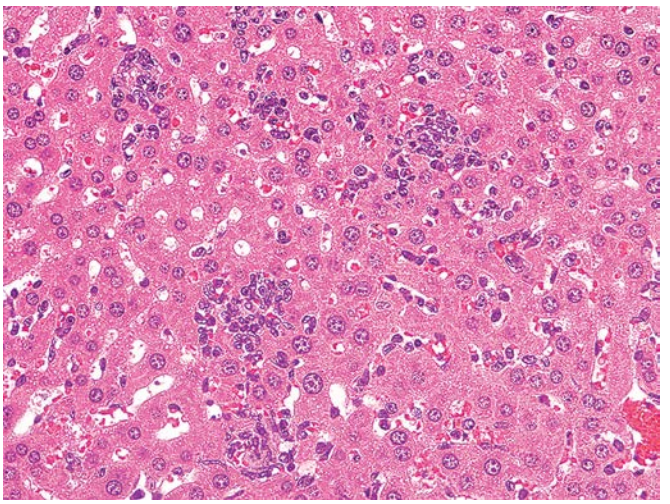
Synonym(s): **Hepatitis**.



Hepatic inflammation, rat liver, H&E. (Reproduced with permission of CRC Press from Cattley, R. et al. 2013. In: Sahota, P., Popp, J., Hardisty, J., Gopinath, C. (eds.) *Toxicologic Pathology: Nonclinical Safety Assessment*. CRC Press, Taylor & Francis Group, Boca Raton, FL, pp. 313–366.)

Hepatic inflammatory cell infiltration is characterized by the accumulation of inflammatory cells in random areas of the liver parenchyma. The cells may include lymphocyte, plasma cells, macrophages, neutrophils, and/or eosinophils in varying combinations. Inflammatory cell infiltration as a diagnostic term is preferable to hepatitis, except when it is accompanied by tissue injury and repair. The lesion may occur spontaneously and may also be induced or exacerbated by drug or chemical treatment.

Differential diagnosis: **Hepatic inflammation**.

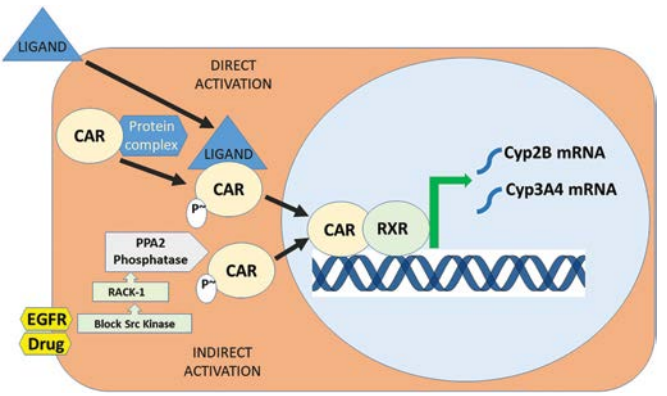


Hepatic inflammatory cell infiltration, mouse liver, H&E. (Reproduced with permission of the Society of Toxicologic Pathology from Thoolen, B. et al. 2010. *Toxicol Pathol* 38(7 Suppl):5S–81S.)

Hepatic intestinal cell metaplasia, see the preferred term **Cholangiofibrosis**.

Hepatic lipoma, see the preferred term **Ito cell tumor**.

Hepatic microsomal enzyme induction is caused by xenobiotics via interaction with various hepatocyte receptors resulting in the induction of P450 enzymes with proliferation of endoplasmic reticulum and sometimes peroxisomes. These changes are manifested microscopically by hepatocytic hypertrophy. Hypertrophy is often zonal, but in severe cases can extend across the entire lobule (panlobular). The finding is characterized by



Hepatic microsomal enzyme induction, mechanism. (Figure courtesy of R. Cattley, Auburn University.)

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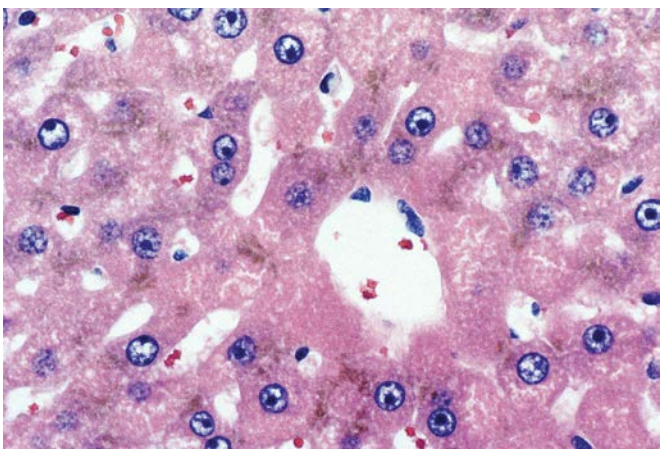
enlarged hepatocytes with a "ground-glass" cytoplasm and enlarged nuclei. Mitotic figures can be seen at an increased frequency compared to controls. Microsomal enzyme induction is also accompanied by increases in liver weight. Higher liver weights compared to study controls is often considered a more sensitive indicator of induction as compared to microscopic evidence of hepatocyte hypertrophy. Microsomal enzyme induction is related to activation of the nuclear constitutively activated receptor (CAR). When unaccompanied by additional hepatic injury, microsomal enzyme induction and hepatocyte hypertrophy is poorly correlated with circulating liver enzyme alterations when evaluating liver clinical chemistry parameters.

Hepatic myelopoiesis, see the preferred term **Hepatic extramedullary hematopoiesis**.

Hepatic perisinusoidal cells, see the preferred term **Hepatic stellate cells**.

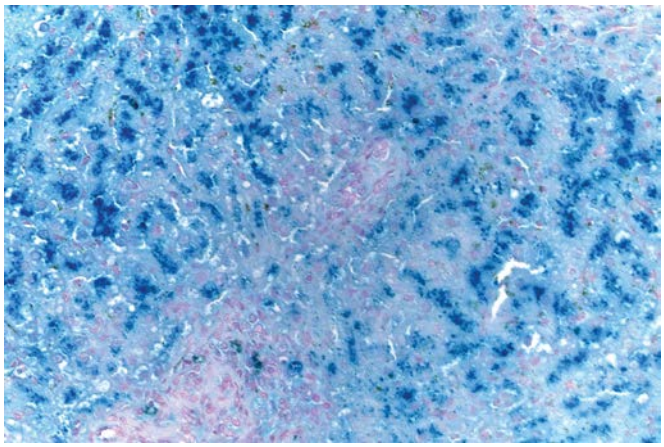
Hepatic perisinusoidal fat-storing cell tumor, see the preferred term **Ito cell tumor**.

Hepatic peroxisome proliferation is a form of hepatocellular adaptation in which hepatocytes accumulate increased cytoplasmic density (number and/or size) of peroxisomes. Peroxisomes are single-membrane–bound organelles that contain oxidative enzymes which catalyze the formation of hydrogen peroxide from fatty acids and amino acids, as well as catalase, which catalyzes the breakdown of hydrogen peroxide. Histologically, hepatic peroxisome proliferation is associated with an increased size of hepatocytes that contain eosinophilic cytoplasmic granules, often more apparent in central lobular hepatocytes. Hepatic peroxisome proliferation results from the activation of peroxisome proliferator-activated receptor-alpha (PPAR-α), which is a member of the steroid-thyroid hormone nuclear receptor superfamily. PPAR-α may be activated by binding to certain xenobiotics, including fibrate drugs/compounds and phthalate esters, as well as endogenous fatty acid metabolites. Hepatic peroxisome proliferation caused by xenobiotics has been exclusively characterized in rats and mice, where it is typically accompanied by hepatocellular hypertrophy and hyperplasia. Long-term administration of xenobiotics that induce peroxisome proliferation has been associated with an increased incidence of hepatocellular neoplasia in rats and mice.



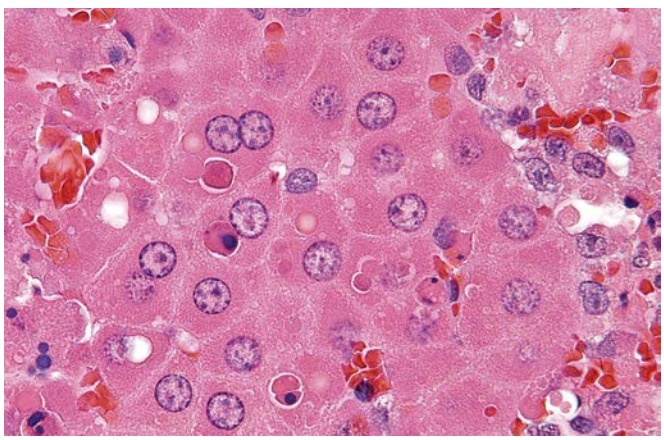
Hepatic peroxisome proliferation, rat liver, H&E. (Reproduced with permission of CRC Press from Cattley, R. et al. 2013. In: Sahota, P., Popp, J., Hardisty, J., Gopinath, C. (eds.) *Toxicologic Pathology: Nonclinical Safety Assessment*. CRC Press, Taylor & Francis Group, Boca Raton, FL, pp. 313–366.)

Hepatic pigment deposition is characterized by the deposition of hemosiderin, lipofuscin, and/or bile pigment in hepatocytes and Kupffer cells. Bile pigments and porphyrins can also accumulate in bile duct epithelium and canaliculi. Definitive diagnosis of a particular pigment is based on the use of histochemical procedures.



Hepatic pigment deposition (lipofuscin), dog liver, Schmorl's stain. (Reproduced with permission of Elsevier from Cattley, R. and Cullen, J. 2013. In: Haschek, W., Rousseux, C., Wallig, B. Bolon, R.O. (eds.) *Handbook of Toxicologic Pathology*, 3rd ed. Academic Press, Elsevier, San Diego, CA, pp. 1509–1566.)

Hepatic single cell necrosis (apoptosis) refers to the death of hepatocytes characterized by condensed cytoplasm with



Hepatic single cell necrosis (apoptosis), rat liver, H&E. (Reproduced with permission of Elsevier from Cattley, R. and Cullen, J. 2013. In: Haschek, W., Rousseux, C., Wallig, B. Bolon, R.O. (eds.) *Handbook of Toxicologic Pathology*, 3rd ed. Academic Press, Elsevier, San Diego, CA, pp. 1509–1566.)

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increased eosinophilic staining. They are not typically associated with inflammatory cell infiltration; however, they may be phagocytosed by macrophages and hepatocytes, where they form intracytoplasmic, round, eosinophilic "apoptotic bodies" surrounded by a halo of clear cytoplasm. They may be nonspecifically labeled using immunohistochemistry (for activated caspase-3) or by terminal deoxynucleotidyl transferase dUTP nick-end labeling (TUNEL). The pathogenesis involves activation of programmed cell death that involves several potential intrinsic and extrinsic inducers, and proteolytic digestion of cell components by enzymes known as effector caspases.

Hepatic sinusoidal dilation, see the preferred term **Hepatic angiectasis**.

Hepatic sinusoidal endothelial cells are specialized cells that line the liver sinusoids and carry blood that abuts the radial plates of hepatocytes within the hepatic lobule. This endothelium is normally fenestrated, and the perivascular space (space of Disse) contains loosely arranged extracellular matrix and pericytes, known as stellate cells or Ito cells. They enable the rapid uptake of plasma solutes by the hepatocytes, and rapid transfer of hepatocellular products into the circulation.

Hepatic stellate cell hyperplasia, see the preferred term **Ito cell hyperplasia**.

Hepatic stellate cells are cells that reside within the space of Disse, a small area between the sinusoids and hepatocytes in the liver. These cells are normally vacuolated and represent a key location of vitamin A storage (as retinol ester) in the liver. Upon activation by cytokines such as TGF-beta, the hepatic stellate cells may differentiate into myofibroblasts which produce collagenous matrix, resulting in fibrosis, contraction, and obstruction of the space of Disse.

Synonym(s): **Hepatic perisinusoidal cells**; **Ito cells**.

Hepatic stellate cell tumor, see the preferred term **Ito cell tumor**.

Hepatic telangiectasis, see the preferred term **Hepatic angiectasis**.

Hepatic zonal necrosis, see the preferred term **Hepatocellular zonal necrosis**.

Hepatitis, see the preferred term **Hepatic inflammation**.

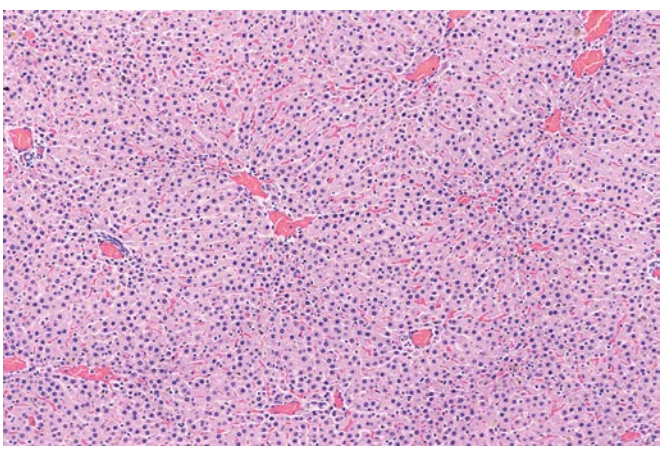
Hepatoblastoma is a malignant neoplasm occasionally observed in mice but rarely seen in other animals. This neoplasm is characterized as a nodule composed of small cells with hyperchromatic nuclei and scant cytoplasm, often arranged in trabeculae, rosettes, or gland-like structures. Mitotic activity is usually high, and metastasis has been reported. Formation of organoid structures, vascular cavities, fibrous connective tissue, and bone may be observed, and even squamous differentiation. Refer to **Liver, Gallbladder, and Exocrine Pancreas** in Appendix 2 for further information.

Hepatocarcinogen is the general term applied to substances that, under experimental conditions of exposure, have or will increase the incidence, multiplicity, or decrease the age of onset of hepatocellular neoplasms (e.g., hepatocellular carcinomas and adenomas).

Hepatocarcinoma, see the preferred term **Hepatocellular carcinoma**.

Hepatocellular adenoma is a benign neoplastic proliferation of hepatocytes that frequently occurs in rodents, either as spontaneous lesions and following treatment with genotoxic and nongenotoxic carcinogenic xenobiotics (see **Hepatocarcinogen** for further information), or in certain strains of genetically engineered mice. Several factors such as species, strain, housing, and diet affect the background incidence in rodents. Histologically, adenomas are nodular, often compressing the adjacent normal parenchyma. Neoplastic hepatocytes may show irregular growth patterns with distortion of the normal lobular architecture but with minimal cellular atypia. Refer to **Liver, Gallbladder, and Exocrine Pancreas** in Appendix 2 for further information.

Hepatocellular atrophy is a lesion in which there is a decrease in size of liver cells. This decrease may be focal, lobular, or generalized in distribution. It is detected as decreased size of trabeculae resulting from decreased hepatocellular cytoplasm, and results in close spacing of hepatocellular nuclei. If significant portions of the liver lobules are involved, closer spacing of portal tracts may be observed. It may be associated with starvation, chronic congestion, fibrosis, and/or pressure resulting from the presence of liver masses. It must be differentiated from fixation and shrinkage artifacts. Although detectable by histopathology, the characterization of generalized or lobular hepatocellular atrophy may be further measured by morphometric analysis.



Hepatocellular atrophy, rat liver, H&E. (Reproduced with permission of the Society of Toxicologic Pathology from Thoolen, B. et al. 2010. *Toxicol Pathol* 38(7 Suppl):5S–81S.)

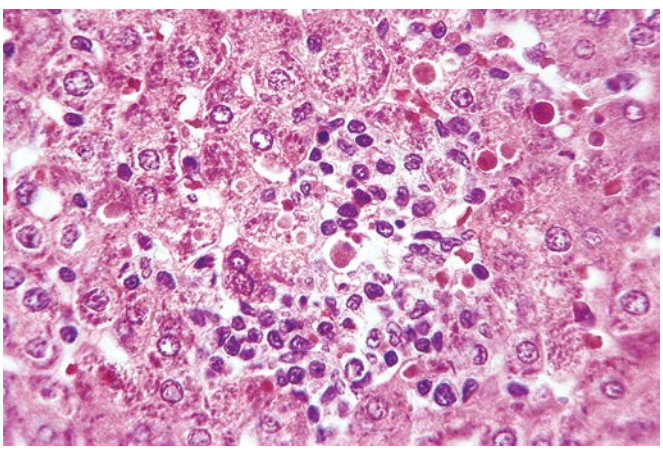
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Hepatocellular carcinoma(s) are locally infiltrating, malignant neoplasms of hepatocytes that lack distinct demarcation. Increased mitotic index and marked cellular pleomorphism may occur with loss of normal lobular architecture. Vascular invasion, local invasion, and metastases to the lungs may be observed. Refer to **Liver, Gallbladder, and Exocrine Pancreas** in Appendix 2 for further information.

Hepatocellular degeneration is a nonspecific term that theoretically represents a cellular condition that may lead to either adaptation and resolution or cell death. Microscopically, it is characterized by a combination of hepatocellular cytoplasmic alterations, suggesting loss of function, and changes in cell size, but the actual pathogenesis is rarely understood simply by microscopic appearance. (See **Hepatocellular intracytoplasmic inclusions** and **Hepatocellular hydropic degeneration** for further information.)

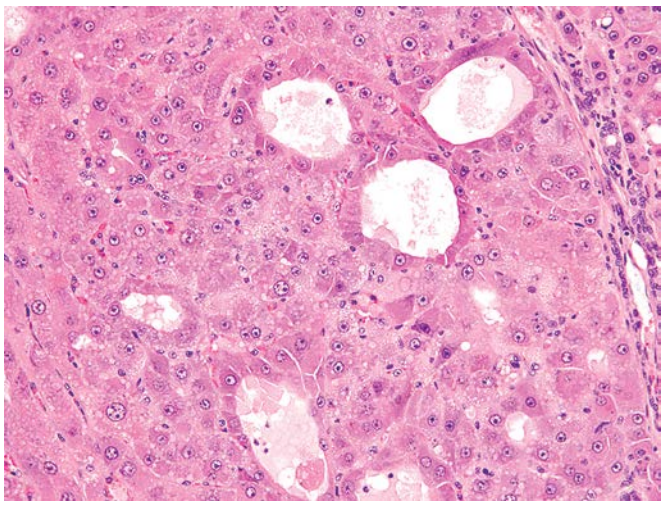
Hepatocellular focal/multifocal necrosis is commonly observed spontaneously in untreated rodents, monkeys, and dogs. The lesion is characterized by single or multiple foci of pale staining hepatocytes, often associated with hemorrhage, inflammation, and fibrosis. Distinction between oncotic necrosis and apoptotic necrosis is difficult by light microscopy. Careful evaluation of the incidence and severity in control and treated animals in comparison with historical control data of the laboratory is necessary to determine if treatment-related effects are present. Due to a highly variable incidence and distribution in untreated laboratory animals, slight increases in incidence in treated animals are not considered treatment effects unless incidence and/or severity of the lesions are increased versus controls or the pattern of distribution differs from that in the control animals. Focal/multifocal hepatocellular necrosis must be distinguished from hepatic extramedullary hematopoiesis, foci of inflammatory cell infiltrates, and inflammatory lesions caused by infectious disease (e.g., mouse hepatitis virus, ectromelia, *Clostridium piliforme*, *Helicobacter hepaticus*, parvo virus, noro virus).

Differential diagnosis: **Hepatic extramedullary hematopoiesis**.



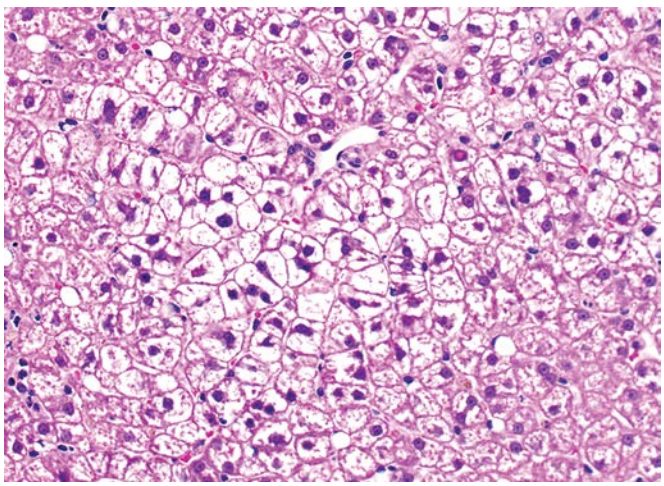
Hepatocellular focal/multifocal necrosis, rat liver, H&E. (Reproduced with permission of the Society of Toxicologic Pathology from Thoolen, B. et al. 2010. *Toxicol Pathol* 38(7 Suppl):5S–81S.)

Hepatocellular glandular metaplasia refers to the apparent change in the organization of hepatocytes wherein the plate architecture is replaced by a glandular architecture. This finding may be observed within nonneoplastic parenchyma, but also as a morphological feature of hepatocellular neoplasms, particularly those that are malignant. It has been observed following treatment with certain hepatotoxic agents such as chlorinated biphenyls. Although the mechanism of the glandular metaplasia is uncertain, some have speculated that the glandular structures represent abnormal differentiation of hepatobiliary precursor cells.



Hepatocellular glandular metaplasia, rat liver, H&E. (Reproduced with permission of the Society of Toxicologic Pathology from Thoolen, B. et al. 2010. *Toxicol Pathol* 38(7 Suppl):5S–81S.)

Hepatocellular glycogen accumulation refers to the increased cytoplasmic accumulation of glycogen within hepatocytes. Glycogen is a multibranched polysaccharide of glucose that serves as a form of energy storage within cells. By light microscopy of formalin-fixed paraffin sections of liver, glycogen

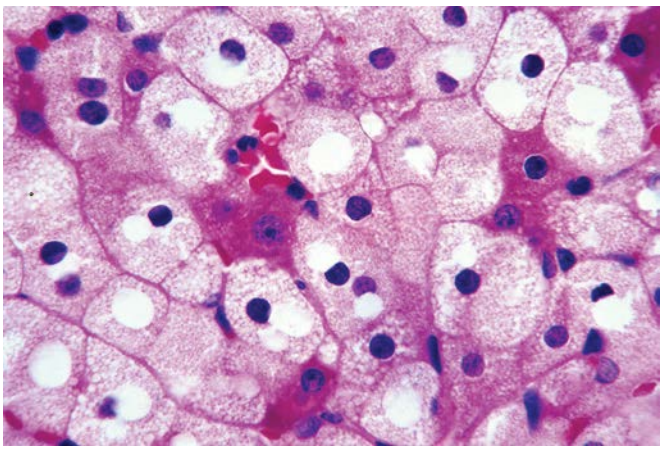


Hepatocellular glycogen accumulation, dog liver, H&E. (Reproduced with permission of Elsevier from Cattley, R. and Cullen, J. 2013. In: Haschek, W., Rousseux, C., Wallig, B. Bolon, R.O. (eds.) *Handbook of Toxicologic Pathology*, 3rd ed. Academic Press, Elsevier, San Diego, CA, pp. 1509–1566.)

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appears as empty clear spaces in the cytoplasm of hepatocytes. This is because glycogen is soluble in water and is extracted during tissue fixation and processing. This may be overcome by evaluation of frozen sections and using a periodic acid-Schiff (PAS) staining technique to stain glycogen, following treatment of replicate sections with and without diastase (glycogen is removed by diastase digestion). In animals, some hepatocellular glycogen accumulation normally occurs after feeding. Therefore, it is important to recognize fed versus non-fed condition (and the time interval following the last feeding) as important variables in assessing hepatocellular glycogen accumulation as either a treatment-related effect,or a normal physiological variation. Certain xenobiotic treatments may result in increasing hepatocellular glycogen accumulation within hepatocytes, likely by inhibiting the breakdown of glycogen.

Hepatocellular hydropic degeneration refers to the enlargement of hepatocytes with loss of cytoplasm staining intensity. It is attributed to the cellular swelling that results from injury that impairs homeostatic control of water and electrolyte content of hepatocytes. It is considered a reversible cellular change, although it may also progress to hepatocellular necrosis if the injury is sustained.



Hepatocellular hydropic degeneration, dog liver, H&E. (Reproduced with permission of Elsevier from Cattley, R. and Cullen, J. 2013. In: Haschek, W., Rousseux, C., Wallig, B. Bolon, R.O. (eds.) *Handbook of Toxicologic Pathology*, 3rd ed. Academic Press, Elsevier, San Diego, CA, pp. 1509–1566.)

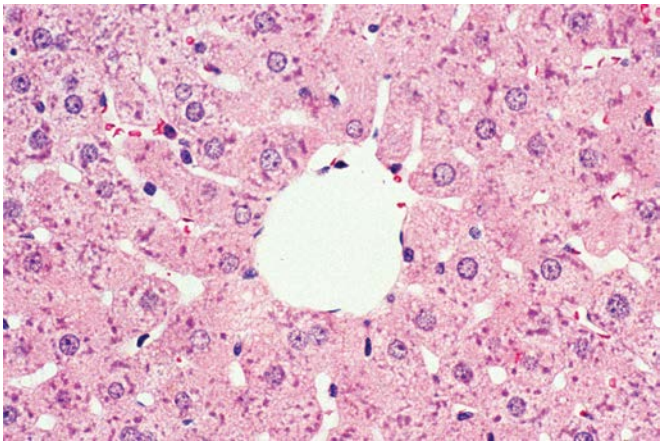
Hepatocellular hyperplasia is characterized by a gross increase in liver size and weight that is associated with increased number of hepatocytes in the liver. The presence of hepatocellular hyperplasia may be inferred from evidence of diffuse (nonfocal) increased replication of hepatocytes that may accompany the liver weight increase. Histologically, this increased replication of hepatocytes may be deduced from the presence of transiently increased frequency of mitotic hepatocytes, when observed during the period in which the liver weight is increasing. Besides mitosis, an increased replication of hepatocytes may be deduced from a transiently increased frequency of replicative DNA synthesis in hepatocytes. This replicative DNA synthesis may be detected using immunohistochemical markers (Ki67, PCNA) or labeling (using isotopically labeled thymidine or thymidine analogs such as bromodeoxyuridine). Besides indirect evidence of hyperplasia, it is possible to provide direct evidence by enumerating the number of hepatocytes in the liver using stereological methods. Xenobiotic-induced hepatocellular hyperplasia is more frequently observed in rodents, while the same xenobiotics only rarely induce this change in dogs, monkeys, and humans. Xenobiotic-induced liver enlargement and weight increases may be a combination of both hepatocellular hypertrophy and hyperplasia (increased numbers of cells), and sometimes this may be difficult to differentiate using routine histological methods. Hepatocellular hyperplasia is generally considered to be an adaptive change, reversible after cessation of treatment. Hepatocellular hyperplasia can be caused by phenobarbital, octylmethylcyclotrasiloxane, and PPAR agonists, among others.

Hepatocellular hyperplasia, non-regenerative is characterized by a proliferation of hepatocytes, often focal, that may span several lobules, and be associated with blood-filled spaces. Refer to **Liver, Gallbladder, and Exocrine Pancreas** in Appendix 2 for further information.

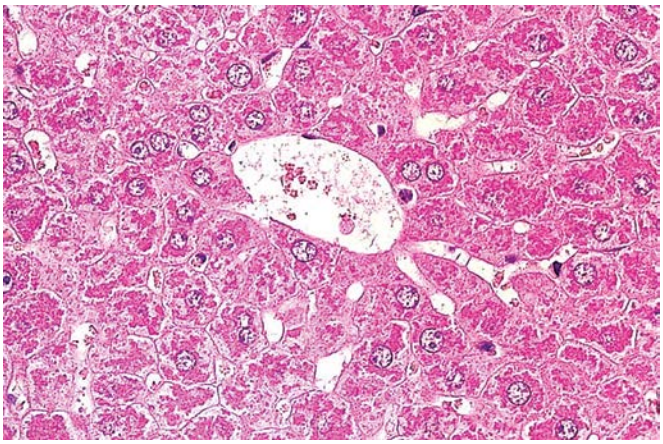
Hepatocellular hyperplasia, regenerative is characterized by a proliferation of hepatocytes, focal to multifocal, that occurs as a result of hepatocellular loss and is generally accompanied by concomitant chronic inflammation and fibrosis. Refer to **Liver, Gallbladder, and Exocrine Pancreas** in Appendix 2 for further information.

Hepatocellular hypertrophy is characterized by a gross increase in liver size and weight. Histologically, panlobular or zonal (centrilobular, periportal, midzonal) distribution of tinctorially distinct, enlarged (hypertrophic) hepatocytes is noted due to increased numbers of one or more organelles (endoplasmic reticulum, peroxisomes, mitochondria). The cytoplasm of hypertrophic hepatocytes may be granular or homogeneous in appearance. These changes may preferentially occur in certain regions of the liver lobule or may be diffuse. Marked hypertrophy may lead to distortion of the hepatocellular cords and sinusoidal compression. Xenobiotic-induced hepatocellular hypertrophy is more frequently observed in rodents, while the same xenobiotics only rarely induce this change in dogs, monkeys, and humans. Drug metabolizing enzyme induction (see **Hepatic microsomal enzyme induction** for further information), and minor liver weight increases (<20% relative to controls) are often not associated with histological changes. Hepatocellular hypertrophy is generally considered to be an adaptive change, reversible after cessation of treatment. Hepatocellular hypertrophy can be caused by phenobarbital-type CYP inducers, 3-hydroxy-3-methyglutaryl coenzyme A (HMG-CoA) reductase inhibitors, and PPAR agonists, among others. Xenobiotic-induced liver enlargement and weight increases may be a combination of both hepatocellular hypertrophy and hyperplasia (increased numbers of cells) and is difficult to differentiate histologically in some instances.

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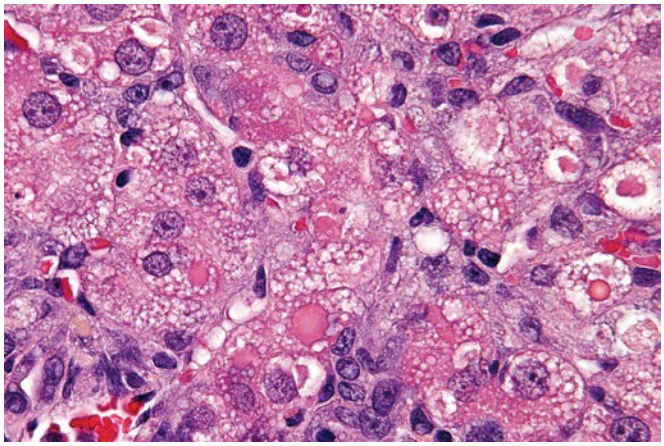


Hepatocellular hypertrophy, with increased endoplasmic reticulum, rat liver, H&E. (Reproduced with permission of CRC Press from Cattley, R. et al. 2013. In: Sahota, P., Popp, J., Hardisty, J., Gopinath, C. (eds.) *Toxicologic Pathology: Nonclinical Safety Assessment*. CRC Press, Taylor & Francis Group, Boca Raton, FL, pp. 313–366.)



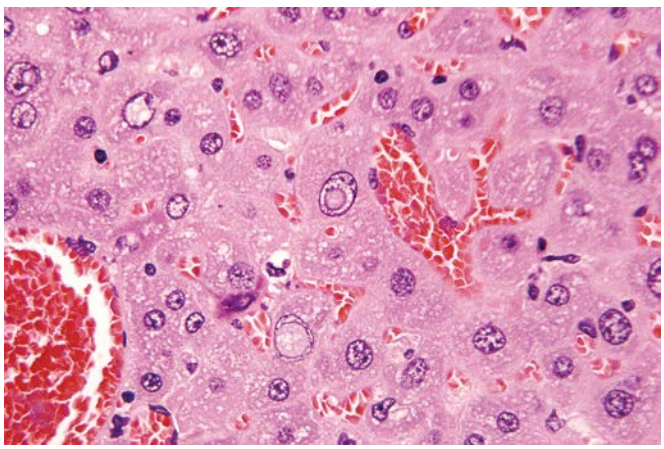
Hepatocellular hypertrophy, with mitochondrial proliferation, rat liver, H&E. (Reproduced with permission of the Society of Toxicologic Pathology from Thoolen, B. et al. 2010. *Toxicol Pathol* 38(7 Suppl):5S–81S.)

Hepatocellular intracytoplasmic inclusions refer to the presence of differentially stained structures within the cytoplasm of hepatocytes. One type of inclusion, Mallory bodies (also known as Mallory-Denk bodies) are lamellated or crystalloid inclusions (aggregates of altered keratin) and are observed in the livers of mice with specific mutations or following certain treatments (i.e., griseofulvin). (See **Mallory bodies** for further information.) Upon evaluation by transmission electron microscopy, cytoplasmic inclusions occur in the rough endoplasmic reticulum or within the cytoplasm but without organelle involvement. Cytoplasmic vacuolar inclusions have also been reported as artifacts of postmortem change in rats that have not been exsanguinated (or inadequately exsanguinated) prior to tissue collection and fixation. These vacuolar inclusions result from the influx of plasma into hepatocytes and endothelial cells.



Hepatocellular intracytoplasmic inclusions, rat liver, H&E. (Reproduced with permission of Elsevier from Cattley, R. and Cullen, J. 2013. In: Haschek, W., Rousseux, C., Wallig, B. Bolon, R.O. (eds.) *Handbook of Toxicologic Pathology*, 3rd ed. Academic Press, Elsevier, San Diego, CA, pp. 1509–1566.)

Hepatocellular intranuclear inclusions refers to the presence of differentially stained structures within the nuclei of hepatocytes. These may occur as an invagination of the cytoplasm into the nucleus, even though the site of invagination may not be observed within the plane of section. The presence of intranuclear inclusions resulting from cytoplasmic invagination is considered a spontaneous aging change in mice and may be observed more frequently in hepatocellular neoplasms. Alternatively, intranuclear inclusions may occur as a consequence of viral infections such as cytomegalovirus.

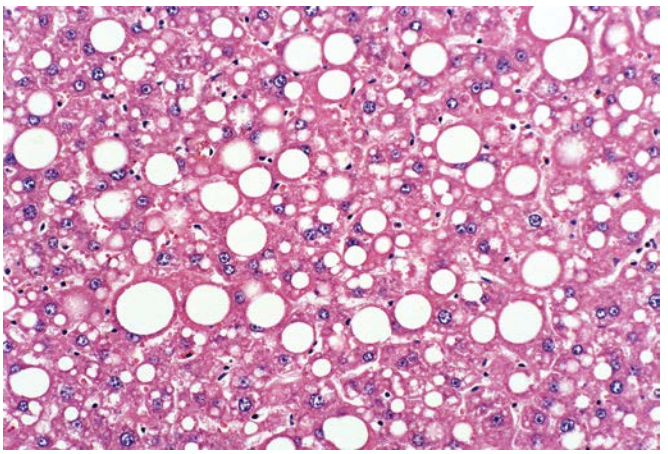


Intranuclear inclusions, mouse liver, H&E. (Reproduced with permission of Elsevier from Cattley, R. and Cullen, J. 2013. In: Haschek, W., Rousseux, C., Wallig, B. Bolon, R.O. (eds.) *Handbook of Toxicologic Pathology*, 3rd ed. Academic Press, Elsevier, San Diego, CA, pp. 1509–1566.)

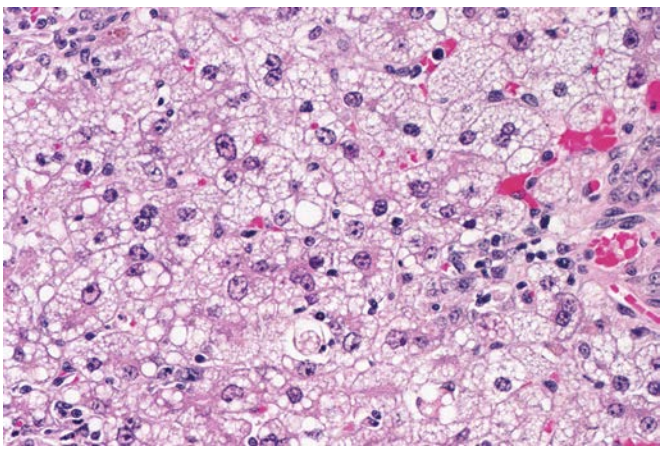
Hepatocellular lipidosis refers to the increased cytoplasmic accumulation of neutral unbound lipid within hepatocytes. By light microscopy in formalin-fixed paraffin sections, lipid appears as optically clear empty spaces in the cytoplasm of hepatocytes. This is because lipid is soluble in ethanol and is extracted during tissue processing. By evaluation of frozen sections wherein special stains have been applied (e.g., oil red O,

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Sudan Black, osmium tetroxide), lipid can be visualized microscopically. Hepatocellular lipid accumulation can occur under conditions of increased lipid mobilization from peripheral adipose stores, such as during starvation or in diabetes mellitus; however, such accumulation may also result following hepatocellular injury by xenobiotics. There are two morphologically distinct subtypes of fatty change: macrovesicular and microvesicular. Macrovesicular fatty change is characterized by the presence of a single clear vacuole that displaces the cytoplasm and pushes the nucleus to the periphery the hepatocyte; this is more often associated with disruption in normal lipid metabolism. In and of itself this form of fatty change is generally benign. Microvesicular fatty change is characterized by the presence of numerous small, clear vacuoles creating a sponge-like appearance within the cytoplasm of the hepatocytes, without cytoplasmic or nuclear displacement. Microvesicular fatty change is more often associated with degrees of toxic injury. Both macrovesicular and microvesicular lipidosis are reversible.



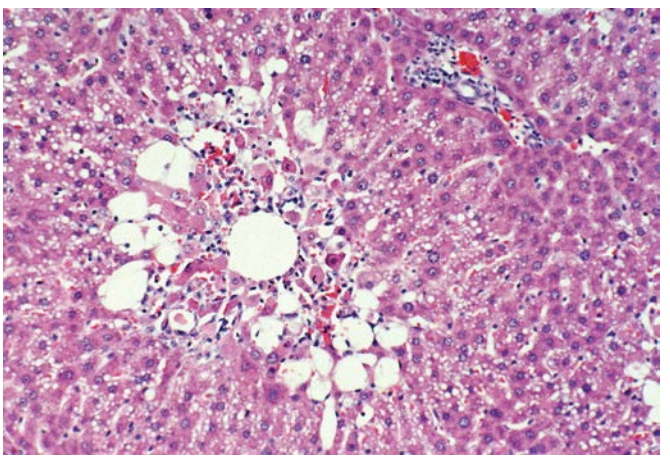
Hepatocellular lipidosis, macrovesicular, rat liver, H&E. (Reproduced with permission of CRC Press from Cattley, R. et al. 2013. In: Sahota, P., Popp, J., Hardisty, J., Gopinath, C. (eds.) *Toxicologic Pathology: Nonclinical Safety Assessment*. CRC Press, Taylor & Francis Group, Boca Raton, FL, pp. 313–366.)



Hepatocellular lipidosis, microvesicular, rat liver, H&E. (Reproduced with permission of Elsevier from Cattley, R. and Cullen, J. 2013. In: Haschek, W., Rousseux, C., Wallig, B. Bolon, R.O. (eds.) *Handbook of Toxicologic Pathology*, 3rd ed. Academic Press, Elsevier, San Diego, CA, pp. 1509–1566.)

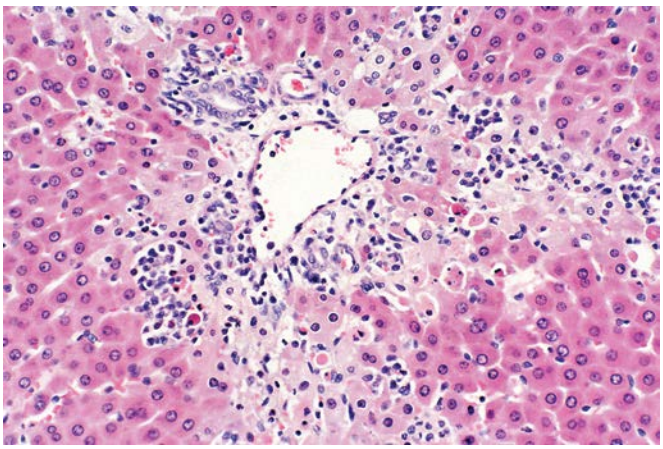
Hepatocellular metaplasia, see the preferred term **Hepatocellular glandular metaplasia** for further information.

Hepatocellular zonal necrosis is a commonly observed xenobiotic-induced change in the liver wherein a certain pattern of distribution is observed (i.e., centrilobular, periportal, or midzonal). These zonal patterns can be diffuse in distribution when secondary to direct or indirect damage to hepatocytes, or due to tissue anoxia. Several other pathological changes such as fatty change, congestion, hemorrhage, inflammation, bile stasis, or fibrosis may accompany hepatocellular zonal necrosis. Centrilobular or periacinar necrosis is characterized by irreversible cell death of centrilobular hepatocytes following exposure to a variety of drugs and toxic substances, including acetaminophen, carbon tetrachloride, chloroform, dimethylnitrosamine (DMN), and tannic acid. Centrilobular hepatocytes are particularly sensitive to injury as they contain high levels of several xenobiotic-metabolizing enzymes that lead to the local generation of reactive metabolites (see **Centrilobular necrosis** for further information). In addition, because of blood flow from the portal area of the lobules to the central vein, central lobular hepatocytes are at greater risk of hypoxic injury than in other regions of the lobule. Midzonal necrosis is a rare form of zonal necrosis that has been caused by furosemide, concavalin-A, and beryllium. In some studies, the role of inducible nitric oxide synthase (iNOS) and Kupffer cell activation have been implicated in midzonal necrosis. Periportal necrosis of hepatocytes in the periportal zone has been caused by α-naphthylisothiocyanate, phosphorus, ferrous sulphate, and allyl alcohol. The increased susceptibility of periportal hepatocytes has been attributed to higher oxygen tension than in other regions, which favors oxygen-dependent metabolic activation of certain xenobiotics (e.g., allyl alcohol). Diffuse necrosis (also called massive necrosis) affects entire lobules in parts of the liver, and has been caused by galactosamine, Fas ligand, Fas agonist antibody, or torsion of a liver lobe. The underlying mechanism for this pattern of necrosis is not well understood.

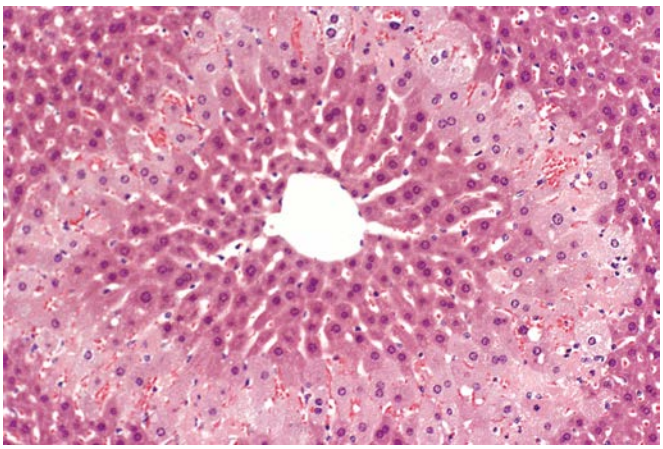


Hepatocellular zonal necrosis, central, rat liver, H&E. (Reproduced with permission of CRC Press from Cattley, R. et al. 2013. In: Sahota, P., Popp, J., Hardisty, J., Gopinath, C. (eds.) *Toxicologic Pathology: Nonclinical Safety Assessment*. CRC Press, Taylor & Francis Group, Boca Raton, FL, pp. 313–366.)

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Hepatocellular zonal necrosis, portal, rat liver, H&E. (Reproduced with permission of Elsevier from Cattley, R. and Cullen, J. 2013. In: Haschek, W., Rousseux, C., Wallig, B. Bolon, R.O. (eds.) *Handbook of Toxicologic Pathology*, 3rd ed. Academic Press, Elsevier, San Diego, CA, pp. 1509–1566.)



Hepatocellular zonal necrosis, midzonal, mouse liver, H&E. (Reproduced with permission of Elsevier from Cattley, R. and Cullen, J. 2013. In: Haschek, W., Rousseux, C., Wallig, B. Bolon, R.O. (eds.) *Handbook of Toxicologic Pathology*, 3rd ed. Academic Press, Elsevier, San Diego, CA, pp. 1509–1566.)

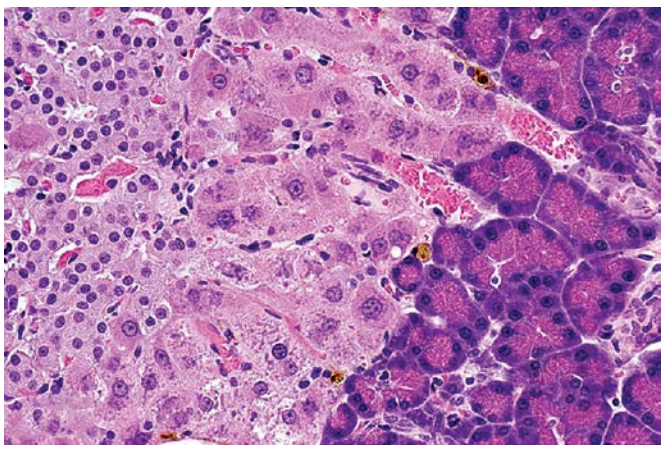
Hepatocholangiocellular adenoma is a benign neoplasm with proliferative mixture of both hepatocytes and intrahepatic bile duct epithelium. Refer to **Liver, Gallbladder, and Exocrine Pancreas** in Appendix 2 for further information.

Hepatocholangiocellular carcinoma is a malignant neoplasm with a proliferative mixture of both hepatocytes and intrahepatic bile duct epithelium. Refer to **Liver, Gallbladder, and Exocrine Pancreas** in Appendix 2 for further information.

Hepatocholangiocellular tumor (benign or malignant), see the preferred terms **Hepatocholangiocellular adenoma** and **carcinoma**.

Hepatocytic metaplasia in the exocrine pancreas occurs due to transdifferentiation of periductal oval cells or acinar/endocrine intermediate transitional cells into foci morphologically identical to liver hepatocytes. These metaplastic hepatic foci are composed of polygonal cells with central nuclei and abundant, finely granular eosinophilic cytoplasm and are often accompanied by mature bile canaliculi. Such foci are located adjacent to ducts and islets of Langerhans. This is considered a spontaneous finding in rats, mice, and hamsters. An increased incidence in toxicology studies may be due to treatment-related pancreatic atrophy followed by this transdifferentiation. Several experimental protocols such as copper depletion followed by copper repletion, ciprofibrate feeding, and multiple subcutaneous injections of cadmium chloride can result in metaplastic hepatic foci in the rat pancreas. Hepatocytic metaplasia may be induced following a single dose of *N*-nitrosobis(2-oxopropyl)amine (NBOP) in hamsters, and by partial obstruction of the main pancreatic duct by cellophane wrapping in monkeys. Metaplastic hepatic foci in the pancreas have also been induced in a mouse model where KGF (FGF7) transgene was overexpressed under the control of a rat insulin transcriptional promoter.

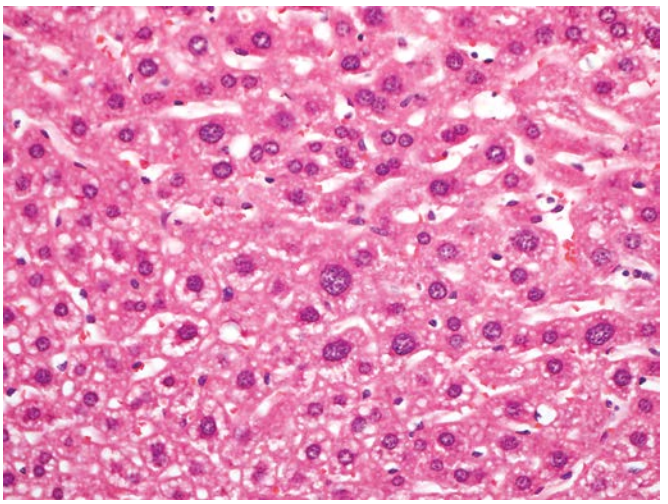
Differential diagnoses: **Pancreatic acinar cell hypertrophy**; **Pancreatic increased peri-insular halos**.



Hepatocytic metaplasia, rat pancreas, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Nolte, T. et al. 2016. *Toxicol Pathol* 29(1 Suppl):1S–124S.)

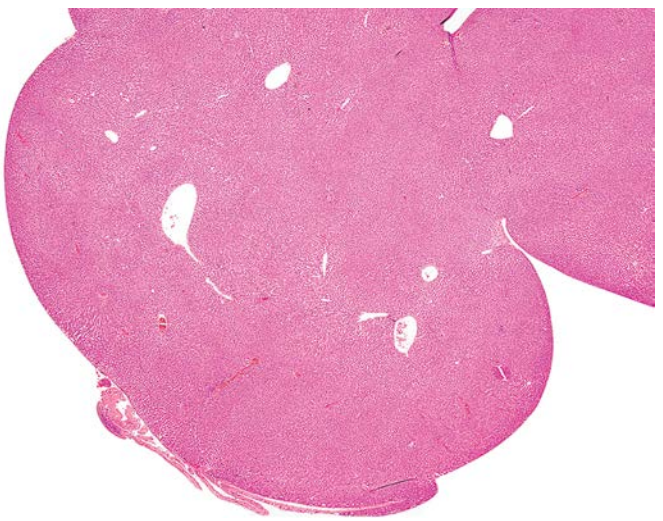
Hepatocytomegaly is a change in the appearance of hepatocytes wherein the amount of cytoplasm is increased, but its staining characteristics are the same as the cytoplasm of unaffected hepatocytes. In some instances, hepatocytomegaly may be accompanied by an increase in nuclear size (karyomegaly), which results from an increase in nuclear ploidy. Although sometimes hepatocytomegaly is considered synonymous with hepatocellular hypertrophy, the latter is often associated with an alteration in staining characteristics of the affected hepatocytes and may be selectively present in defined regions of the lobule; for example, as in centrilobular hypertrophy. Hepatocytomegaly associated with karyomegaly is often observed as a spontaneous aging change, particularly in mice but also in rats.

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Hepatocytomegaly, karyomegaly, mouse liver, H&E. (Figure courtesy of R. Cattley, Auburn University.)

Hepatodiaphragmatic nodule is a grossly visible nodule that occurs on the diaphragmatic surface of the median liver lobe. It is a protrusion of the liver that does not penetrate the diaphragm but is covered by the thin fibrous tendon of the diaphragm. The nodule is composed of hepatic parenchyma that resembles normal tissue except for the frequent presence of hepatocytes with elongated nucleoli-like, basophilic intranuclear inclusions. It is a spontaneous finding in rats but not in mice. Many authors have speculated that it is a congenital lesion, since its occurrence is not age related. In rare instances, its frequency is increased by treatment (e.g., nitrofen treatment of pregnant rats). When observed, a hepatodiaphragmatic nodule should not be confused for a hepatocellular neoplasm.



Hepatodiaphragmatic nodule, rat liver, H&E. (Reproduced with permission of the Society of Toxicologic Pathology from Thoolen, B. et al. 2010. *Toxicol Pathol* 38(7 Suppl):5S–81S.)

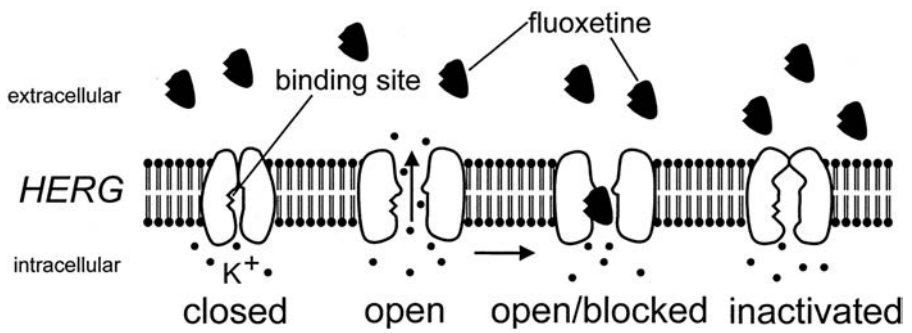
Hepatotoxicity is a general term referring to any degenerative change in the liver due to treatment or exposure of a test substance, environmental agent, or chemical. See **Liver toxicity** for further information.

hERG channel is a potassium ion channel (Ikr) in mammals that is critical in the normal repolarization of the cardiac muscles after each contraction. It is named after the human ether-a-go-go–related gene (hERG) because of the shaking (go-go–like) activity produced in fruit flies when the channel was activated. Blockage of this channel has been associated with cardiac arrhythmias and torsade de points. In the 1990s, several marketed drugs were withdrawn as their use was associated with cardiac arrhythmia and sudden death that was eventually shown to be a consequence of hERG inhibition. Consequently, it is now very common to assess the potential of compounds to inhibit hERG channel activity during the discovery phase of drug development to eliminate potential cardiac liabilities (see figure below).

Hermaphroditism is a congenital condition in which a single organism has male and female gonads or an intersex gonad (ovotestis). Pseudohermaphroditism is a condition in which the organism has typical gonads of one sex but has secondary sex characteristics of the opposite sex.

Heterotopic acinar pancreas is a lesion characterized by the presence of normal-appearing focal or multifocal exocrine pancreatic tissue in the wall of the gallbladder. It has been observed in mice as a spontaneous developmental anomaly.

Heterotopic hepatocyte is a lesion characterized by the presence of normal-appearing hepatocytes in the wall of the



A model of the state-dependent inhibition of the hERG channel by the antidepressant fluoxetine, which rapidly binds to open channels blocking the activity. (Thomas, D. et al. 2002. *J Pharmacol Exptl Therapeutics* 300:543–548.)

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gallbladder. It has been observed in mice as a spontaneous developmental anomaly.

Heterozygote is a gene in a diploid organism where the two alleles (copies) are not identical. Normally this is due to a mutation (change in DNA sequence) in one allele.

Hibernoma is a neoplastic growth arising from brown adipose cells. In animals, these tumors are usually multilobulated, the lobules being separated by a delicate collagenous stroma. The neoplastic cells resemble the normal brown adipose cell counterpart, with a round-to-polygonal morphology and an eosinophilic, finely vacuolated cytoplasm with small variably sized vacuoles and a round, usually central to paracentral nucleus containing a small round nucleolus (typical hibernoma cell). Refer to **Bone, Muscle, and Tooth** in Appendix 2 for further information.

Hidradenoma, see the preferred term **Eccrine gland carcinoma**.

High-density lipoproteins (HDL) refers to a class of lipoproteins that absorb cholesterol and return it to the liver. HDLs are also referred to as "good cholesterol."

High endothelial venule hypertrophy is an increase in size and prominence of endothelial cells of the specialized postcapillary venules in the paracortex of lymph nodes, and T-cell areas of the mucosa-associated lymphoid tissue. Venules may be dilated and accompanied by increased migration of lymphocytes from the circulation into the adjacent lymphoid tissue. Hypertrophy may be accompanied by hyperplasia of high endothelial venules (HEVs). HEVs are morphologically characterized as thin-walled blood vessels with prominent columnar epithelium. HEVs become hypertrophied in response to immune stimulation. Lymphocytes are often increased in one or more compartments of the affected lymphoid tissue.

Highest non-severely toxic dose (HNSTD) is the highest dose level that does not produce mortality, life-threatening toxicities, or irreversible findings in repeat-dose toxicity studies. The HNSTD is referenced in ICH S9 guideline (Nonclinical Evaluation for Anticancer Pharmaceuticals, 2010) as an optional approach to the no observed adverse effect level (NOAEL) in determining a starting dose in clinical trials with anticancer agents, (1/6 of the HNSTD in non-rodents).

High-throughput sequencing is the active determination of the DNA or RNA sequence by methods that allow a rapid processing of multiple samples in parallel. High-throughput sequencing is essential for sequencing large amounts of DNA, e.g., whole genomes.

Hirsutism is a type of hypertrichosis caused by excessive androgen hormones resulting in excessive hair growth in a male-specific pattern, usually in females or prepubescent males. See **Hypertrichosis** for further information.

Histiocytic aggregates, see the preferred term **Macrophage hyperplasia**.

Histiocytic hyperplasia, see the preferred term **Macrophage hyperplasia**.

Histiocytic infiltrates, see the preferred term **Macrophage hyperplasia**.

Histiocytic sarcoma is a systemic tumor made up of a uniform population of rounded to oval and spindloid cells manifesting a mixture of round, elongated, or folded nuclei and often includes multinucleated cells. Refer to **Hematopoietic System** in Appendix 2 for further information.

Histiocytoma, fibrous benign, see the preferred term **Fibroma**.

Histiocytoma, fibrous malignant, see the preferred term **Fibrosarcoma, pleomorphic**.

Histiocytosis is an increased number of histiocytes (tissue macrophages) within any tissue. Tissue macrophages are derived from blood monocytes and are a feature of chronic inflammation. In lymph nodes, in particular in the sinuses of lymph nodes, residing macrophages are called histiocytes. The number of histiocytes in draining lymph nodes can be increased due to different stimuli, and an increased number of histiocytes in the sinus of a lymph node is called histiocytosis or "sinus histiocytosis."

Histone is a major protein component of chromatin, the matrix that builds up chromosomes. DNA is wound around the histone proteins forming the nucleosomes, which then further condense as chromosomes.

Hodgkin lymphoma is a specific form of lymphoma predominantly found in humans, but has also been described, though rarely, in other species where it is referred to as "Hodgkin's-like." Histologically the neoplasm consists of sheets of neoplastic lymphocytes containing characteristic Reed-Sternberg cells. Refer to **Lymphoid System** in Appendix 2 for further information.

Homogenizing cell change, see the preferred terms **Neuronal necrosis**; **Retinal single cell necrosis**.

Homozygote is composed of two alleles (copies) of a diploid gene that are identical in their sequence.

Horn cyst, see the preferred term **Squamous cyst**.

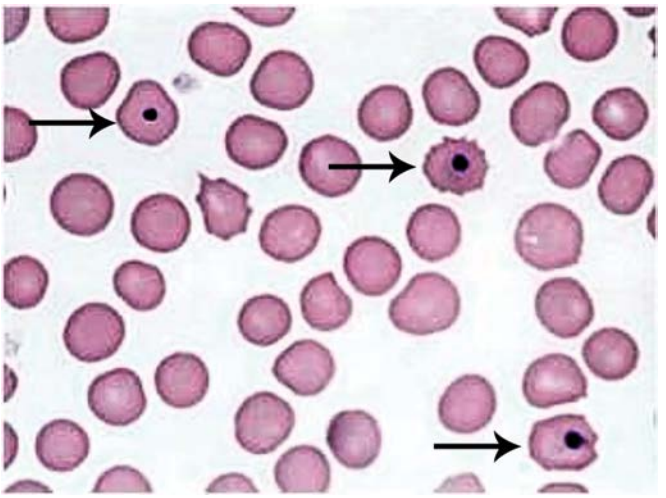
Host-mediated assay is a genotoxicity test where indicator cells (often the same *Salmonella typhimurium* strains as used in the Ames test) and the chemical being investigated,

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are coadministered to an animal, usually a rodent host. The aim is to provide an in vivo metabolism and disposition of the chemical. Subsequently, the test cells are recovered from the mammalian host and the mutant formation is assessed in vitro. Host-mediated mutagenicity assays are rarely performed in drug development, where they have been superseded by in vivo assays. See **Eukaryotic mutagenicity tests** for further information.

Howell-Jolly body is a small red blood cell inclusion composed of nuclear remnants. They often occur as singular inclusions, but on occasion may be multiple. They are visible on Romanowsky-stained smears and appear as deeply basophilic, pyknotic, and spherical inclusions. They are most often seen in dyserythropoietic anemia. They are often found associated with the following conditions: cytotoxic therapy (cyclophosphamide, chlorambucil, or nitrosourea), megaloblastic anemia, inherited or acquired splenic dysfunction or splenectomy, and red blood cell enzyme deficiencies such as glucose-6-phosphate dehydrogenase deficiency. In normal people and most other mammals, Howell-Jolly bodies are rapidly removed by the spleen. Therefore, the presence of Howell-Jolly bodies in peripheral blood usually indicates splenic dysfunction or absence, or an accelerated or dysfunctional erythropoiesis such that a higher incidence of red cells with nuclear fragments are in circulation. In mice, Howell-Jolly bodies are not removed and serve as the basis of the micronuclei genotoxicity screening assay. High frequencies of micronuclei in mice treated with test compounds suggest that either a whole chromosome or a fragment of a chromosome has not been incorporated into one of the daughter nuclei during cell division.

Synonym(s): **Micronucleus**.



Howell Jolly bodies (arrows), blood smear, mouse.

Howship's lacunae refer to an area of bone which is or has undergone osteoclastic resorption and has a concave or pitted appearance compared to adjacent unresorbed bone. Osteoclasts or young osteoblasts may or may not be present within the lacunae.

Synonym(s): **Erosion pits**.

HPRT locus is a gene locus for hypoxanthine guanine phosphoribosyl transferase, an enzyme involved in purine metabolism. It is used as a test system for gene mutations in cells. See **Eukaryotic mutagenicity tests** for further information.

Human equivalent dose (HED) is a term used to define the safe starting dose for a clinical trial based on animal data. Usually the HED is calculated from the no observable adverse effect level (NOAEL) data generated from animal toxicity studies using body surface area conversion factors. Thus, the animal dose in mg/kg is converted to a surface area dose mg/m^2, using the species-specific conversion factor; this dose-per-surface area value is then converted to the HED using the human body surface area conversion factors.

Hyaline cast is a cylindrical, homogeneous or glassy deposit within the lumen of renal tubules frequently composed of albumin. The most common example is the eosinophilic hyaline cast occurring as a feature of chronic progressive nephropathy (CPN) in the aging laboratory rat, particularly in advanced stages of the disease. Hyaline casts are not restricted to CPN but can be seen in relatively low incidence in some cases of chemical injury to either renal glomeruli or tubules.

Synonym(s): **Renal tubular proteinosis**; **renal tubular cast**.

Hyaline degeneration is a type of cellular degeneration characterized by a hyaline or waxy appearance of the cytoplasm or extracellular matrix. It has been used in a number of tissues including, but not limited to, skeletal muscle, arteries and arterioles, kidney, liver, nasal cavity, and bone to describe the presence of an amorphous, pale, or sometimes densely eosinophilic material.

Synonym(s): **Hyalinization**.

Hyaline droplet is any microscopically visible, intracytoplasmic, rounded droplet of homogeneous, glass-like, or amorphous structure, usually representing phagolysosomes. The most common example occurs in the S2 segment of kidney tubules in normal male rats as they attain maturity and begin to produce alpha 2u-globulin (α-2u-g), ill-defined tracts of α-2u-g eosinophilic hyaline droplets that run from the subcapsular cortex down into the deep cortex. These droplets vary from scattered, small, round forms to cells which are apically congested with round droplets; however, when the protein is complexed with a xenobiotic, the droplet-congested cells disappear and the droplets assume more angular, crystal-like shapes. The normal and altered patterns are best visualized with Mallory Heidenhain stain or by fluorescence microscopy. Hyaline droplets of different composition include those associated with histiocytic sarcoma, which contain lysozyme secreted by the neoplastic mononuclear cells; hyaline droplets in sporadic S3 segment cells of advanced chronic progressive nephropathy (CPN) in aging laboratory rats, which contain albumin; reddish-brown amorphous droplets of unknown composition observed in the cortical proximal tubules of aged female rats; and in association with chronic anthraquinone administration in both sexes of rats. Hyaline droplets also

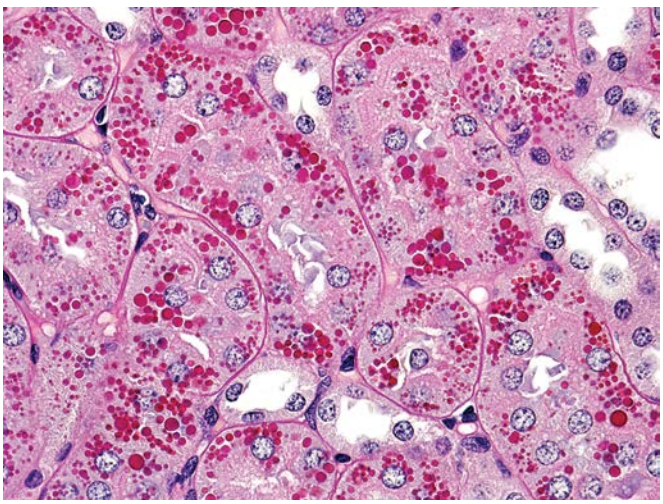
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typically accompany instances of albuminuria, hemoglobinuria, and myoglobinuria.

Hyaline droplet accumulation, see the preferred term **Hyaline droplet nephropathy**.

Hyaline droplet nephropathy represents an accumulation of homogeneous droplets in the cytoplasm of renal proximal tubule cells. The best-known condition is the unique α-2u-g nephropathy syndrome in male rats, but a form of hyaline droplet nephropathy also occurs in male and female rats treated with anthraquinone. In the latter case, the droplets are reddish brown to brown after staining with hematoxylin and eosin (H&E) and are positive for periodic-acid Schiff (PAS) reagent. Hyaline droplet nephropathy also occurs in the proximal tubules of mice and rats that have a significant body burden of histiocytic sarcoma.

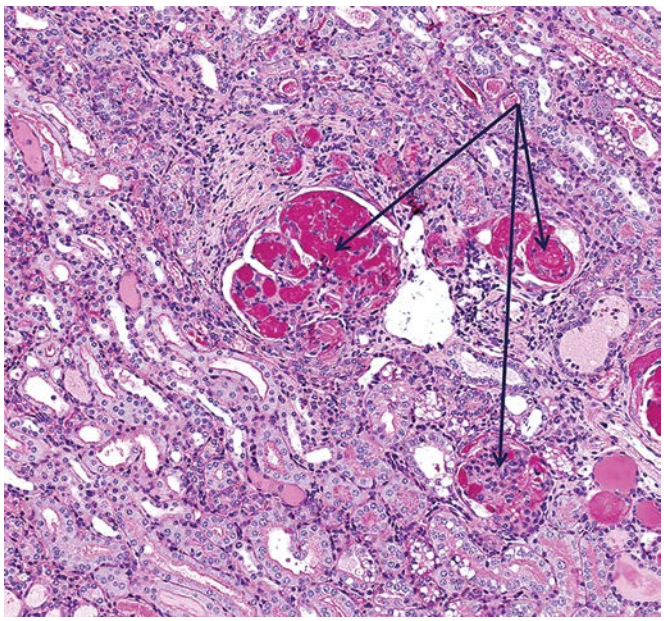
Synonym(s): **Hyaline droplet accumulation**; **alpha 2u-globulin (α-2u-g) hyaline droplet nephropathy**.



Hyaline droplet nephropathy, anthraquinone, kidney, female rat, PAS.

Hyaline droplets, also see the preferred term **Eosinophilic globules**.

Hyaline glomerulopathy is a form of renal glomerular enlargement in which the mesangium is progressively replaced with eosinophilic, amyloid-like, hyaline material and the glomerular tuft becomes hypocellular. The material stains positively with periodic-acid Schiff (PAS) stain, but is negative for amyloid. It occurs spontaneously in certain strains of mice, including the B6C3F$_1$ mouse. Ultrastructurally, there are subendothelial deposits of linear, lamellar, fibrillar, or tubulofibrillary structures. A similar glomerular alteration in humans is known as immunotactoid glomerulopathy, as it is associated with IgG and complement labeling. In mice, a cocktail of polyclonal, anti-mouse IgG-IgM-IgA weakly stains the accumulating material. The condition has been induced in the mouse and rat by chronic administration of pulegone, a monoterpene ketone present in certain species of the mint family, particularly Pennyroyal.



Hyaline glomerulopathy, mouse kidney, PAS.

Hyalinization, see the preferred term **Hyaline degeneration**.

Hyalitis, see the preferred term **Vitreal inflammatory cell infiltrate**.

Hydrocephalus is a congenital or acquired condition in which excessive cerebrospinal fluid (CSF) accumulates within the ventricles of the brain. Hydrocephalus may be due to obstruction of CSF flow, increases in CSF production, and/or decreases in CSF egress via arachnoid villi. Increased pressure on tissues surrounding the affected ventricles results in degeneration of the surrounding nervous tissue. See **Blood-CSF barrier** and Appendix 3 for information on CSF flow. In nonclinical reports, ventricular dilatation is often used to describe hydrocephalus grossly. A related term is hydromyelia, which is excessive CSF within the spinal cord. See **Hydromyelia** for further information.

Hydrocortisone, see the preferred term **Glucocorticoid**.

Hydrometra, see the preferred term **Uterine luminal dilation**.

Hydromyelia is dilation of the central canal of the spinal cord. Hydromyelia may arise as a consequence of other malformations (e.g., congenital hydrocephalus) that disrupt the normal flow of CSF. Specifically, Dandy-Walker- or Arnold-Chiari–associated malformations have been associated with hydromyelia. These conditions disrupt the flow of CSF such that there is increased pressure and subsequent expansion of the central canal, which remains in communication with the ventricular system of the brain. Rising pressure in the central canal can lead to rupture and leakage of fluid into the adjacent parenchyma of the cord, most often into the parenchyma of the dorsal funiculi. Although used synonymously, syringomyelia refers more specifically to

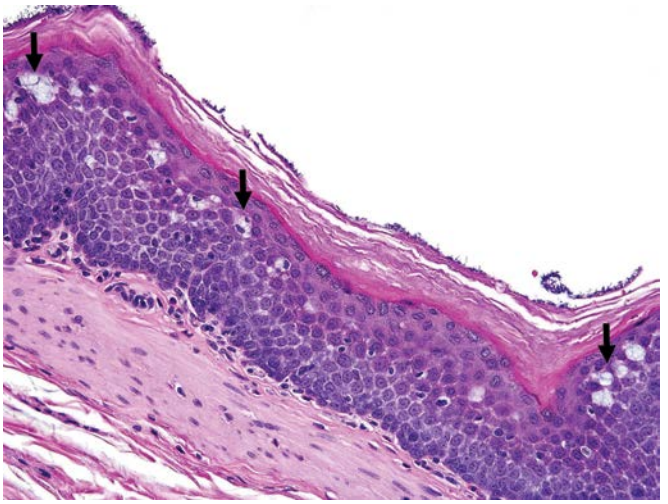
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dissection and cavitation of the spinal cord parenchyma (syrinx formation), rather than expansion of the central canal (hydromyelia). See **Syringomyelia** for further information.

Synonym(s): **Dilated central canal of the spinal cord**; **dilated spinal cord**.

Hydropic change is a type of cellular degeneration characterized by swelling of the cell. Cells may have an overall pallor or indistinct vacuoles. If the vacuoles break down, a cytoplasmic "lake" can form, which may take on more of the eosin stain and appear as droplets. Hydropic change can result from ischemia or toxic insult to cells. Loss of blood supply results in decreased intracellular oxygen tension as well as ATP depletion. This is accompanied by loss of oxidative phosphorylation causing decreased ATP generation and failure of the Na+K+ pump, which leads to increased intracellular sodium; water passively follows, resulting in cellular swelling. Chemical toxicity can produce direct cell membrane injury or release highly toxic and reactive free radicals causing lipid peroxidation and cell membrane damage with increased influx of sodium and water causing cellular swelling.

Synonym(s): **Hydropic degeneration**; **vacuolar degeneration**.



Hydropic change in the nonglandular portion of the stomach of a rat, H&E. Epithelial cells beneath the cornified layer contain variably sized clear cytoplasmic vacuoles (as indicated with arrows). The underlying basal epithelium is more basophilic with an increased number of mitotic figures indicating a secondary process of increased proliferation. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

Hydropic degeneration, see the preferred terms **Hydropic change** and **Vacuolar degeneration**.

Hydrothorax is characterized by the accumulation of clear fluid in the thoracic cavity. Under normal conditions, there is only a small amount of fluid present within this cavity, the role being to reduce friction during respiratory movements. The amount of fluid is controlled by lymphatic drainage via the thoracic duct, and any disruption of this drainage can lead to accumulation of fluid. This condition is rarely seen in laboratory animals, but the most common etiologies involve neoplasia and infections. There may be an associated pulmonary mesothelial proliferation and inflammation.

Differential diagnoses: **Chylothorax**; **Hemothorax**; **Pyothorax**.

Hydroureter, see the preferred term **Ureteral dilation**.

Hyperadrenocorticism is a condition that results from hypersecretion of hormones from the adrenal gland cortex. Pituitary-dependent hyperadrenocorticism is due to functional pituitary gland adenomas or carcinomas, and hypersecretion of ACTH leads to adrenal gland hypertrophy and hyperplasia, with increased synthesis of corticosteroids. Likewise, tumors of the adrenal gland that are functional and hypersecrete corticosteroids may result in a similar disease state. Both pituitary and adrenal gland–dependent forms are unresponsive to feedback inhibition signals. Typically, hyperadrenocorticism produces exaggerated corticosteroid affects in the animal, including hair loss, fat redistribution, hyperpigmentation, hypercholesterolemia, and increased risk of infection. Hyperadrenocorticism occurs spontaneously in the dog, rat, mouse, and hamster, and can be experimentally induced in most mammals by use of exogenous corticosteroids.

Synonym(s): **Cushing's disease**.

Hypercellularity is an increase in the number of cells within a tissue. For example, there can be an increase in cells due to influx of inflammatory cells during a response to infection or necrosis. Bone marrow hypercellularity can result due to a regenerative response secondary to blood loss or inflammation.

Hyperchromatosis, neuronal, see the preferred term **Dark neuron artifact**.

Hyperemia is the active accumulation of blood within vessels in the tissues due to increased blood flow. The term is primarily used to refer to an increased reddening of the skin, often localized, as an in-life finding.

Hypergastrinemia is abnormal excess gastrin production, occurring for example following treatment with proton pump inhibitors and is responsible for enterochromaffin-like cell hyperplasia, which may progress to neoplasia (carcinoid tumors). (See **Gastric carcinoid** or **Gastric neuroendocrine tumor** for further information.)

Hyperkeratosis is an increase in the number of layers of the stratum corneum (keratinized epidermal cells), and when used in isolation usually refers to the preferred term epidermal hyperkeratosis. See **Epidermal hyperkeratosis** and **Adnexal hyperkeratosis** for further information.

Hyperkinesis consists of a number of conditions where movement is greatly increased. It can be used to describe an overactive restlessness in children, abnormal or heightened muscle movement, or uncontrollable muscle movements. In animal

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studies, this is observed as increased spontaneous activity or stereotypical behavior (e.g., induced by amphetamines). Clinically, it can be quantitated using the Connors' Teacher Rating scale. This scale is used to quantitate hyperkinesis in children. It was the term applied to what is now referred to as attention-deficit/hyperactivity disorder (ADHD).

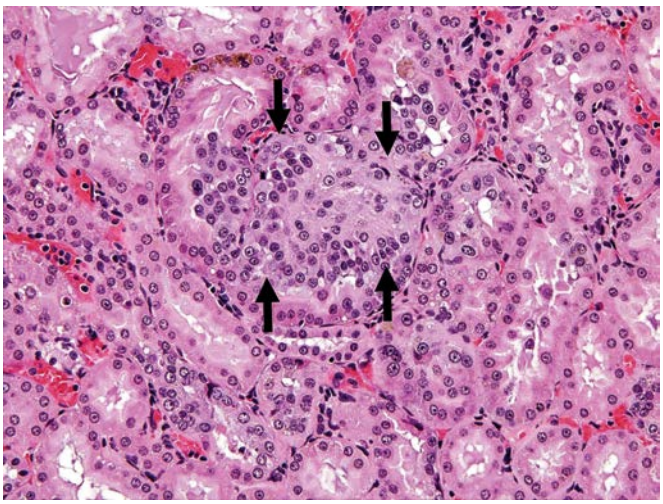
Hyperosteoidosis, see the preferred term **Increased osteoid**.

Hyperostosis (proliferative or nonproliferative), see the preferred term **Bone increased**.

Hyperpigmentation is an increase in pigmentation of the skin, either focal or diffuse, due to increased production of melanosomes containing melanin within melanocytes. In the skin, melanocytes continually produce melanosomes, which are transferred to the epidermal cells. Increased numbers, or larger melanosomes, will result in increased pigmentation. Ultraviolet (UV) exposure and some types of skin irritation will cause hyperplasia of the melanocytes, which can lead to hyperpigmentation. Inflammation, healing from injury, or hormonal stimulation can result in the increased production of melanosomes and thus increased pigmentation. Hyperpigmentation can be a sign of systemic diseases such as hyperthyroidism or hypoadrenocorticism. Some compounds can cause hyperpigmentation directly, including many antineoplastic agents. Compounds that cause phototoxicity can also result in hyperpigmentation after sun exposure.

Hyperplasia is an increase in the number of cells within a tissue or organ, resulting in enlargement. Hyperplasia can be adaptive (physiological) or pathological, such as in the case of hormonal stimulation, infection, or preneoplastic lesions. Hyperplasia is generally considered to be reversible.

Hyperplasia, atypical is an area of hyperplasia with signs of cellular atypia. The features of atypia vary depending on the tissue/organ, but in general consist of cellular and nuclear pleomorphism (variation in size and shape), hyperchromatism with cytoplasmic basophilia (cytoplasm appears more blue), loss of polarity (e.g., change in the normal location of the nucleus), increased nuclear/cytoplasmic ratio (the size of the nucleus increases relative to the entire cell), and increased mitotic activity. Atypical hyperplasia is often considered a preneoplastic condition and is on the continuum with adenoma. Tetrabromobisphenol A has been shown to cause atypical hyperplasia of the uterine endometrium in rats.



Hyperplasia, atypical in the kidney of a rat, H&E. Arrows highlight a central focus of tubular epithelial cell crowding with increased nuclear:cytoplasmic ratio and basophilia.

Hyperplasia, gastrointestinal is an increase in the number of a cell type, often occurring concurrently with hypertrophy (an increase in the size of cells due to increased cytoplasm). Refer to **Gastrointestinal Tract** in Appendix 2 for further information.

Hypertension is a sustained (long term) increase in arterial blood pressure. Higher blood pressure may occur for short periods early in the morning, after exercise, or under conditions of stress. It generally has no detectable symptoms in the short term. If the pressure is high enough, symptoms can include headache, dizziness, blurred vision, nausea, and pulsations in the neck or head. If the pressure is long enough, it can lead to serious health issues such as cardiovascular failure or stroke. Drugs that may induce hypertension include alcohol, amphetamines cyclosporine, antidepressants, and caffeine.

Hypertrichosis is an abnormal amount of hair growth, which can be generalized (over the entire body) or localized, resulting in abnormally thick, long hair in the affected regions. Hypertrichosis can be congenital or acquired. Congenital hypertrichosis is usually genetic in origin. Acquired hypertrichosis can occur at any time during life and also can be generalized or localized. The latter can be the result of head injuries, especially if there is damage to the pituitary or hypothalamus, thyroid disorders (hyperthyroidism or hypothyroidism), and some systemic malignancies. Some compounds can cause hypertrichosis, including cyclosporine, minoxidil, phenytoin, vasodilators, or diazoxide. Hypertrichosis is generally androgen-independent and does not affect androgen-dependent areas. Hirsutism is a type of hypertrichosis caused by excessive androgen hormones, resulting in hair growth in a male-specific pattern, in females and prepubescent males.

Hypertrophic gastritis is an uncommon lesion in humans characterized by diffuse to variably distributed areas of enlarged, thickened, and convoluted rugal folds (resembling the surface of the brain) affecting the glandular stomach, often with local and peripheral edema and systemic protein loss. Microscopically, there is pronounced hyperplasia of the foveolar epithelium with atrophy and loss of parietal and chief cells. Gastric glands may be dilated, variably filled by inflammatory cell debris, and may penetrate the muscularis mucosa.

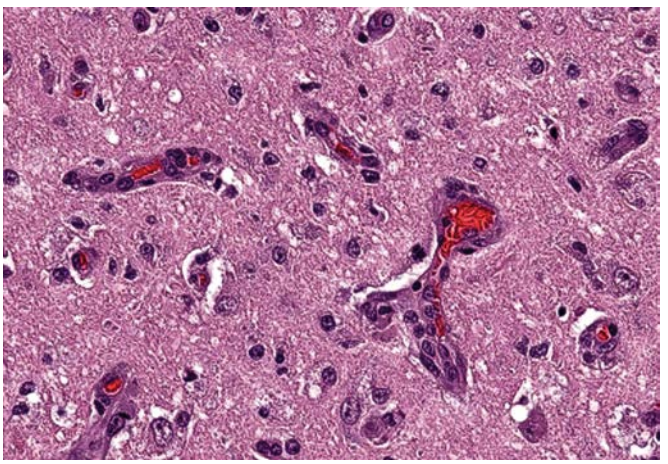
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The lamina propria shows a variable amount of edema and chronic inflammatory cell infiltration with scattered eosinophils. Prominent vertical strands of smooth muscle in the lamina propria are also identifiable. The etiology of hypertrophic gastritis (Menetrier's disease) in humans is unknown, but both increased signaling by transforming growth factor-α and infection with *Helicobacter pylori* or cytomegalovirus have been implicated. A similar disease occurs in some inbred strains of mice (where it may be described as adenomatous hyperplasia); however, this mechanism is less clearly understood. Idiopathic hypertrophic gastritis has been described as a breed-specific entity in dogs (Basenjis, boxers, and bull terriers). In other species, gastric parasitism may also cause reactive inflammation and hyperplasia of the stomach mucosa: Monkeys parasitized by *Nochtia nochti* develop plaques of gastric rugal hypertrophy at the pyloric-fundic region, and equine gastric hypertrophy has been associated with *Habronema megastoma* and *Trichostrongylus axei* infestation.

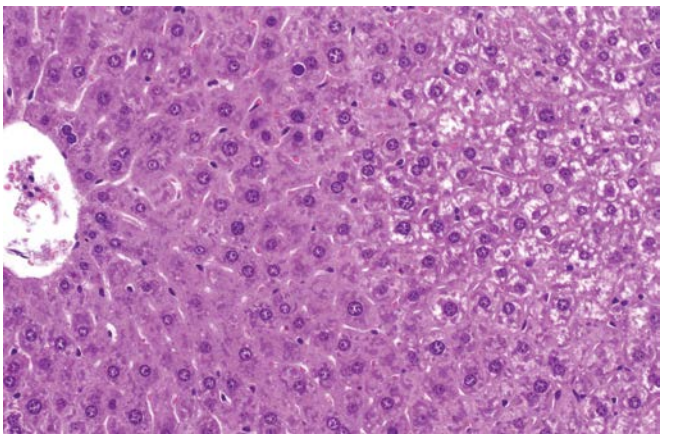
Synonym(s): **Hypertrophic gastropathy**; **giant hypertrophic gastritis**; **protein-losing gastropathy**; **Menetrier's disease**.

Hypertrophic gastropathy, see the preferred term **Hypertrophic gastritis**.

Hypertrophy is an increase in the size of individual cells or the increase in the size of an organ due to increased cell size (but not cell number; see **Hyperplasia** for further information). Increased cell size can be very difficult to appreciate microscopically if the change is widespread. Hepatocellular hypertrophy may be due to pathologic lipid storage (lipidosis) or smooth endoplasmic reticulum proliferation from cytochrome P450 monooxygenase enzyme induction following exposure to xenobiotics such as phenobarbital, 3-methylcholanthrene, ethanol, PCBs, and DDT. See **Cytomegaly** for further information.



Hypertrophy of the endothelial cells in the brain of a dog, H&E. Note marked enlargement of these cells lining small blood vessels.



Hypertrophy of centrilobular hepatocytes in a rodent, H&E. Hepatocytes surrounding the central vein (left side of image) are larger and there is greater distance between nuclei. Normal-sized hepatocytes (right) contain glycogen (clear space in cytoplasm). (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

Hyperventilation is a condition wherein a subject has breathed too quickly or deeply, and the breathing rate or depth increase leads to an imbalance in blood gases. The blood oxygen increases and carbon dioxide levels decrease. This can cause a decrease in blood flow to the brain and other vital organs, leading to bloating, burping, excessive flatulence, abdominal pressure/pain, dizziness, fainting, confusion, and agitation. It can also lead to a drop in blood calcium, which may result in numbness/tingling (arms/mouth), spasms or cramps in the hands and feet, and/or muscle twitching. Hyperventilation often occurs in association with anxiety (panic attacks), but it can also be a sign of serious conditions such as infection, bleeding, or heart attack.

Hypoadrenocorticism is any condition that prevents production or secretion of corticosteroids from the adrenal gland. Adrenalectomy or nonfunctional tumors of the pituitary gland resulting in loss of serum adrenocorticotropic hormone (ACTH) are common causes; however, in many cases the cause of adrenal gland hyposecretion is idiopathic atrophy. Prolonged administration of exogenous steroids and sudden withdrawal is another common cause, due to induced cortical atrophy with insufficient recovery time after withdrawal. The consequences of adrenal gland hyposecretion are hyponatremia, hypochloremia, hypoglycemia, and hyperkalemia that may become life threatening with subsequent bradycardia and circulatory collapse (Addisonian crisis).

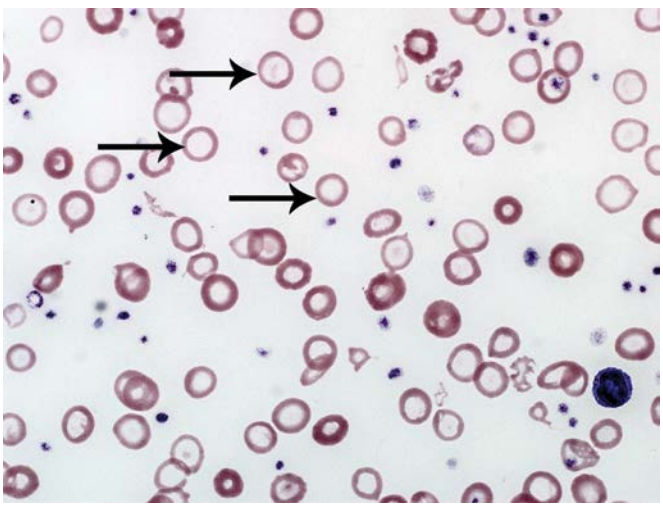
Synonym(s): **Addison's disease**.

Hypocellularity is decreased number of cells. For example, the bone marrow is the main site of hematopoiesis in most adult mammalian species and is comprised of stem cells and immature and mature cells of various hematopoietic lineages. When there is a reduction in the number of cells, this is described as hypocellularity of the bone marrow. When degeneration or loss of cells occurs slowly, there is often

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replacement by adipocytes while with rapid loss the space in the bone marrow may appear empty. See **Atrophy** for further information.

Hypochromasia is a term with two common definitions. On blood smear examination, it refers to increased central pallor of red blood cells; only a thin ring of hemoglobinized cytoplasm is stained, which makes these cells clearer than their counterparts with a normal hemoglobinized cytoplasm. Hypochromasia also refers to decreased mean corpuscular hemoglobin content (MCHC) below the reference range. In this instance, it does not always correlate with the presence of hypochromic red blood cells on blood smear examination. The presence of hypochromic red blood cells will be detected on blood smears before an effect is recognized on the MCHC parameter. Hypochromasia indicates a decrease in red blood cell hemoglobinization and impaired heme synthesis. Depending on the etiology, hypochromasia can be associated with other red blood cell morphology abnormalities, such as microcytosis and poikylocytosis with advanced iron deficiency. Etiologies of hypochromasia are multiple, and can be due to deficiencies (e.g., iron, folate), excess (e.g., zinc), or bone marrow injury/diseases (e.g., sideroblastic anemia, myelodysplastic syndromes, neoplasia, genetic disorders).



Hypochromasia (arrows), peripheral blood smear, cynomolgus monkey.

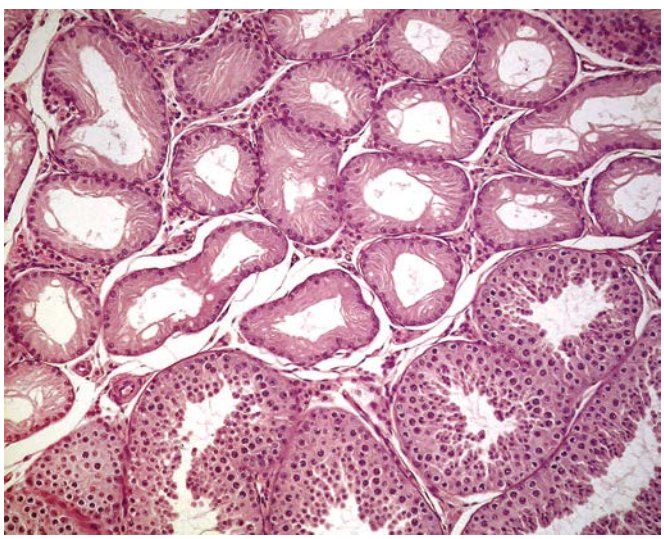
Hypodermis, see the preferred term **Subcutis**.

Hypopigmentation is a clinical term that refers to a decrease in skin pigmentation relative to the normal pigmentation of an individual animal. Skin pigmentation in mammals is the result of the presence of various pigments, of which melanin is the most important. Hypopigmentation is usually subdivided into hypomelanosis or amelanosis (deficit or absence of melanin production or transfer, respectively) and hypomelanocytosis or amelanocytosis (loss of melanocytes), and can be congenital or acquired. Mechanistically, hypomelanosis and amelanosis can be due to a deficit in melanocyte development and migration, melanin synthesis, melanin packaging into melanosomes and melanosome formation, and transfer of melanosomes to keratinocytes. Interference with the synthetic processes of melanin has been reported following administration of alpha-tocopherol or calpain inhibitors, while melanosome transfer to keratocytes can be inhibited by serine proteases inhibitors. Melanocyte loss can be associated with autoimmune reactions.

Hypoplasia refers to partial failure of a tissue or organ to develop from an existing primordium or anlagen. See **Aplasia** for further information.

Hypospermatogenesis is a common testicular background finding in the purpose-bred beagle dog, less so in the cynomolgus monkey, and generally not reported in rodents. The main characteristic of hypospermatogenesis is an inadequate or reduced proportion of one or more germ cell layers within the seminiferous tubule, and is unaccompanied by few, if any, degenerative germ cells. The distribution tends to be multifocal in arrangement. Hypospermatogenesis may be a congenital abnormality and reflect an intermittent inefficiency of spermatogonia to divide and produce progeny. The incidence can vary widely between animals and is unrelated to sexual maturity. Hypospermatogenesis can be exacerbated by drugs that affect spermatogonial proliferation; therefore, a dose-related increase should be considered potentially drug-related.

Differential diagnoses: **Seminiferous tubule atrophy**; **Sexual immaturity**; **Testicular hypoplasia**; **Testicular tubular degeneration/atrophy**.



Hypospermatogenesis, seminiferous tubules, dog, H&E.

Hypotension results from a lower than normal arterial blood pressure. Current guidelines identify normal in humans as below 120/80 mm Hg. In dogs, normal blood pressure may range from 120–160/60–90 mm Hg, and in cynomolgus monkeys the normal range is 120/60 mm Hg with a pulse rate of about 195 beats per minute. While low blood pressure is

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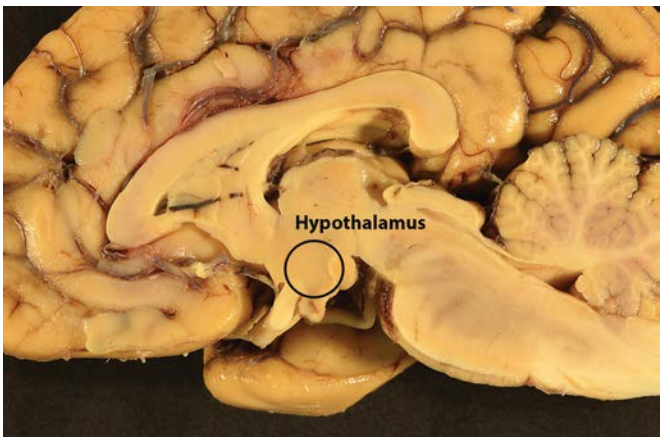
desirable, if it goes below the threshold to deliver adequate oxygen and nutrients to tissues, it can cause dizziness and fainting (syncope), lack of concentration, blurred vision, nausea, fatigue, thirst, cold or clammy skin, or rapid shallow breathing. A sudden fall of just 20 mm Hg can also cause this. If arterial blood pressure falls below the threshold to keep the capillaries open, it can be life threatening. Causes of low blood pressure can be heart problems, pregnancy, endocrine problems, dehydration, blood or other fluid loss, allergic reactions, and excessive sun exposure.

Hypothalamic inhibiting hormones are generated in the hypothalamus and are designed to inhibit hormone production and release from the anterior pituitary gland. Melanocyte-stimulating hormone (MSH)-inhibiting hormone (inhibits release of melanocyte-stimulating hormone), prolactin-inhibiting hormone (inhibits production and release of prolactin), and somatostatin (inhibits growth hormone production and release) are the primary hypothalamic inhibitory hormones.

Hypothalamic-pituitary-adrenal gland (HPA) axis is a multiorgan feedback system that utilizes multiple hormones produced in the hypothalamus, pituitary gland, and adrenal gland, in order to maintain homeostasis of behavioral, neuroendocrine, autonomic, and immune systems. Hormones produced in one organ are up- or down-regulated through feedback from hormones produced at another organ, and in response to the demands of the body and during stress. The HPA axis has a circadian rhythm in most mammals, reflecting the periods of natural rest and activity of the species. The paraventricular nucleus of the hypothalamus produces corticotropin-releasing hormone (CRH) and vasopressin, which stimulate adrenocorticotropic hormone (ACTH) release from the anterior pituitary gland. ACTH in turn stimulates glucocorticoid (primarily cortisol) production and release from the adrenal cortex. As glucocorticoid levels rise, they serve to negatively influence the production of CRH and ACTH from the hypothalamus and pituitary gland, respectively, thus regulating production through feedback inhibition of positive stimulators. The HPA axis is implicated as a central mechanism of the stress response.

Hypothalamic-releasing hormones are multiple hormones generated by the arcuate, paraventricular, periventricular, and supraoptic nuclei of the hypothalamus that stimulate the anterior pituitary gland to produce and release its hormones. The releasing hormones target cells of the anterior pituitary gland, which in turn release their hormones into the general circulation for distribution to the target organs. The releasing hormones include growth hormone–releasing hormone (GHRH), dopamine, gonodatropin-releasing hormone (GnRH), thyrotropin-releasing hormone (TRH), and corticotropin-releasing factor (CRH).

Hypothalamus is a portion of the diencephalon of the brain. As an endocrine organ, neurons within the supraoptic and paraventricular nuclei of the hypothalamus produce and transport neurohormones to their distal axon terminals in the pituitary gland, where they deliver the granules of antidiuretic hormone (ADH) and oxytocin (OT) to the neurohypophysis for distribution into the general circulation (the hypothalamo-neurohypophyseal tract). Releasing- and release-inhibiting hormones that are synthesized in the arcuate, paraventricular, periventricular, and supraoptic nuclei of the hypothalamus control anterior pituitary hormone secretion (the hypothalamic-pituitary-target organ axes). Corticotropin releasing hormone (CRH), gonadotropin-releasing hormone (GnRH), growth hormone–releasing hormone (GHRH), prolactin-releasing hormone (PRH), prolactin-inhibiting hormone (PIH), somatostatin, and thyrotropin-releasing hormone (TRH) are released from these nuclei into the pituitary portal vessels that deliver them to the adenohypophysis where they influence pituitary hormone production and secretion. The endocrine function of the hypothalamus is regulated by feedback of peripheral hormones, by emotional and physical stressors, and is central to body homeostasis and reproductive and survival modalities.



Brain, hypothalamus, chimpanzee (*Pan troglodytes*), H&E.

Hypoxia, or low arterial oxygen levels, is a term generally applied to the inadequate delivery of oxygen to tissues due to a low oxygen concentration in the blood. The causes vary and can include low oxygen concentration in the atmosphere (as in high altitude sickness), pulmonary disorders, circulatory deficiencies, anemia, edema, or other tissue conditions where the circulation cannot deliver adequate oxygen. Symptoms generally include shortness of breath, labored or difficult breathing (dyspnea), rapid pulse, sudden loss of consciousness (syncope), delirium or euphoria, angina pectoris (local pain due to low oxygenation of the myocardium) and lack of skin coloration (cyanosis).

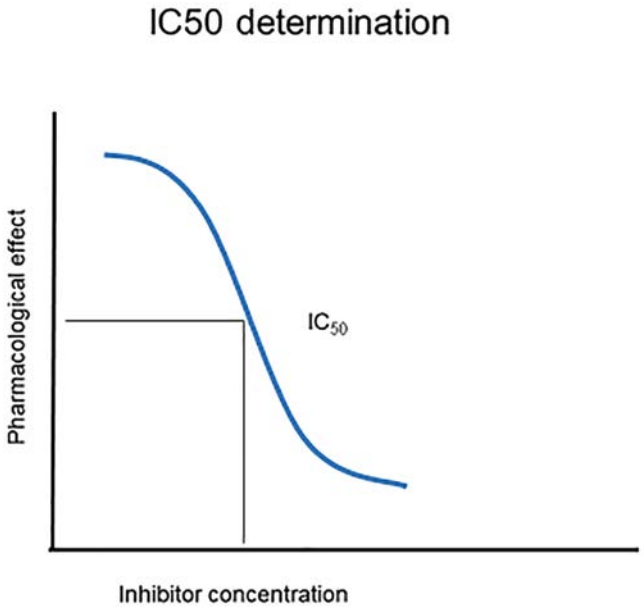
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IARC is an acronym for the International Agency for Research on Cancer, a specialized agency within the World Health Organization whose aim is to promote international collaboration in cancer research. The agency has developed a classification scheme for carcinogens, mainly in terms of hazard identification.

Iatrogenic refers to a condition which is the result of a diagnostic or therapeutic intervention. An example is iatrogenic Cushing's syndrome (hyperadrenocorticism) of dogs which is the result of exogenous administration of glucocorticoids or megestrol acetate.

IC_{50} is a term for the median inhibitory concentration or a measure of the effectiveness of a compound to inhibit a biological or biochemical function). It is the concentration of a compound (drug) that inhibits 50% of the maximal inhibition achievable in the system (see graphical representation below). For an inhibitory compound, this is the equivalent of the ED_{50}. See **ED_{50}** for further information.



ICH is an acronym for the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. This tripartite organization, with representatives from the European, United States, and Japanese drug regulatory agencies and the corresponding pharmaceutical industry associations, has developed and maintained globally applicable guidelines for determining the safety, efficacy, and quality of drugs in development. The guidelines are designated with the suffixes Q for quality, E for efficacy, S for safety, and M for multidisciplinary (guidelines which cover more than one of the other areas). The harmonization of technical requirements has increased the efficiency of drug development and decreased the duplication of activities. A full list of quittance documents may be obtained from the ICH website (www.ich.org).

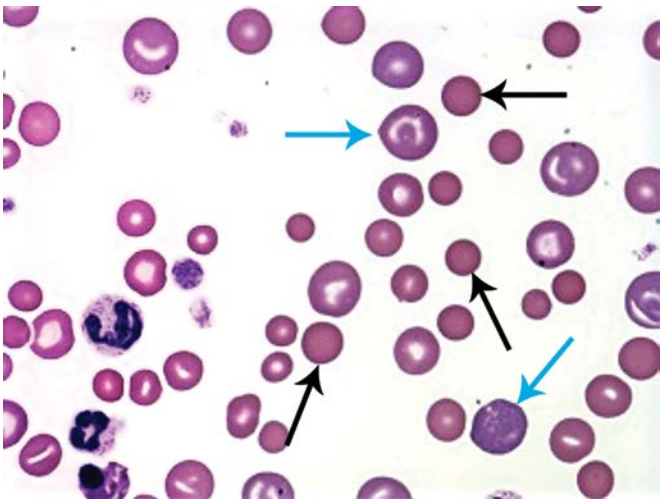
ICSH is an acronym for interstitial cell-stimulating hormone (ICSH). See **Interstitial cell-stimulating hormone (ICSH)** for further information.

Idiosyncratic drug reaction (IDR) is an unpredictable drug reaction that does not occur in most patients. This is also known as a Type B reaction and can be life threating. See **Adverse Drug Reaction** for further information.

Immature indicates that the specific tissue (e.g., testes or ovary) has not attained the morphological appearance that is required for proper function. It is most relevant for tissues that undergo significant postnatal development. A xenobiotic-related increase in the incidence of immature tissues should be carefully evaluated because it may represent random biological variability or a test article–mediated delay in maturity. The latter may be direct (mediated through direct trophic factor interaction), or indirect (mediated through decreased caloric intake or other perturbations in metabolism). Additional in-life and post-life information is critical for diagnosing and contextualizing xenobiotic-mediated immaturity.

Immune-mediated hemolytic anemia is characterized by immune destruction of erythrocytes that have been coated with immunoglobulins, complement, or both. The antibodies involved in immune-mediated anemia can be either autoantibodies or alloantibodies against erythrocytic antigens that have been altered through secondary causes. If the antibodies involved are IgM in nature, they will fix complement and cause direct lysis of erythrocytes (intravascular hemolysis). Since IgG antibodies do not typically bind complement, they act as opsonins and facilitate increased erythrocyte destruction through the hepatosplenic monocyte phagocyte system (MPS) resulting in extravascular hemolysis. Immune-mediated anemia is usually regenerative in nature with increased polychromasia noted on peripheral smears. Spherocytes, eccentrocytes, or bite cells are often observed on the peripheral blood smear as evidence of partial phagocytosis of erythrocytes by cells of the MPS system. The Coombs test may be helpful in diagnosing immune-mediated hemolytic anemia, as it detects the presence of IgG or complement bound to the red cell surface. Secondary causes of immune-mediated hemolytic anemia include infections, neoplasia, drugs, vaccines,

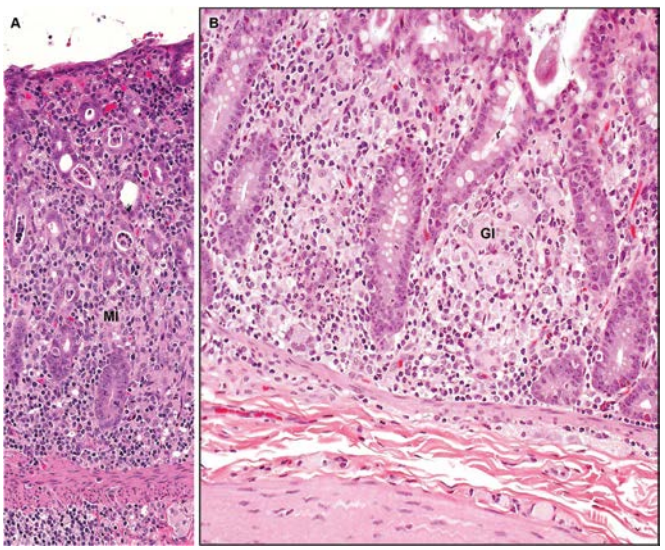
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Micro-spherocytes (black arrows) and polychromasia (blue arrows) in a case of autoimmune hemolytic anemia.

blood transfusions, bee stings, snake bites, and immune disorders such as systemic lupus erythematosus, hypothyroidism, and primary and secondary immunodeficiency.

Immune-mediated hypersensitivity may be associated with test article–induced inflammatory reactions. For example, oxazolone, trinitrobenzenesulfonic acid acts as a hapten and induces a severe granulomatous reaction in the distal colon. Inflammatory lesions can be induced by pathogenic bacteria (e.g., *Bacillus pilliformis*, salmonella, *Citrobacter freundii*, *Helicobacter* species) or viruses (e.g., norovirus, mouse hepatitis virus) if there has been a barrier breakdown or in immunodeficient animals. Dextran sodium sulphate carrageenan, acetic acid, and sodium hydroxide cause significant intestinal injury with ulceration, abnormal villous pattern, and inflammation in rodents, dogs, and rabbits. Treatment-related ulcerative and inflammatory



(A) Colon, mucosa, cynomolgus monkey. H&E. MI = mixed cell inflammation of the lamina propria. (B) Colon, mucosa cynomolgus monkey. GI = granulomatous inflammation of the lamina propria.

lesions have been commonly observed in the large intestine and cecum more than in the small intestine. Suppurative or granulomatous inflammation may be more prominently associated with ulceration.

Immunoblastic lymphoma is a systemic tumor comprised of large immunoblastic cells in which cells with abundant pyrinophilic cytoplasm may also be present. Refer to **Hematopoietic System** in Appendix 2 for further information.

Immunotoxicity assessment is required for all compounds which demonstrate effects on immune-related organs (e.g., lymph nodes, thymus, spleen) in toxicity studies. These studies involve examining the potential effects of the agent on white blood cell distribution (immune phenotyping) and the ability of the animal to mount an antibody response to an antigen challenge. Immune phenotyping of blood cells is described in the ICH S8 guideline (Immunotoxicity Studies for Human Pharmaceuticals, 2006).

Impaction results from an aggregation of material that prevents ingesta from moving along the gastrointestinal tract. Generally, the organ becomes distended proximally, with thinning of the muscular and mucosal layers. Impaction is generally used to describe a macroscopically observed lesion that creates a physical barrier or obstruction to normal flow of material. Microscopically, the term **Dilatation** is most commonly used. See **Dilatation** for further information.

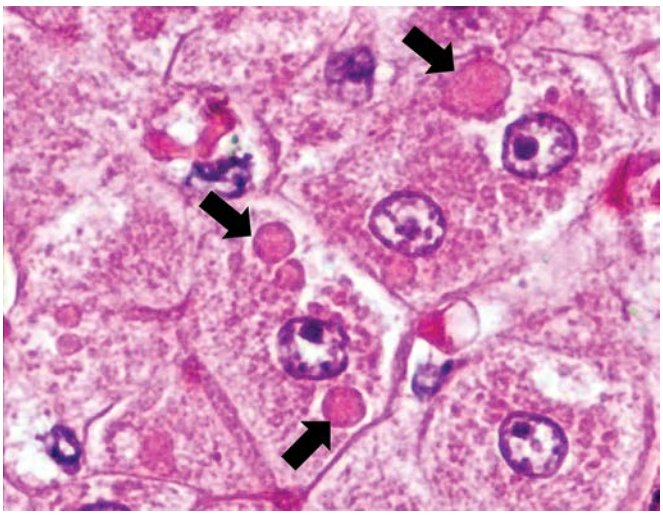
Imperforate hymen, see the preferred term **Vaginal imperforation**.

Implantation is the adherence and insertion of the fertilized egg (zygote) into the uterus wall a few days after fertilization.

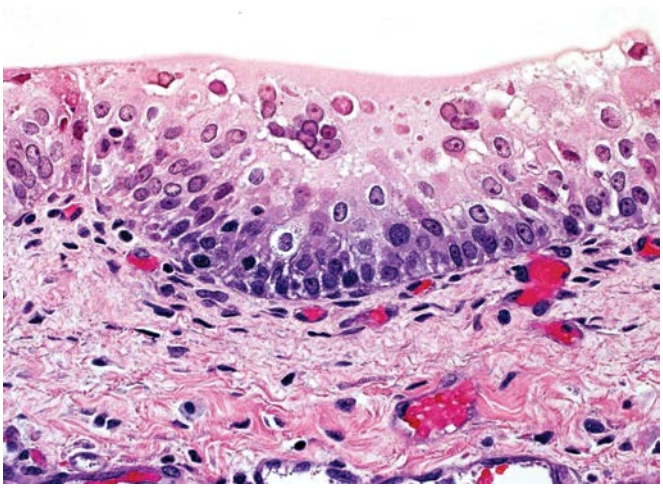
Inclusion body is a distinctive, well-demarcated, often round, proteinaceous structure within the cytoplasm and/or nucleus of a cell. Inclusion bodies typically indicate viral infection, with their location(s), size, shape, and color being diagnostic for a specific group of viruses, but they also can occur spontaneously in atrophy and in lead toxicosis. Inclusion bodies are most commonly identified within hepatocytes, epithelial cells, endothelial cells, and neurons. They are typically single within a cell. An inclusion body within the cytoplasm of a cell is referred to as "intracytoplasmic," while those within the nucleus are termed "intranuclear." The latter frequently results in the margination of chromatin rendering the cell less functional. Both intranuclear and intracytoplasmic inclusion bodies are seen in infections with cytomegaloviruses, morbilliviruses, and circoviruses. Eosinophilic or acidophilic inclusion bodies are typically intracytoplasmic (occasionally intranuclear) and subjectively pink to red upon hematoxylin and eosin (H&E) staining. Viruses with eosinophilic intracytoplasmic inclusion bodies include the poxviruses, iridoviruses, rhabdoviruses, and paramyxoviruses. For example, poxviruses form infective, large, eosinophilic intracytoplasmic inclusion

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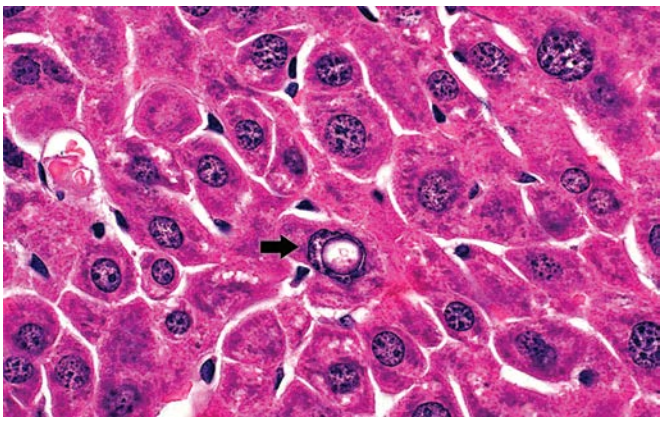
bodies within squamous epithelia. Systemic poxviruses cause similar inclusion bodies in cells throughout the body and are typically fatal. Eosinophilic intranuclear inclusion bodies are seen in infections with alpha-herpesviruses. Basophilic inclusion bodies are typically intranuclear, subjectively appear dark blue to purple with H&E staining, and tend to marginate the chromatin. Viruses with basophilic intranuclear inclusion bodies include alpha-herpesviruses, papillomaviruses, polyomaviruses, parvoviruses, and rhabdoviruses. For example, alpha-herpesviruses often form small basophilic intranuclear inclusion bodies within endothelial cells. Amphophilic inclusion bodies are typically intranuclear and subjectively pale blue upon H&E staining. Chromatin margination may not be evident. Viruses with typically amphophilic intranuclear inclusion bodies include adenoviruses, papillomaviruses, cytomegaloviruses, and polyomaviruses. For example, adenoviruses often form large amphophilic intranuclear inclusion bodies



Inclusion bodies in the liver of a nonhuman primate, H&E. Arrows highlight large round, eosinophilic inclusions that are present within the cytoplasm of hepatocytes.



Inclusion bodies in the urinary bladder of a nonhuman primate with measles, H&E. Numerous eosinophilic round inclusion bodies are present within the mucosal epithelial cells.



Invagination of cytoplasm into the nucleus (pseudoinclusion, as indicated with arrow) in a hepatocyte of a mouse administered *N*-nitrosodiethylamine (DEN) and carbon tetrachloride (CCl_4), H&E.

within pulmonary epithelial cells, hepatocytes, endothelial cells, and pancreatic acinar cells, especially in cases of immunosuppression. Pseudoinclusion bodies are invaginations of cytoplasm into the nucleus, giving the impression of an inclusion body. They are common in hepatocytes of rodents and may also be seen in some tumors. Lead inclusions are large, brick-shaped intranuclear inclusions typically seen within the renal tubular epithelium in cases of lead poisoning. These inclusions stain bright pink/magenta with acid-fast stains.

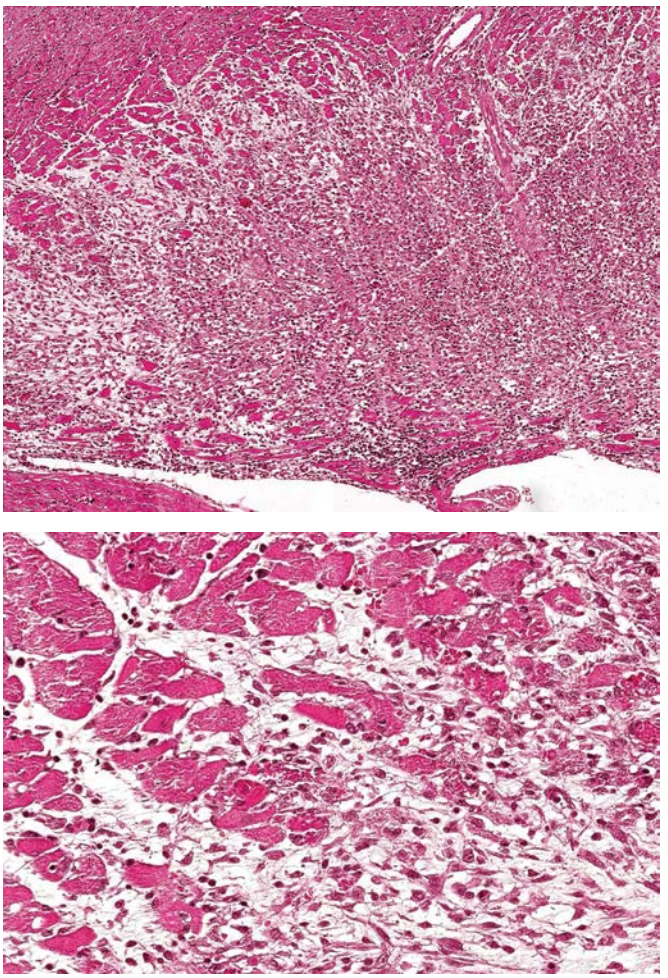
Increased size, retinal pigment epithelium, see the preferred term **Retinal pigment epithelium hypertrophy**.

IND is an acronym for investigational new drug application, which is a sponsor's request to FDA for authorization to administer an investigational new drug to humans, accomplished by completing an FDA Form 1571. FDA authorization must be received prior to interstate shipment and administration of any new drug that is not the subject of an approved new drug application. In Europe this is known as a clinical trial application.

IND documentation is the documentation needed to support an application to initiate clinical trials with a new drug candidate. This generally requires information on the manufacture, formulation, and quality of the trial drug, preclinical information on the pharmacology profile, toxicity, metabolism and disposition of the drug candidate, and the Investigator's Brochure and the protocol for the intended clinical trial. See **Investigator's Brochure** for further information.

Infarct is an area of irreversible tissue injury resulting in necrosis of a portion of the affected organ. Infarcts may be followed by reperfusion, wherein the obstruction or lack of blood flow is long enough in duration (generally hours) but is reversed or restored after cell death or by non-reperfusion, in which case the obstruction to blood flow is permanent. There can be differing susceptibility to infarction across

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Infarct in the myocardium of a rat, H&E. On low magnification, there is a large area of cardiomyocyte degeneration and loss characterized by increased clear space and loss of cellular detail. In the higher magnification image, there is degeneration and necrosis of remaining myofibers, mononuclear cell infiltrates, and fibroplasia. (Reproduced with the permission Germann, P. and Morawietz, G. (eds). *Toxicopathology Case Collection CD-ROM*. European Society of Toxicologic Pathology.)

tissues with some organs having a greater likelihood of necrosis as their vascularization is end-artery (kidney, heart) compared to other tissues with a dual blood supply (e.g., gastrointestinal tract, lung).

Infiltrate is a term used to describe an aggregate or collection of cells in a tissue, generally white blood cells, in locations or numbers not typically found, without other features of inflammation. Additional descriptors can be used to further classify the type of cellular infiltrate. Neutrophilic is used to describe aggregates of predominantly polymorphonuclear leukocytes; eosinophilic is used for that subtype of leukocyte. Mononuclear cell describes aggregates of mononuclear cells, which may be either lymphocytes and/or macrophages. A population of predominantly macrophages may be referred to as histiocytic. A population of lymphocytes would be referred to as lymphocytic. Under certain immunologic stimuli, lymphocyte populations may be predominantly plasma cells, and this would be referred to as plasmacytic or lymphoplasmacytic. When the cell population does not have one predominant cell type, the descriptor inflammatory cell or mixed inflammatory cell may be used. Focal small cellular infiltrates can be seen in almost any tissue.

Inflammation is a term used to describe a constellation of morphologic changes following tissue injury or response to infectious agents. In toxicologic pathology, the recommended approach is to be descriptive rather than to use disease-based diagnoses that might imply a pathogenesis, for example "hepatitis." The initial insult results in dilatation of local blood vessels and increased permeability to allow leukocytes and plasma proteins to enter the damaged area. In toxicologic pathology, it can be challenging to precisely determine the stage or "age" of inflammation, as the pathologist is examining tissue at a single time point following repeated exposure to a test article. For routine toxicology studies, it is best to omit chronicity modifiers, and rely on cell type. Typical cell type modifiers include neutrophilic, eosinophilic, lymphocytic, mononuclear cell, lymphoplasmacytic, histiocytic, or granulomatous that are used to characterize the predominant cell populating the affected area. If there is not one predominant cell type, then a modifier of mixed cell is appropriate.

Inflammatory bowel disease (IBD) is a chronic inflammatory condition in humans, represented by at least two different disease entities: Crohn's disease and ulcerative colitis. Both are considered multifactorial in origin with perturbations of environmental, genetic, gut microbiota, and immune factors all contributing to the disease phenotype. The precise pathogenesis is not yet fully understood; however, both can be debilitating, causing diarrhea, abdominal pain, fatigue, and weight loss. Crohn's disease is characterized by a variably severe transmural granulomatous inflammation of the intestinal mucosa, affecting different sections of the small and large intestine and progressing in some cases to fistulation. Ulcerative colitis is a nongranulomatous inflammatory disease restricted to the colon but in some instances extending diffusely to the rectum. With ulcerative colitis, chronic-active inflammation is contained within the mucosal layer, with neutrophilic, mixed to mononuclear infiltrates resulting in epithelial damage and disruption of normal crypt architecture. In nonclinical species, natural diseases occur that are referred to as IBD that resemble the human diseases in many respects; however, the multifactorial nature of these conditions make comparisons difficult. In dogs, IBD may refer to any number of conditions of the small and large intestine, including lymphoplasmacytic enteritis/colitis (LPE), eosinophilic enteritis/gastroenteritis/colitis, histiocytic ulcerative colitis, and regional granulomatous colitis. In rodents, there are several transgenic and spontaneous models of IBD that reflect different aspects of the pathogenesis in humans. In addition, there

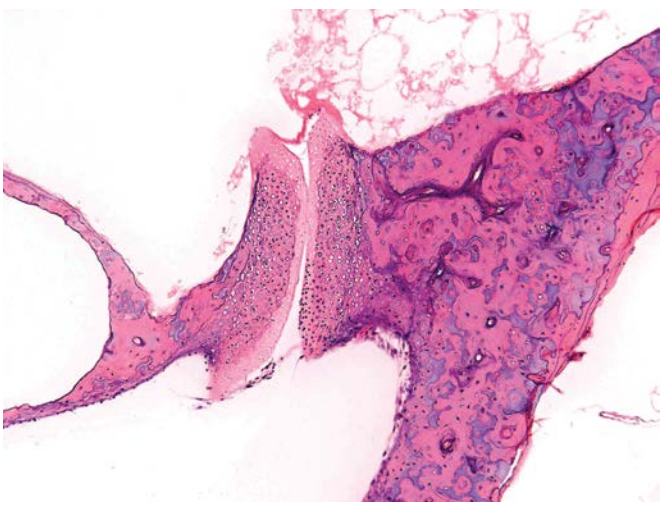
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are chemically induced models used in rodents and other species (e.g., monkeys). Of these, trinitrobenzene sulfonic acid (TNBS)-induced colitis, oxazolone-induced colitis, and dextran sulphate sodium (DSS)-induced colitis models are best known. TNBS elicits Th-1 driven immune response as seen with Crohn's disease, whereas oxazolone elicits a Th-2 response as seen in ulcerative colitis. In macaques, lymphoplasmacytic typhlocolitis is often an intractable cause of diarrhea in colony-housed animals. The pathogenesis of colitis in macaques is poorly understood; initial bacterial infection, subsequent hypersensitization to other antigens, and stress have all been implicated. Other idiopathic intestinal inflammatory diseases in monkeys include cicatrizing ulcerative colitis in macaques, and chronic colitis of callitrichids (cotton-top tamarins).

Infundibuloma, see the preferred term **Pituicytoma**.

Inhalation toxicology is the study of any adverse effects of an agent delivered by the inhalation route of administration. These studies typically are conducted using nose-only inhalation devices for rodents, and masks or hoods for non-rodent species. Delivered dose calculations have historically utilized the proportion of the administered dose with a particle size below the inhalation threshold, determined gravimetrically, or separate aerosol analysis of the test agent concentration and particle size distribution. Systemic exposure determined from plasma concentration measurements may also be used to determine the extent of exposure. Toxicity studies by the inhalation route are required for all pharmaceutical agents intended for pulmonary delivery.

Initiation is usually the first step in tumor formation, followed by tumor promotion and progression. Tumor initiation is generally thought to be irreversible, and is often associated with a mutation.

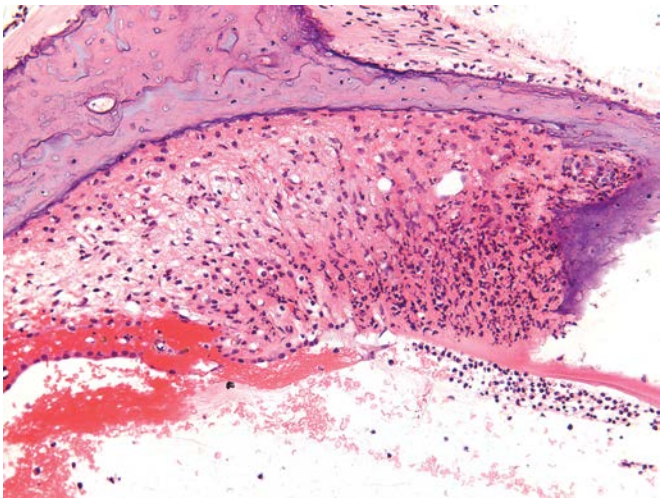


Inner ear cartilage necrosis, oval window footplates, chinchilla, H&E. (Image courtesy of K. Schafer, Vet Path Services, Mason, Ohio.)

Inner ear cartilage necrosis is characterized by the absence of nuclei in the lacuna of the cartilage of the footplates of the stapes and the corresponding rim of the oval window. Severe irritants instilled into the middle ear produce necrosis of the cartilage.

Inner ear edema consists of expansion of the mucosa in and around the cochlea by empty spaces or spaces containing fine granular or slightly eosinophilic (proteinaceous) material. Edema may involve one or more compartments of the cochlea, including the round window membrane and the scala vestibuli, scala media, and/or scala tympani (refer to Appendix 3 for further information). Injury to the lining epithelium of these tissues may result in edema and loose expansion of the mucosa in the spaces adjacent to the otic capsule (osseous labyrinth of the inner ear), and the modiolus (conical bony core of the cochlea). Injury and toxins or rarely infectious organisms may be the cause of the inflammation. Irritants may also induce fluid accumulation in the submembranous spaces adjacent to the bone due to injury to the lining epithelium.

Differential diagnosis: **Inner ear fibrosis**.

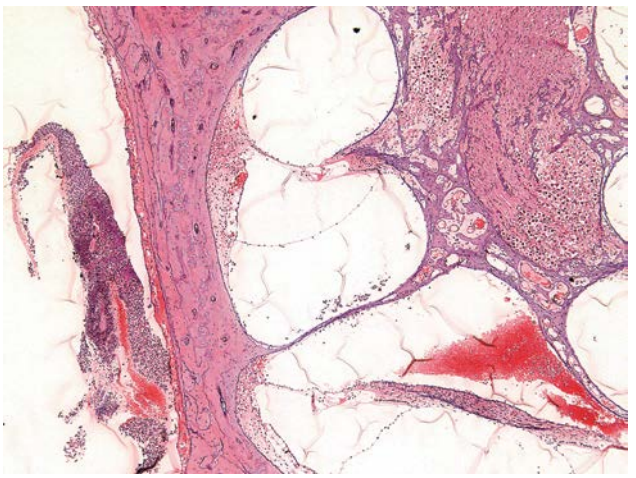


Inner ear edema with inflammation and hemorrhage, spiral ligament, chinchilla, H&E. See **Inner ear inflammation** and **Inner ear hemorrhage** for additional illustrations. (Image courtesy of K. Schafer, Vet Path Services, Mason, Ohio.)

Inner ear fibrosis consists of mature collagen replacement within the membranes of one or more of the round windows, scala vestibuli, scala media, and scala tympani. Fibroblasts originate from these membranes and other tympani compartments. Thickening of the membranes by loose connective tissue may also cause membrane irregularities with epithelial folds. Fibrosis is usually due to nonspecific irritants or injury, can be age related, and results in hearing loss.

Inner ear hemorrhage consists of free blood within the scala vestibuli, scala media, and/or scala tympani. Hemorrhage likely arises from the stria vascularis if in the scala media, and from the mucosal lining the wall if in the scala tympani and/or scala vestibuli. One must be mindful of blood contamination as a handling artifact.

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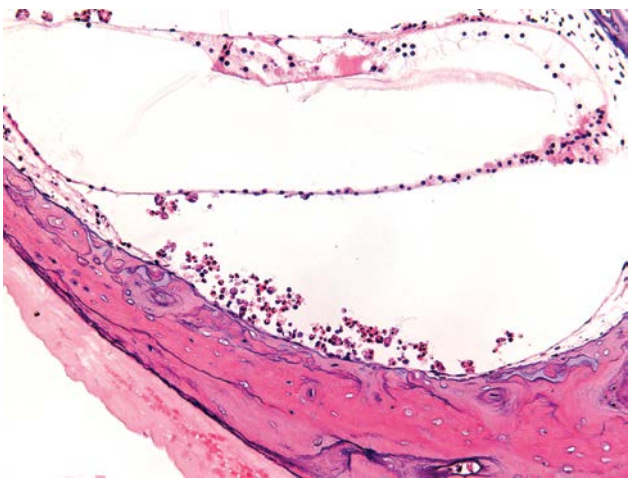


Inner ear hemorrhage associated with inflammation, cochlea, chinchilla, H&E. See **Inner ear edema** for an additional illustration. (Image courtesy of K. Schafer, Vet Path Services, Mason, Ohio.)

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Inner ear inflammation consists of focal or diffuse accumulations of inflammatory cells (neutrophils or heterophils [rabbit, chinchilla, and guinea pig], eosinophils, macrophages, lymphocytes, plasma cells, and multinucleated giant cells) within one or more compartments of the inner ear, particularly in fluid-filled spaces of the scala vestibuli, scala tympani, scala media, or in the lining of the cochlea (refer to Appendix 3 for further information). Proteinaceous exudates with few inflammatory cells may be a predominant finding. The predominant cell types depend on the cause and the duration of the inflammation. Inflammation may secondarily damage other ear components, including hair cells and stria vascularis (refer to Appendix 3 for further information). Infiltrates of inflammatory cells are usually a reflection of injury by a nonspecific irritant, but could potentially be due to infectious agents, which need to be distinguished from injury by a toxic insult. Nonspecific irritants, injury and toxins, or rarely infectious organisms may be the cause of the inflammation.

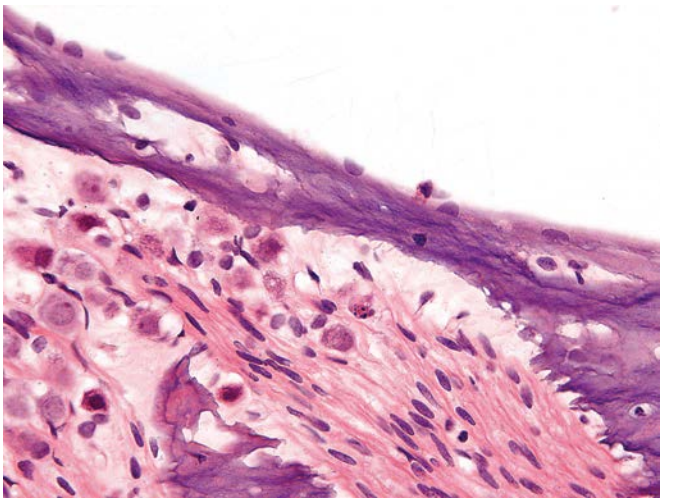
Synonym(s): **Otitis interna**.



Inner ear inflammation with cellular debris, cochlea, chinchilla, H&E. See **Inner ear edema** for additional illustration. (Image courtesy of K. Schafer, Vet Path Services, Mason, Ohio.)

Inner ear neuronal necrosis of the neuronal cell bodies of the spiral or vestibular ganglion results in shrunken and hypereosinophilic cytoplasm of the neurons.

Differential diagnosis: **Dark neuron artifact**.



Inner ear neuronal necrosis and spiral ganglion decreased cellularity, cochlea, chinchilla, H&E. (Image courtesy of K. Schafer, Vet Path Services, Mason, Ohio.)

Inner ear new bone formation consists of increased activity of osteoblasts and increased bone formation along the internal surface of the cochlea. Possible underlying causes include chronic irritants, injury, severe toxicity, or aging.

Inspissated material is a substance that has undergone an increase in density due to loss of fluid. Examples of inspissated material include thickened secretions in a duct (e.g., bile) or sinus. Protein-rich edema fluid and cell debris in an area of necrosis and inflammation can undergo inspissation. This condensed material may lead to blockage of the space in which it accumulates, serve as the beginning of a calculus, or be found in the center of an abscess or granuloma.

Interdigitating cell, see the preferred terms **Dendritic cell** and **Epidermal dendritic cell**.

Intermedin, see the preferred term **Melanocyte-stimulating hormone**.

Interspecies extrapolation, see **Allometric scaling** for further information.

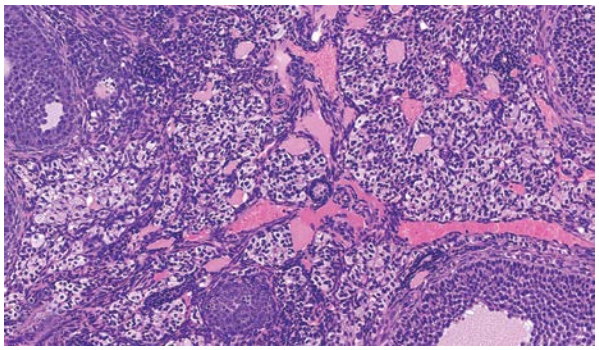
Interstitial cell adenoma, see the preferred term **Leydig cell adenoma**.

Interstitial cell hyperplasia, see the preferred term **Leydig cell hyperplasia**.

Interstitial cell hypertrophy is characterized by enlarged cells with increased cytoplasm that is usually clear or slightly eosinophilic. In age-related ovarian atrophy, interstitial cells will appear more abundant. Hypertrophy will occur with administration of gonadotropins (LH). See **Leydig cell hypertrophy** for further information.

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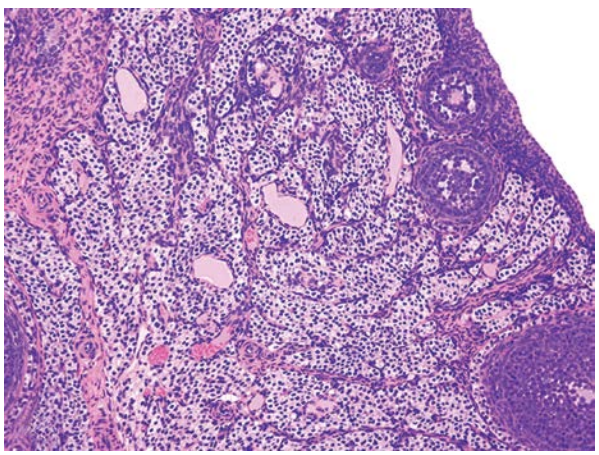
Interstitial cell-stimulating hormone (ICSH) is a type of luteinizing hormone produced in males that stimulates Leydig cell production of testosterone.



Interstitial cell hypertrophy, ovary, mouse, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Dixon et al. 2014.)

Interstitial cell tumor, benign, see the preferred term **Leydig cell adenoma**.

Interstitial cell vacuolation consists of vacuolation that is more than the normal fine cytoplasmic vacuolation observed. Xenobiotic-induced inhibition of steroid synthesis or phospholipidosis are primary rule-outs.



Interstitial cell vacuolation, ovary, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Dixon et al. 2014.)

Interstitial nephritis is focal (or occasionally generalized) interstitial (i.e., intertubular) infiltration of mononuclear inflammatory cells, usually dominated by lymphocytes, plasma cells, and/or macrophages. There may also be increased fibrosis, thus chronic interstitial nephritis.

Intestinal adenocarcinoma is a malignant neoplasm arising from enterocytes of the intestinal mucosa characterized by invasion through muscularis mucosa or deeper layers of the intestinal wall. The pattern of neoplastic growth may be solid, papillary, mucinous, signet ring, cystic, and/or scirrhous type. Refer to **Gastrointestinal Tract** in Appendix 2 for further information.

Differential diagnoses: **Intestinal diverticulum**; **Intestinal atypical mucosal hyperplasia**; **Intestinal adenoma**.

Synonym(s): **Intestinal carcinoma**.

Intestinal adenoma is a polypoid, sessile, or papillary neoplasm arising from enterocytes. Intestinal adenomas may be associated with glandular or cystic diverticula and progress to a malignant type in experimentally induced neoplasms. Refer to **Gastrointestinal Tract** in Appendix 2 for further information.

Differential diagnoses: **Intestinal diverticulum**; **Intestinal atypical mucosal hyperplasia**; **Intestinal adenocarcinoma**.

Synonym(s): **Intestinal polyp**; **intestinal adenomatous polyp**.

Intestinal amyloid is an extracellular deposit of polypeptide fragments of a chemically diverse group of glycoproteins in intestinal mucosa, connective tissue, and/or blood vessel walls. The spontaneous incidence of systemic amyloid deposits, predominantly in lamina propria of intestinal villi, is rare in BALB/c, C3H, and B6C3F1 mice but common in CD-1, C57B6, albino, Swiss Webster, SJL mice, and Syrian hamsters, and is extremely rare in rats. A number of factors including sex, diet, housing conditions, stress, endocrine status, and microbiological/parasitic status are reported to influence the occurrence of amyloid in susceptible strains of mice. The incidence of amyloid also increases with age. Histologically, amyloid appears as pale amorphous, homogenous eosinophilic material with hematoxylin and eosin (H&E) stain and shows apple green birefringence under polarized light (Congo red stain). Drug-induced amyloidosis is extremely rare in nonclinical species and humans. Amyloid can be induced in susceptible strains of mice with casein, silver nitrate, and lipopolysaccharide administration. Rats tend to be resistant to xenobiotic-induced amyloid deposits.

Synonym(s): **Intestinal amyloidosis**; **Intestinal amyloid deposition**.

Intestinal amyloid deposition, see the preferred term **Intestinal amyloid**.

Intestinal amyloidosis, see the preferred term **Intestinal amyloid**.

Intestinal atypical herniation, see the preferred term **Intestinal diverticulum**.

Intestinal atypical "'pseudoinvasion," see the preferred term **Intestinal diverticulum**.

Intestinal crypt abscess is often associated with severe inflammation of the intestinal mucosa where crypts are filled or distended with acute inflammatory cells, mucus, bacteria, and necrotic cell debris. Crypt abscesses are reported in several animal models of irritable bowel disease (IBD). It is also noted in various infectious diseases such as Tyzzer disease in the mouse, rat, and hamster, transmissible ileal hyperplasia in the hamster, *Giardia muris* infection in mice and rats, *Citrobacter rodentium* infection in mice, and Campylobacter infection in rodents, dogs, and monkeys.

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Intestinal crypt herniation is an invagination of the mucosal crypts of Lieberkühn into underlying lymphoid tissue (lymphoid aggregates and Peyer patches) of the large and small intestine. Although often noted as a spontaneous finding, it is also associated with mucosal inflammation and depletion of the underlying lymphoid tissues. Penetration of mucosal structures into the deeper layers beyond the muscularis mucosa may be described as crypt herniation but can also be described as a diverticulum.

Intestinal cystic or atypical diverticulum, see the preferred term **Intestinal diverticulum**.

Intestinal dilatation is a macroscopic finding characterized by dilatation of the lumen due to a defect in neuromuscular function in animals and humans, or due to changes in gut microflora in rodents. Histologically the mucosa, submucosa, and muscularis of the affected part of intestine appear thin due to expansion of the lumen. Degeneration of the muscle fibers and ganglia cells in the nerve plexus may be present. Tribromoethanol (Avertin) and chloral hydrate administered intraperitoneally as an anesthetic has been associated with dilatation of the ileum in rodents. Treatment of rodents with antibiotics also causes cecal enlargement (dilatation) without significant histopathological changes, probably as a result of changes in the cecal microflora. Administration of some antibiotics, starches, polyols, lactose, fibers, and vehicles that have an osmotic effect can also cause an enlarged, dilated cecum in rodents. Megaileus with inflammation (megaileitis) characterized by a necrotizing transmural ileitis with necrosis of the mucosa and muscularis, edema, and predominantly infiltration of mononuclear cells is sometimes seen in rats with Tyzzer disease (infection with *Clostridium piliforme*). Treatment of rats with calcium channel antagonists can cause megacolon as a result of constipation.

Differential diagnosis: Intestinal distention.

Synonym(s): **Intestinal dilation**; **megaileus**; **cecomegaly**; **megacolon**.

Intestinal dilation, see the preferred term **Intestinal dilatation**.

Intestinal diverticulosis, see the preferred term **Intestinal diverticulum**.

Intestinal diverticulum is morphologically similar to diverticulum of glandular stomach (refer to **Glandular stomach diverticulum** for further information). Spontaneous and induced intestinal diverticula occur more frequently in mice, especially Cdx-2 knockout mice.

Differential diagnoses: **Intestinal adenoma**; **Intestinal adenocarcinoma**.

Synonym(s): **Intestinal cystic adenomatous hyperplasia**; **intestinal diverticulosis**; **intestinal atypical cystic hyperplasia**; **intestinal cystic hyperplasia with growth into the intestinal wall**; **intestinal cystic adenomatous hyperplasia**; **intestinal atypical herniation**; **intestinal atypical "pseudoinvasion"**; **intestinal atypical hamartoma**.

Intestinal ectopic tissue is characterized by the presence of morphologically normal-appearing pancreatic acinar cells in the mucosa or submucosa of the intestines; this finding may also contain islets of Langerhans.

Intestinal erosion/ulcer is localized loss of the mucosa due to necrosis with either partial mucosal penetration (erosion) or with full penetration of the mucosa to the muscularis mucosa (ulcer). It is often associated with submucosal edema, hemorrhage, hemosiderin pigmentation, bacterial infection, inflammation, granulation tissue, fibrosis, and regenerative epithelial hyperplasia. Administration of nonsteroidal anti-inflammatory agents, cytotoxic anticancer drugs, ionizing radiation, cysteamine, propionitrile, and 1-methy-4-pheny-1,2,3,6-tetrahydropyridine (MPTP) are capable of producing erosion/ ulcers of intestines. Erosion and ulceration are commonly observed in immunodeficient mice or rats, due to viral and bacterial infections. This lesion is typically diagnosed under the single, combined term of erosion/ulcer with an appropriate severity grade in most instances.

Intestinal infiltrate is characterized by an inflammatory cell infiltration of the lamina propria and/or submucosa of intestines with neutrophils (infiltrate, neutrophil), eosinophils (infiltrate, eosinophil) or mononuclear cells (infiltrate, mononuclear cell) or a combination (infiltrate, mixed) without other histological features of inflammation such as hemorrhage, edema, or fibroplasia. Intestinal infiltrates are normally present in laboratory animals.

Intestinal inflammation can be focal, multifocal, or diffuse infiltration of the lamina propria and/or submucosa with neutrophils (neutrophil inflammation) or mononuclear cell (mononuclear cell inflammation) or a combination (mixed cell inflammation), and associated with additional histological features of inflammation (e.g., hemorrhage, edema, fibroplasia). Administration of nonsteroidal anti-inflammatory agents and antimitotic anticancer agents are common causes for neutrophilic and mixed cell inflammatory lesions with fibrosis in both humans and laboratory animals. Because of the presence of numerous commensal bacteria in the intestine, inflammatory changes are noted after any nonspecific loss of mucosa/submucosa followed by a variable fibroblastic response. The reactive responses of adjacent epithelial cells may be intense, and in some cases may even mimic preneoplastic alterations.

Intestinalization, see the preferred term **Intestinal metaplasia**.

Intestinal metaplasia occurs when epithelium of one type becomes replaced with a specialized intestinal columnar epithelium, typically containing goblet cells. It can be seen

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in the esophagus and pylorus of rats. This change is associated with significant risk of progression to dysplastic epithelial change and ultimately, neoplastic transformation. It also occurs in the stomach, sometimes replete with brush border, intestinal enzyme secretion (alkaline phosphatase), and other features of intestinal epithelium. When of a well-developed, small intestinal type, it is referred to as "complete" metaplasia, whereas "incomplete" forms more resemble colonic epithelium, with mucin droplets in the cytoplasm and absence of a brush border. In rodents, it has been noted in the context of gastric cancer induced by polychlorinated biphenyls and variably with genotoxic carcinogens such as n-methyl-n-nitro-n nitrosoguanidine. Despite the association with cancer in some circumstances, it may also occur in association with other nonneoplastic conditions such as radiation or *Helicobacter* infection. As such, it is not considered to always represent a preneoplastic change.

Synonym(s): **Intestinal metaplasia**.

Intestinal mucosal atrophy is characterized by a reduction in villus height, villus number, and crypt length with dilated crypts in the small intestine. Atrophy change in the large intestine is characterized by a decrease in size and number of mucous cells in shortened glands leading to a reduction in mucosal thickness. Atrophy of the mucosa may be related to reduced mitotic capabilities and/or increased cell loss through apoptosis or necrosis that results in reduced depth of crypts in the small intestine, and mucous glands in the large intestine. Villous and mucosal atrophy without damage to the underlying lamina propria or to the proliferative cell population is typically reversible. Sustained reduced mitotic capabilities and/or increased cell loss through apoptosis or necrosis with damage to the lamina propria may be followed by erosion/ulceration, hemorrhage, and secondary infection. Atrophy of the intestinal mucosa is observed after fasting, parenteral nutrition, hypophysectomy, thyroidectomy, and in segments of surgically bypassed intestine in rodents. Ionizing radiation, T-2 toxin, ricin, triparanol, alpha1 receptor agonist, alpha2 receptor antagonist, several anticancer, antiviral, cytostatic, and cytotoxic agents induce villous stunting by inhibition of mitosis in the precursor cells of the crypts.

Differential diagnosis: **Intestinal dilatation**.

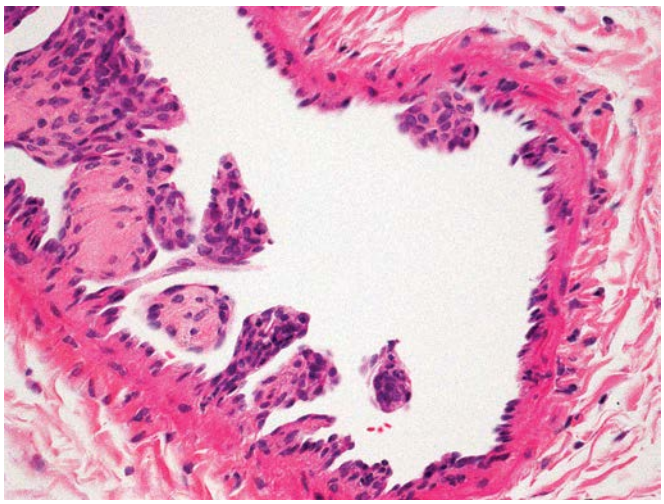
Intestinal squamous cysts are lined by keratinized stratified squamous epithelium in the mucosa, muscularis, or serosa of the small and large intestines. The lumen frequently contains keratinized material. Squamous cysts are often congenital in origin and have been described in the muscularis of the colon and rectum of rodents. Cysts can occur secondary to a variety of pathological changes of the epithelium, often in response to inflammatory processes. They are thought to be associated with focal weakness or discontinuity of the muscularis resulting in herniation through the submucosa and mucosa to the serosa.

Differential diagnoses: **Meckel diverticulum**; **Intestinal cystic or atypical diverticulum**.

Intimal proliferation is the expansion of the tunica intima of an artery or vein; it can be segmental or circumferential and asymmetrical or symmetrical. This change is caused by the propagation of smooth muscle cells or, less likely, fibroblasts. Intimal proliferation has been reported as a spontaneous finding and as a drug-induced change (e.g., allylamine, phosphodiesterase inhibitors), and as a finding caused by mechanical trauma (e.g., chronic indwelling venous catheters) in multiple species.

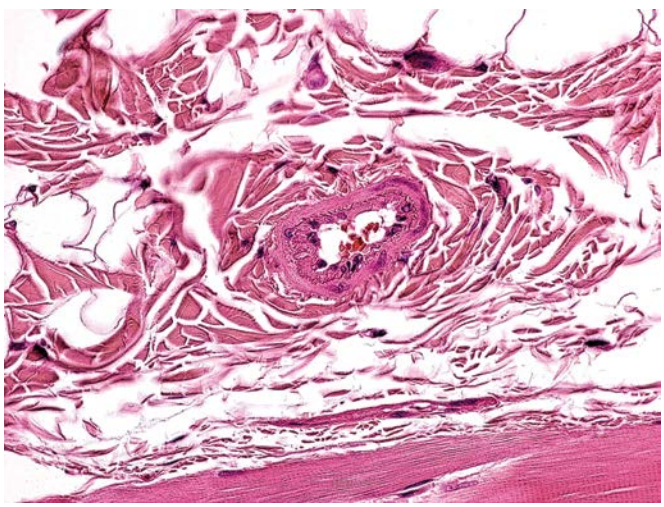
Differential diagnoses: **Intimal thickening**; **Arterial intramural plaque**.

Synonym(s): **Arterial intimal hyperplasia**.



Intimal proliferation, indwelling catheter site, rat, H&E. (Image courtesy of Malcolm Gains.)

Intimal thickening develops due to the deposition of an acellular matrix within the intima of blood vessels, between the endothelium and elastic lamina. The composition of the matrix has not been identified. This change has been seen in the vasculature of the subcutis and dermis of Sprague Dawley rats. In spontaneously hypertensive rats, smooth muscle cells



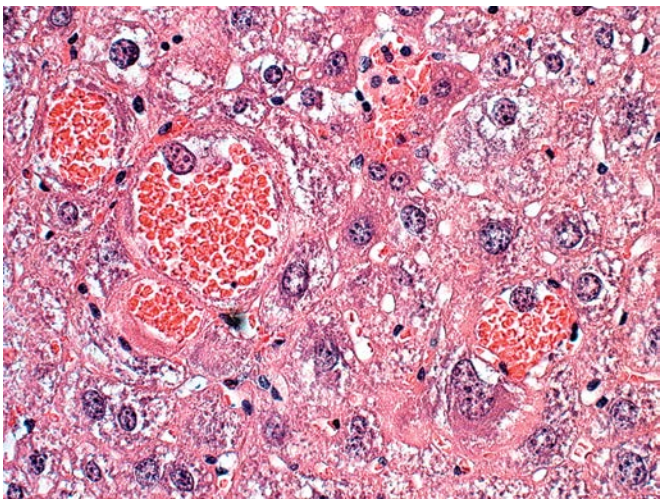
Arterial intimal thickening, subcutis, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology.)

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and fibroblasts may gradually infiltrate the acellular material. The pathogenesis of this change is unknown.

Differential diagnosis: **Intimal proliferation**.

Intrahepatocellular erythrocytes is the presence of single or small clusters of markedly enlarged hepatocytes containing intact erythrocytes containing a peripherally located nucleus. Affected hepatocytes are enlarged, often with eccentric nuclei.



Intrahepatocellular erythrocytes, mouse liver, H&E. (Reproduced with permission of the Society of Toxicologic Pathology from Thoolen, B. et al. 2010. *Toxicol Pathol* 38(7 Suppl):5S–81S.)

It has been observed in mice and may be observed as either a spontaneous or treatment-related effect. There is no known functional consequence, and the underlying mechanism is unknown.

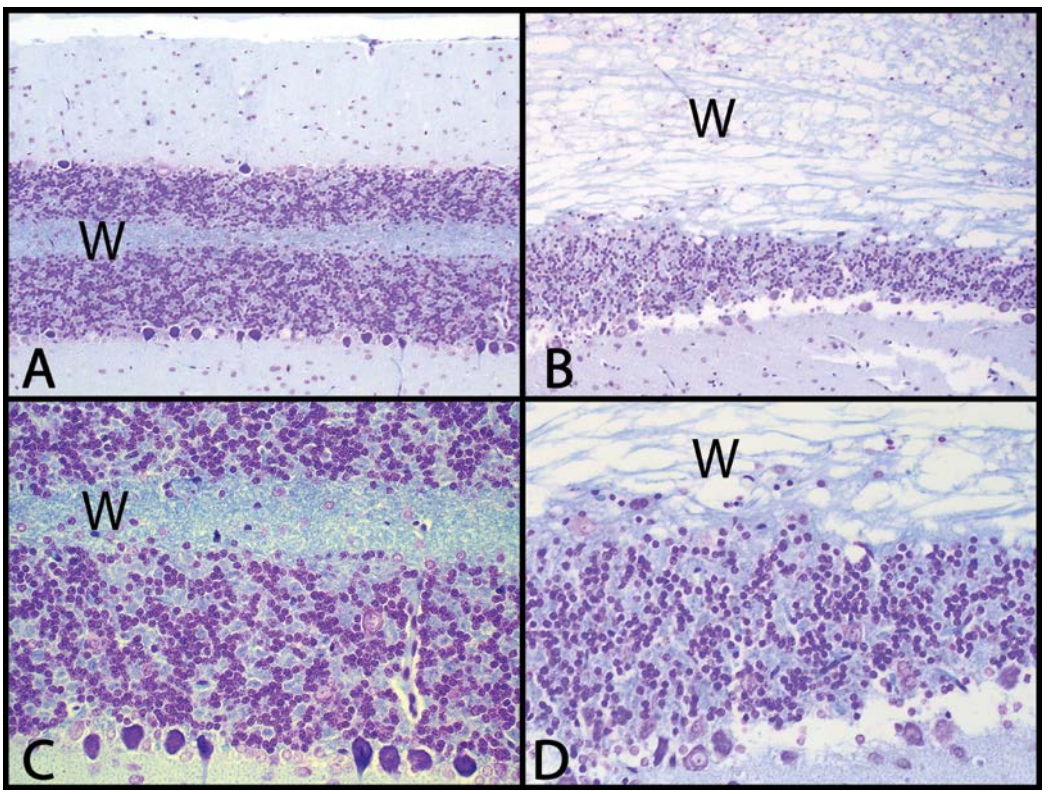
Differential diagnoses: **Hepatic angiectasis**; **Hepatic cystic degeneration**.

Synonym(s): **Emperipolesis**; **cytoplasmic inclusions**; **hepatic erythrophagocytosis**.

Intramucosal neuroendocrine cell tumor, see the preferred term **Stomach neuroendocrine cell tumor, benign/malignant**.

Intramural schwannoma is a less common tumor of intramural Schwann cells which appear as poorly defined bundles of polygonal or fusiform cells. Intramural schwannomas generally arise within the left ventricular wall or intraventricular septum, appearing as discrete nodular masses, and are less well delineated and more invasive than endocardial Schwannomas, sometimes interdigitating with the surrounding myocardial fibers. Refer to **Cardiovascular System** in Appendix 2 for further information.

Intramyelinic edema is an accumulation of edema fluid between layers of axonal myelin. Microscopically the edema appears as a vacuolar change of the myelin surrounding the axon, conferring a spongiform appearance to the tissue when larger areas are affected. Transmission electron microscopy (TEM) is confirmative and



Intramyelinic edema, hexachlorophene toxicity, rat. (A & C) Control. Normal thickness of cerebellar cortical white matter (W). (B & D) Hexachlorophene treatment. Marked expansion and pallor of the cerebellar cortical white matter (W) due to the edematous changes. Rat. Luxol fast blue and Cresyl Violet stain. (Copyright 2018 Georg Krinke, AnaPath GmbH, Switzerland. Used with permission.)

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reveals separation of myelin lamellae at the intraperiod line of oligodendrocytes (CNS) or Schwann cells. Swelling of the cell body may also occur as part of this process. Secondarily, there may be degeneration of myelin, cell bodies, and/or axons; however, in the absence of these sequelae, intramyelinic edema may be a reversible change. Some lipophilic toxins that cross the blood-brain barrier may cause intramyelinic edema. Hexachlorophene, once ubiquitous as an antimicrobial additive to soaps and detergents, is a classic example, causing an uncoupling of mitochondrial oxidative phosphorylation and a breakdown of the normal Na^+-K^+ pumps that maintain integrity of the myelin sheath. Hexachlorophene has a pronounced effect along the optic tract; however, other compounds may affect different regions. In addition to TEM, immunohistochemistry (glial fibrillary acidic protein [GFAP]) may be useful to exclude astrocytes as the source of vacuolar change. In rodent models as well in humans with natural disease, magnetic resonance imaging (MRI) is used to diagnose and map the occurrence of this finding (see figure at the previous page bottom).

Synonym(s): **Myelin edema**; **myelin vacuolation**; **leukoencephalopathy**.

Reference: https://ntp.niehs.nih.gov/nnl/nervous/brain/inmyeledem/index.htm

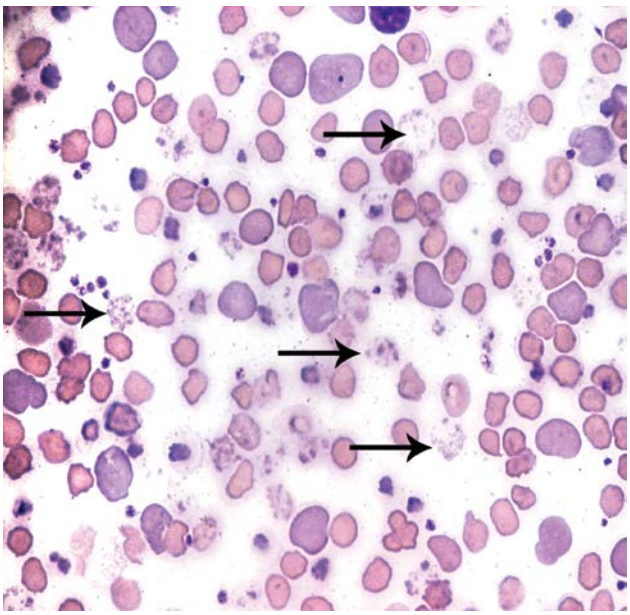
Intranuclear cytoplasmic invagination, see the preferred term **Inclusion body, pseudoinclusion**.

Intraocular malignant melanoma, see the preferred term **Uveal melanoma**.

Intraocular schwannoma is a rare, malignant tumor of Schwann cells of intraocular ciliary nerves in rats and mice and other laboratory animals. The lesion is located in the iris and involves the ciliary body (uvea), invades the cornea, and fills the anterior chamber. Refer to **Special Senses** in Appendix 2 for further information.

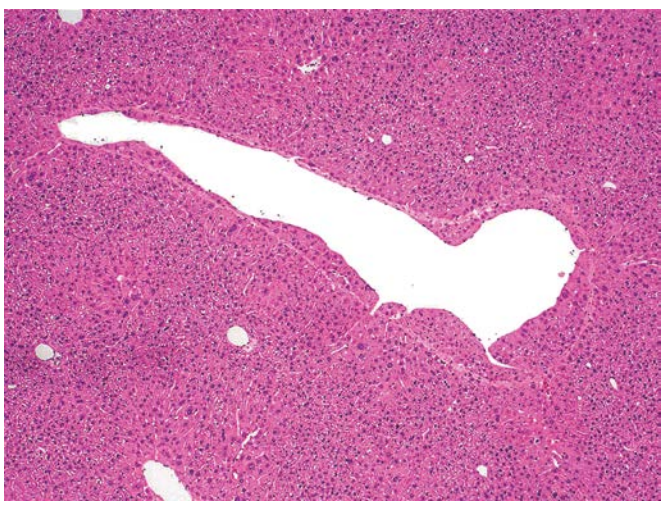
Intrauterine growth retardation (IUGR) is a feature of a newborn with low birth weight. The most severely affected has been described as a "runt."

Intravascular hemolysis refers to the lysis of red blood cells with the release of hemoglobin. Intravascular hemolysis refers to red cell destruction that occurs within the circulation and is associated with hemolytic anemia, hemoglobinemia, and hemoglobinuria. There are four major categories of factors that accelerate red cell removal including the following: abnormalities of cell shape or size (e.g., spherocytosis, elliptocytosis, schistocytes, sickle cells), membrane defects (e.g., abnormalities of ankyrin, or sialoproteins), external factors (e.g., oxidative damage, complement lysis, heat-induced damage, trauma), and dysfunction of vasculature or organs (e.g., splenomegaly, microangiopathy, abnormal shear forces, prosthetic valves). Profound intravascular hemolysis can be detected as reddish-brown plasma in a centrifuged blood sample and/or red urine. Other suggestive findings of intravascular hemolysis include increased levels of serum LDH and indirect bilirubin, decreased serum haptoglobin, and increased urinary urobilinogen.



Severe hemolytic anemia, blood smear, B3C3F1 mouse, administered phenylhydrazine. Note marked polychromasia, spherocytosis, and fragmentation of red blood cells. Because the mouse has more limited clearance than other species, ghost-cell fragments (arrows) remain in circulation longer following intravascular hemolysis.

Intravascular hepatocytes refer to the subintimal proliferation of hepatocytes in the wall of medium and large sized hepatic veins. These hepatocytes protrude into the lumen of the affected veins and the change appears to be limited to livers in mice. Although the endothelial lining remains intact, these protrusions are sometimes mistaken for evidence of intravascular invasion, particularly when observed following



Intravascular hepatocytes, mouse liver, H&E (Reproduced with permission of the Society of Toxicologic Pathology from Thoolen et al. 2010.)

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administration of a carcinogen. It is only rarely observed in either control or treated mice.

Intravenous injection is the administration of a solution directly into the venous system, typically done by sterile needle and syringe with a rapid or slow push on the syringe plunger. This represents the mode of administration that will achieve the highest systemic concentration of the injectate, bypassing the various natural systemic absorption barriers (e.g., skin, gastrointestinal mucosa).

Intron is the noncoding part of a gene within the genome. Introns are removed upon mRNA splicing from pre-mRNA during transcription.

Intussusception is the inversion or "telescoping" of one segment of the intestine into another. The invaginated (usually proximal) portion is called the intussusceptum and the receiving (usually distal) portion is called the intussuscipiens. In humans, it occurs more commonly in children. Many instances are idiopathic, however obstructive or inflammatory lesions may precipitate an event, presumably by interfering with normal peristaltic motion. Mechanistically, the same mechanism generally applies across species. One review of dogs and cats identified the enterocolic junction as most frequently involved, with abdominal pain, palpable mass, and in some cases, bloody diarrhea. In animals, heavy infestation with intestinal parasites is also a consideration in occurrences of intussusception. In a beagle, intraperitoneal injection of the mycotoxin citrinin caused peritonitis and intestinal intussusception. As a spontaneous finding in beagles, it has been reported at an incidence of 0.1%. Experimentally, rotaviral infection was thought to sensitize mice to the inflammatory effects of LPS toxin, resulting in an intussusception in some instances.

In utero refers to "in the uterus" and is the standard reference relative to gestation.

Investigator's Brochure (IB) is a document that provides a clinical investigator with clinical and nonclinical information about an investigational new drug that is relevant to the study with that drug in human subjects.

In vitro stems from the Latin term "in glass" and in practice is used to describe the chemical or biological systems in an artificial environment meant to simulate natural conditions within the body or living organism (e.g., cells or tissues growing in media in culture plates outside their natural environment within a biologic or ecosystem). In toxicology, they are used to determine the potential effects of a chemical agent or an experimental drug compound. See **In vitro toxicity tests** for further information.

In vitro toxicity tests use an in vitro model to evaluate endpoints reflective of tissue or cellular injury in a living organism. These tests are generally limited to cell or organ system models designed to react to chemical insult in a manner that correlates with biophysical and/or biochemical changes associated with adverse events in a living organism. In vitro toxicity tests with relevance to the cell, tissue, or organ system of interest are important tools in screening, and for the ultimate goal of reducing the use of whole (living) animals in toxicity testing.

In vivo stems from the Latin term "in or within, the living" and in practice is used to describe "in the whole animal or organism," rather than in isolated cells or tissues.

In vivo toxicity tests are studies conducted in whole animals. In toxicology, they are used to determine the potential adverse effects of a chemical or an experimental compound. These include single and repeat-dose toxicity studies, in vivo genotoxicity studies, reproductive toxicity studies, carcinogenicity studies, and studies with special endpoints such as immune toxicity and dependency.

Involucrum refers to an area of reactive bone which encapsulates a separated piece of necrotic bone (sequestrum) from adjacent living tissue.

Involution is a physiological process characterized by the return of a tissue with the potential to enlarge and increase in function to its quiescent state following functional use of the organ. This is best understood in the context of the uterus and mammary glands, where pregnancy induces hypertrophy and hyperplasia of both tissues. The thymus is another example where self-reactive lymphocytes are eliminated by apoptosis during the process of thymic development (at a young age), resulting in a smaller thymus in the adult. Other tissues that may undergo involution include lymph nodes draining one area, or throughout the body following resolution of an immune response.

Iridal-corneal adhesion, see the preferred term **Iris adhesion**.

Iridal fetal membrane, see the preferred term **Vitreal persistent fetal vasculature (PFV)**.

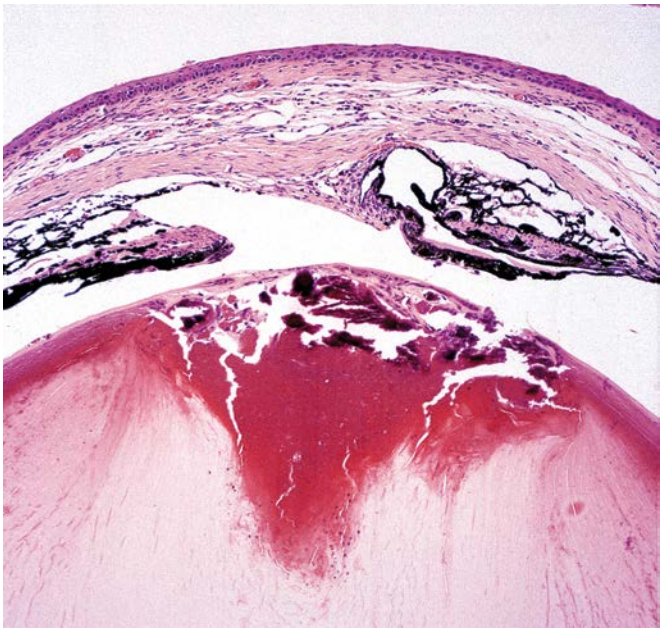
Iridocorneal fibroplasia or strands, see the preferred term **Iris adhesion**.

Iridocyclitis, see the preferred term **Iris inflammation**.

Iris adhesion is an abnormal fibrovascular or fibrous attachment across the iris or between the iris and adjacent structures, including the posterior cornea (anterior adhesion), lens (posterior adhesion), and trabecular meshwork (peripheral anterior adhesion). This adhesion may occur as a malformation in rats but rarely in mice. Iris adhesions are acquired in association with cataracts, trauma, degeneration, inflammation, neoplasms, and laser photocoagulation in the anterior chamber or the iris and ciliary body. Contraction of an adhesion on the lens may contribute to lens dislocation. Posterior adhesions may block the flow of aqueous humor and contribute to glaucoma.

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Synonym(s): **Anterior synechia (cornea)**; **posterior synechia (lens)**; **iridocorneal fibroplasia or strands**; **iridal-corneal adhesion**.



Iris adhesion (anterior adhesion to cornea and posterior adhesion to lens) with lens fiber degeneration, mineralization and epithelial fibroplasia, C57BL/6 mouse, H&E. See **Lens capsule hypertrophy** for an additional illustration.

Iris atrophy is thinning and loss of the iris stroma and vasculature resulting in irregular architecture. Posterior epithelial cells may be enlarged and contain pigment, and the ciliary processes may be enlarged. This occurs as a spontaneous malformation in mice and dogs, and is an age-related change associated with glaucoma or secondary to chronic inflammation or diseases in most species.

Synonym(s): **Iris degeneration**.

Iris congestion or erythrocyte pooling in dilated blood vessels of the iris commonly occurs during postmortem pooling of blood, and this diagnosis should be used as a clinical and not a histopathology term.

Differential diagnosis: **Iris vascular dilation**.

Iris decreased pigmentation consists of decreases in the size or number of melanocytes and decreased melanin pigment in the stroma of the iris in pigmented strains of animals. Pigment changes may be congenital or found with atrophy and inflammation but is most frequently age related.

Synonym(s): **Iris discoloration**; **alteration in iris color**.

Iris degeneration, see the preferred term **Iris atrophy**.

Iris discoloration, see the preferred term **Iris increased pigmentation**.

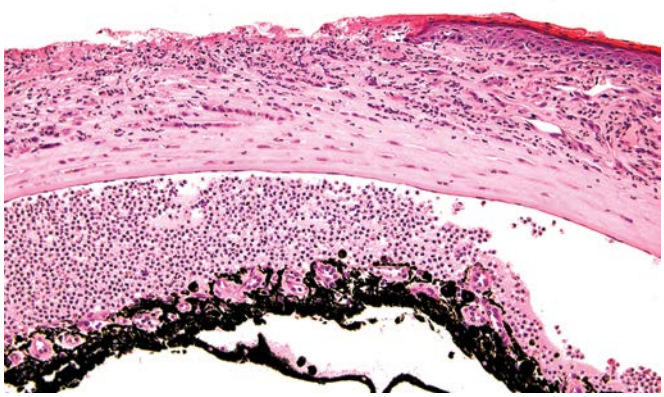
Iris epithelial cytoplasmic vacuolation consists of well-demarcated, clear spaces within the pigmented and nonpigmented epithelial cells of the iris as a result of injury and/or metabolic changes. This finding occurs in association with several diseases, and from administration of xenobiotics (disobutamide and 6-aminonicotinamide) and cationic amphiphilic drugs that induce phospholipidosis. Vacuoles may also be associated with decreased pigmentation, and present in other ocular compartments (see **Corneal vacuolation**; **Ciliary body epithelial cytoplasmic vacuolation**; **Lens vacuolation**; **Retinal cytoplasmic vacuolation**; **Retinal extracellular vacuolation**; **Retinal pigment epithelium vacuolation**). Vacuoles may also be an artifact from delays in fixation. See **Lysosomal storage disease**; **Phospholipidosis**; **Lipid accumulation**; **Fatty change**; **Mucopolysaccharidosis** for further information.

Iris increased pigmentation consists of increases in the size or number of melanocytes and increased melanin pigment in the stroma of the iris in pigmented strains of animals. Pigment changes may be congenital or found with inflammation or aging. Latanoprost, a topical administered for the treatment of glaucoma, causes irreversible increased pigmentation in humans and animals. Sloughing of heavily pigmented cells into the filtration angle may occlude the trabecular meshwork and contribute to glaucoma.

Differential diagnoses: Intraocular melanoma; Melanocyte hyperplasia.

Synonym(s): **Iris discoloration**; **alteration in iris color**.

Iris inflammation consists of focal or diffuse accumulations of inflammatory cells (granulocytes or heterophils [rabbit], macrophages, lymphocytes, plasma cells, and multinucleated giant cells) in the iris, often with involvement of the ciliary body, choroid, the anterior and posterior chambers, vitreous, and retina. The inflammation may be accompanied by edema, hemorrhage, altered uveal pigmentation, fibrosis, and adhesions. Inflammation may be secondary to trauma, malformations, infections, hyperglycemia, and



Iris inflammation with corneal inflammation and ulcer, B6C3F1 mouse, H&E. See **Filtration angle narrowed** for an additional illustration. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

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neoplasms. The uvea is a major target of autoimmune disorders. Iridal inflammation may occur after administration of chemicals and xenobiotics such as cyclophosphamide, and after intravitreal injection or the implantation of medical devices. Severe inflammation may extend throughout the eye and result in phthisis bulbi.

Differential diagnosis: **Iris inflammatory cell infiltrate**.
Synonym(s): **Uveitis**; **iritis**; **iridocyclitis**.

Iris inflammatory cell infiltrate is the presence of small numbers of leukocytes within the iris stroma and epithelium, in the absence of inflammatory changes (edema, congestion, hemorrhage, and necrosis or cellular debris).

Iris malformation, see the preferred term **Optic fissure malformation**.

Iris persistent pupillary membrane, see the preferred term **Vitreal persistent fetal vasculature**.

Iris vascular dilation is erythrocyte pooling in dilated blood vessels of the iris in the presence of concurrent inflammation.

Iritis, see the preferred term **Iris inflammation**.

Irreversible effect(s) is a change in a tissue or test system that precludes the return of normal function or structure, usually assessed over a defined period of time.

Irritants are a classification of chemicals that result in biochemical and/or biophysical changes such as soreness or irritation at the site of exposure, either topically (e.g., skin, eye) or in an internal organ system (e.g., gastrointestinal tract, pulmonary tree).

Irwin test is a set of observations that may be incorporated into a rodent toxicity study to determine the effects of a compound on behavior and physiological function, particularly as related to the central nervous system. It may also be termed a functional observation battery (FOB); endpoints assessed may be classified as autonomic, neuromuscular, sensorimotor, and behavioral (see figure below).

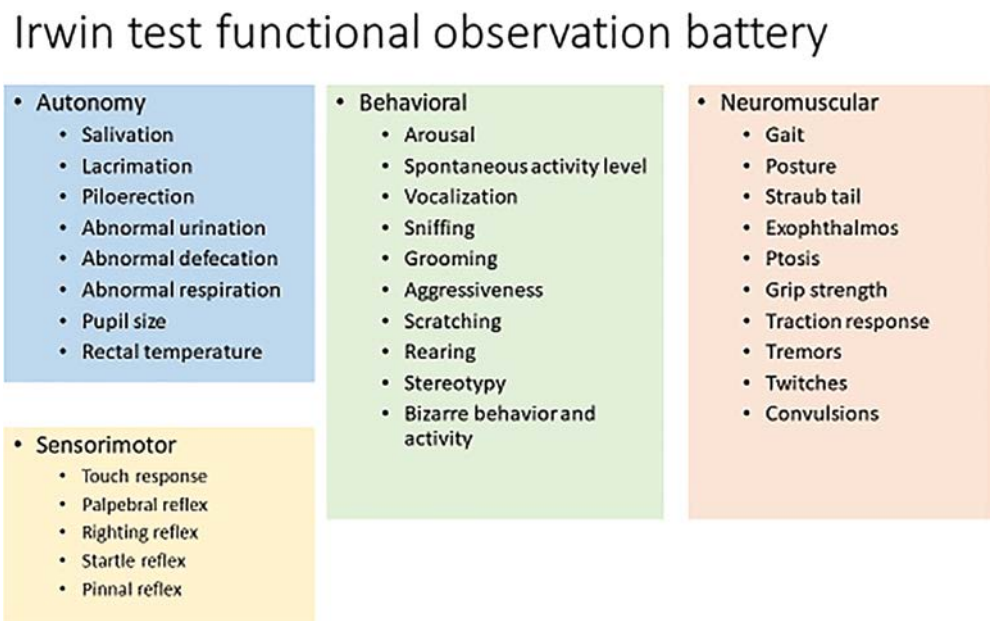
Ischemia is the interruption or loss of normal blood flow to a tissue. Vessels can be blocked by an obstruction (e.g., embolus, thrombus). Blood flow can also be interrupted secondary to vasoconstriction and forces such as trauma, compression, and shear forces. This loss can be transient and associated with little tissue degeneration or be more prolonged and result in necrosis. There is tissue variability in sensitivity to loss of oxygenation (hypoxia) resulting from ischemia. For example, the brain is highly sensitive to ischemia, which can lead to ATP depletion and biochemical changes that result in cellular injury and necrosis. Ischemia affecting skeletal muscle is better tolerated. Blood flow restoration to tissues with reversible damage supports recovery; however, cellular injury can also be increased during reperfusion through free radical generation, inflammation, and biochemical alterations (i.e., ischemia-reperfusion injury).

Ischemic cell change, see the preferred term **Retinal single cell necrosis**.

Islet-acinar tumor benign, see the preferred term **Acinar-islet cell tumor, benign**.

Islet-acinar tumor malignant, see the preferred term **Acinar-islet cell tumor, malignant**.

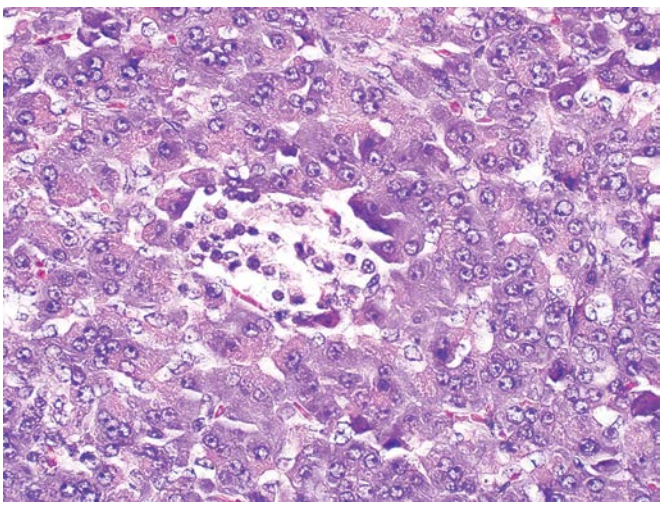
Islet atrophy rarely occurs spontaneously in the pancreas of aged rodents and other lab animals; however, it is better



The Irwin functional observation battery showing the nervous system function assigned to the various observations.

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described from rodent models of diabetes. The islets may be smaller in diameter and composed of islet cells that have decreased cytoplasm. Atrophy primarily affects the β cells (decreased number), and there is typically an increase in non-β cells within the islets. Alpha (α) cells become randomly distributed throughout the islet rather than the normal peripheral distribution. It most commonly occurs in diabetic animals and may progress to islet fibrosis.



Pancreas, atrophy, islet, cynomolgus monkey, H&E.

Islet cell adenoma, benign is a neoplasm (adenoma) composed of cells from the islets of Langerhans. See Appendix 2 for more information.

Islet cell carcinoma, malignant is a neoplasm composed of the cells of the islets of Langerhans, usually β cells, and is locally invasive, and composed of cells that are more atypical/pleomorphic with frequent mitoses as compared to adenomas. See **Endocrine Glands** in Appendix 2 for more information.

Islet cell hyperplasia, see the preferred term **Endocrine pancreas cell hyperplasia**.

Islet cell tumor benign, see the preferred term **Islet cell adenoma, benign**.

Islet cell tumor malignant, see the preferred term **Islet cell carcinoma, malignant**.

Islet fibrosis is characterized by collagen deposition within the pancreatic islet following inflammation, hemorrhage, and/or necrosis. It occurs spontaneously in the Zucker diabetic fatty (ZDF) rat model and other diabetic rat models. Histologically, islet fibrosis may involve one islet (focal), several islets (multifocal), or all islets (diffuse); islet cells often have decreased cytoplasm, and there may also be decreased numbers of islet cells. Fibrosis can rarely occur as a spontaneous background lesion in older rats and mice, but more commonly occurs following end-stage atrophy secondary to chronic diabetes mellitus.

Islet pigmentation is the accumulation of pigment such as iron, lipofuscin (secondary to lipid peroxidation), or hemoglobin that occurs within pancreatic islets or between islet cells. The presence of hemosiderin-laden macrophages indicates previous hemorrhage within the affected pigmented areas, whereas lipofuscin pigmentation suggests increased cell turnover secondary to cell death. Islet pigmentation is described in both rats and mice.

Ito cell, see the preferred term **Perisinusoidal fat-storing cell**.

Ito cell hyperplasia is a focal or diffuse increase in numbers of Ito cells (also known as stellate cells or perisinusoidal fat-storing cells). These cells may form clusters or extend along rows of hepatocytes, and contain multiple cytoplasmic clear vacuoles of varying size. Refer to **Liver, Gallbladder, and Exocrine Pancreas** in Appendix 2 for further information.

Ito cell tumor is a benign neoplasm composed of Ito cells (also known as stellate cells or perisinusoidal fat-storing cells). These cells vary in appearance from lipid-containing cells containing clear cytoplasmic vacuoles, to spindle-shape with minimal cytoplasm. Refer to **Liver, Gallbladder, and Exocrine Pancreas** in Appendix 2 for further information.

IUGR is an acronym for intrauterine growth retardation. See **Intrauterine growth retardation (IUGR)** for further information.

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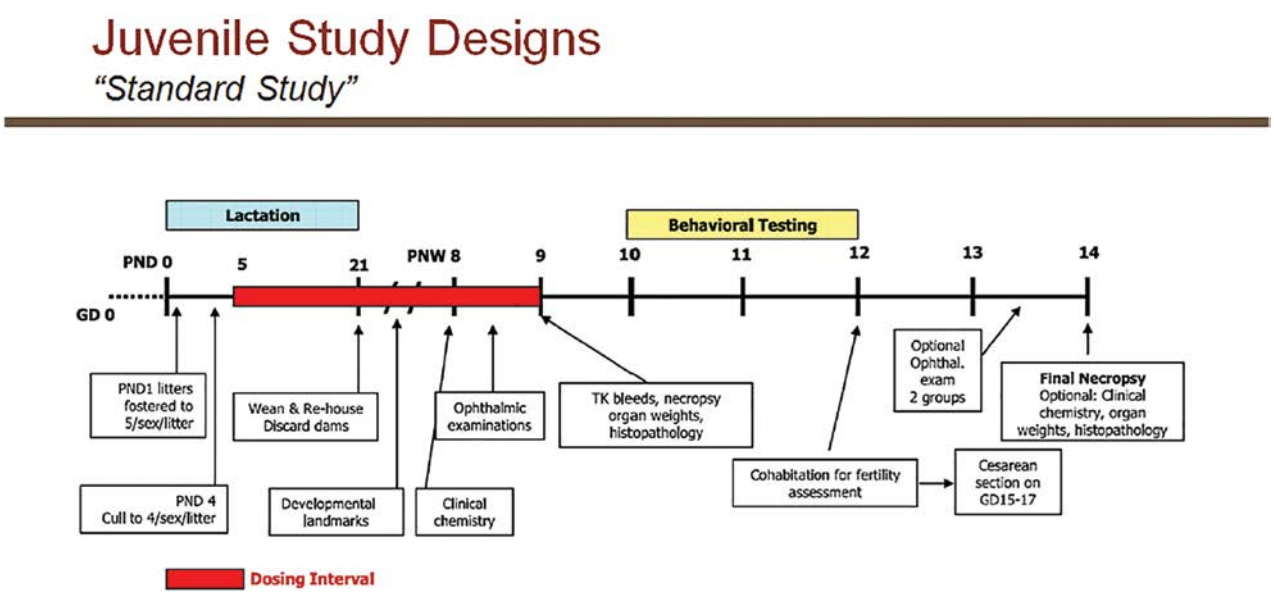
J

Juvenile toxicity refers to adverse events caused by a substance (e.g., chemical, drug), a pathogen (e.g., microorganism, virus) or any other agent (e.g., radiation) that could affect the offspring until adulthood.

Juvenile toxicity studies are performed to support pediatric drug development in which animals are treated from shortly after birth, usually until they attain sexual maturity, to assess the effect of the drug candidates on early postnatal development, growth, and sexual development (see figure below).

Juxtaglomerular body or apparatus in the kidney consists of the complex of renin-containing, specialized smooth muscle-like (myoepithelial) juxtaglomerular cells wrapped around the afferent arteriole immediately prior to its entrance into the glomerulus in conjunction with the area of the distal convoluted tubule (i.e., macula densa) that comes into contact with its parent glomerulus at this point. This apparatus functions in the regulation of blood flow through the kidney and the glomerular filtration rate. The macula densa cells are responsive to variations in sodium chloride concentrations in the distal tubule. One of the responses to increased sodium is renin secretion, which causes arteriolar constriction and reduction of the glomerular filtration rate. This process is known as the tubuloglomerular feedback loop.

Juxtaglomerular cell hypertrophy and hyperplasia is characterized by enlargement (hypertrophy) and an increase in the number (hyperplasia) of the renin-secreting myoepithelial cells in the kidney following administration of select pharmaceuticals such as angiotensin 1 converting enzyme (ACE) inhibitors (e.g., captopril) or angiotensin II type 1 receptor antagonists (angiotensin receptor blockers [ARBs]; e.g., losartan), and is reversible after cessation of exposure. Refer to **Urinary System** in Appendix 2 for further information.



A schematic representation of the design of juvenile toxicity studies. (From Cappon G.D. et al. 2009. *Birth Defects Res, Part B* 86:463–469.)

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K

Karyolysis is disintegration of the nucleus in cells undergoing necrosis. This appears as loss of nuclear staining in routine hematoxylin and eosin (H&E) stained sections.

Karyomegaly is an increase in the size of the nucleus of a cell.

Karyorrhexis is fragmentation of the nucleus of a cell occurring during the process of apoptosis or necrosis.

Karyotype is the microscopic appearance of chromosomes in a eukaryotic cell, including the number, form, size, etc.

Keratin cyst, see the preferred term **Squamous cyst**.

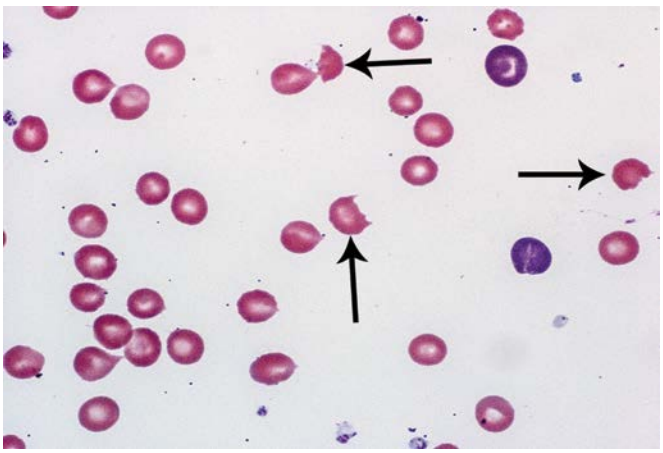
Keratinization is the process of differentiation of epidermal cells from the stem cells in the stratum basale to the more superficial differentiated layers (e.g., spinous layer, granular layer, and cornified or horny layer). It is sometimes utilized to define the last step of the process where epidermal cells undergo cornification. In toxicologic pathology, keratinization is also used to identify the appearance and accumulation of cornified cells in locations where epithelial cell differentiation does not include this step (e.g., oral mucosa). The basal proliferating keratinocytes express cytokeratins 5 and 14 while the differentiated layers express keratins 1 and 10. A cluster of genes called epidermal differentiation complex controls the terminal differentiation to cornified cells.

Keratitis, see the preferred term **Corneal inflammation**.

Keratoacanthoma is a benign neoplasm of hair follicles. Its characteristic presentation is a cystic, shaftless, dilated follicular structure invaginating into the dermis/hypodermis with a thickened epithelial wall, and an opening pore to the epidermis. Refer to **Skin** in Appendix 2 for further information.

Keratoconjunctivitis sicca (KCS) is a clinical description of an inflammatory disease of the cornea and conjunctiva caused by decreased tear production ("dry eye"), and abnormalities of orbital and nictitans glands in animals and humans. Histological correlates include changes to one or more corneal layers and the conjunctiva. See the following for further information: **Corneal vacuolation**; **Corneal epithelial atrophy**; **Corneal keratinization**; **Corneal erosion**; **Corneal ulcer**; **Corneal neovascularization**; **Corneal fibroplasia**; **Corneal stromal fibrosis**; **Corneal inflammation**; and **Conjunctiva inflammation**.

Keratocytes are red blood cells (RBCs) that contain one or two projections that appear as "horns" (*kerat* is Latin for horn). Prekeratocytes ("blister" cells) are RBCs that contain an intact hole that forms a keratocyte after rupture. Keratocytes can form following microvascular injury with deposition of fibrin strands, iron deficiency anemia and subsequent oxidative damage, myelodysplastic syndrome, or due to drug toxicity (i.e., doxorubicin). Following fragmentation of the surface projections, schistocytes are formed.



Keratocytes (arrows), peripheral blood smear, monkey.

Keratopathy, see the preferred term **Corneal inflammation**.

Kupffer cell hypertrophy/hyperplasia is characterized by an increase in number and/or size of Kupffer cells in small aggregates or nodules within the sinusoids of the liver. In advanced instances, the lesion may consist of nodules or sheets of oval to spindle-shaped cells. Refer to **Liver, Gallbladder, and Exocrine Pancreas** in Appendix 2 for further information.

Kupffer cells are tissue macrophages that normally reside in the liver on the luminal surface of the sinusoidal endothelial cells and are members the mononuclear phagocyte system. Kupffer cells, as other macrophages, act as phagocytes that are capable of removing proteins, bacterial lipopolysaccharides, particulates, and other substances from the blood. Kupffer cells express Fc and complement receptors, which are active in the binding of substances that are bound to antibodies and complement (C3b, C4b, and C1q). Activation of Kupffer cells may lead to cytokine release that may promote hepatocellular injury, hepatic inflammation, and fibrosis.

Kupffer cell sarcoma, see the preferred term **Hepatic histiocytic sarcoma**.

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L

Labyrinthitis, see the preferred term **Inner ear inflammation**.

Lacrimal gland adenocarcinoma in laboratory animals consists of an expansive distorted, invasive mass of acini lined by moderately to poorly differentiated cuboidal cells with cellular pleomorphism, atypia, and mitotic figures. Refer to **Special Senses** in Appendix 2 for further information.

Lacrimal gland adenoma in laboratory animals consists of a lobular and expansive mass of tubules and acini lined by well-differentiated cuboidal cells with round nuclei, relatively normal cytoplasmic secretory (serous) vacuoles, and few mitotic figures. Refer to **Special Senses** in Appendix 2 for further information.

Lacrimal gland atrophy consists of a focal, multifocal, or diffuse decrease in the size of acini or ducts, often with flattened epithelium lacking secretory differentiation. Lobules may be irregular, acinar luminal size may be increased or decreased, and stromal fibrosis may be present. Atrophy may occur in association with retroorbital bleeding, inflammation, infectious diseases, and nutritional deficiencies and is reported as a spontaneous finding in rats and mice.

Lacrimal gland granulomatous inflammation consists of focal or diffuse accumulations of epithelioid macrophages, multinucleated giant cells, lymphocytes, and plasma cells involving alveoli, ducts, and interstitial stroma. Exogenous (hair shafts from retroorbital bleeding) or endogenous foreign bodies may or may not be identified as the inciting agent. Granulomatous inflammation increases in frequency with age, particularly in rats.

Synonym(s): **Granulomatous dacryoadenitis**.

Lacrimal gland Harderian metaplasia, see the preferred term **Harderian gland alteration**.

Lacrimal gland hyperplasia consists of well-demarcated, noncompressive, and tinctorially distinct foci of glandular alveoli that contain increased numbers of cells with relatively normal cytoplasmic secretory (serous) vacuoles. Refer to **Special Senses** in Appendix 2 for further information.

Lacrimal gland inflammation consists of focal or diffuse accumulations of inflammatory cells (granulocytes or heterophils [rabbit], macrophages, lymphocytes, and plasma cells) in and around the acini, ducts, and interstitial stroma accompanied by other inflammatory indicators including interstitial edema, congestion, hemorrhage, and necrosis or cellular debris. Squamous metaplasia of the acini, hyperkeratinization of duct epithelium, and interstitial fibrosis may occur in chronic inflammation. Hemorrhage is usually found with inflammation associated with retrobulbar blood sampling, and diffuse inflammation is associated with infectious diseases.

Differential diagnoses: **Duct-associated lymphoid tissue**; **Lacrimal gland inflammatory cell infiltrate**; **Lacrimal gland granulomatous inflammation**.

Synonym(s): **Dacryoadenitis**.

Lacrimal gland inflammatory cell infiltrate consists of small numbers of leukocytes associated with acini, ducts, or interstitium, in the absence of obvious inflammation. Lymphocytic infiltrates increase as an age-related change and may be associated with Harderian gland alteration in the lacrimal gland acini. Infiltrates around ducts may be difficult to differentiate from duct-associated lymphoid tissue.

Differential diagnoses: **Duct-associated lymphoid tissue**; **Lacrimal gland inflammation**.

Lacrimal gland karyomegaly in the acinar epithelial cells consists of enlarged or irregularly shaped nuclei with increased basophilia, sometimes with eosinophilic intranuclear inclusions (cytoplasmic invaginations), and increased cell size. Karyomegaly is androgen dependent in sexually mature male rats, is observed as an aging change in mice, and is found with murine cytomegalovirus infections.

Synonym(s): **Cytomegalic**; **nuclear pleomorphism**; **polyploidy**.

Lactic acid (lactate) dehydrogenase (LDH) is commonly used as a serum analyte in toxicity testing; however, when measured as total enzyme activity and not separated into specific isoforms, LDH is nonspecific for generalized tissue injury, as rich sources can be derived from the liver and skeletal muscle that can contribute to circulating serum levels. The release of LDH into the culture medium is also used as an indication of cytotoxicity in in vitro systems.

Lactotroph cell is a subset of acidophil cells which produce prolactin (luteotropin). See the preferred term **Pituitary acidophil cell**.

Synonym(s): **Mammotroph cell**.

Lamellar bone refers to bone formed by properly aligned osteoblasts that lay down type I collagen fibers running longitudinally to the bone surface which can be best appreciated using polarized light microscopy. In cortical bone, the collagen fibers are oriented in concentric circles around a central blood vessel. In trabecular bone, the fibers appear as linear or curvilinear packets.

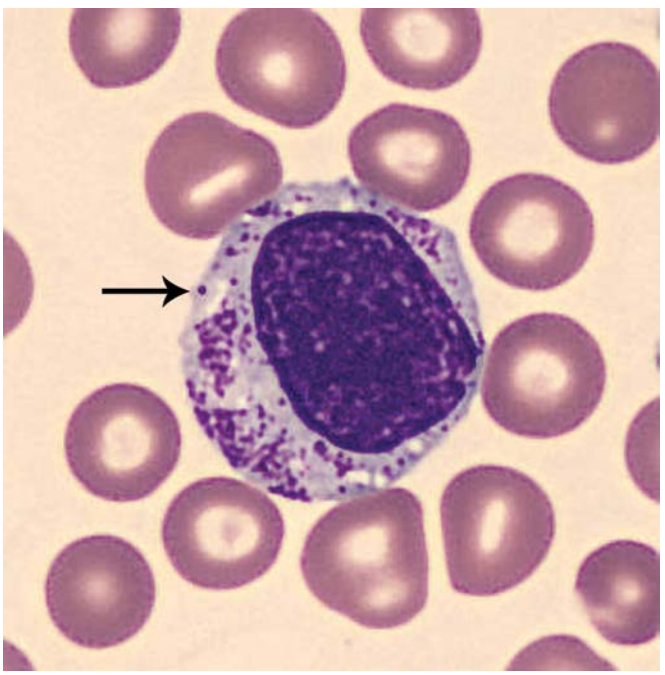
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Lamellar necrosis in the brain is a type of nonspecific necrosis indicating a layer of neurons within a region of the brain where there is functional or anatomic layering. This can occur in the cortex, hippocampus, or cerebellum. See **Neuronal necrosis** and **Polioencephalomalacia** for further information.

Langerhans cell, see the preferred term **Epidermal dendritic cell**.

Large granular lymphocyte (LGL) leukemia is one of the most common forms of lymphoma in the Fischer rat, and almost always presents in the leukemic phase (i.e., neoplastic lymphocytes in the blood). The main organs involved are the spleen, liver, and bone marrow. Refer to **Hematopoietic System** in Appendix 2 for further information).

Large granular lymphocytes are white blood cells with cytotoxic activity that are either $CD8^+$ T cells or natural killer (NK) cells. Both cells types have a similar morphological appearance of large lymphocytes (15–20 μm) with abundant lightly basophilic cytoplasm containing coarse azurophilic granules in their cytoplasm and a round to reniform eccentric nucleus with a dense chromatin pattern. They are more frequently observed in circulation in ruminants.



Large granular lymphocyte (arrow), blood smear, rat.

Large lymphocytes are mononuclear white blood cells that are approximately the size of neutrophils or slightly larger (~10–15 μm in diameter). As small lymphocytes respond to immunological stimulation, they become larger and there is a development continuum between small and large lymphocytes. The morphology of large lymphocytes is highly variable. Their cytoplasm is more abundant than in small lymphocytes, lightly basophilic, and may contain small numbers of small azurophilic granules. Their nucleus is variable in shape from round to reniform to multilobulated. The chromatin is still condensed and does not contain nucleoli. As for reactive lymphocytes, large lymphocytes are nonspecific indicators of antigenic stimulation.

Laryngeal epithelial alteration is the term used to describe a subtle epithelial change that occurs in the rodent larynx, typically at the base of the epiglottis. It represents a focal flattening and loss of cilia that may indicate the beginning of metaplastic transformation to a squamous phenotype. Laryngeal epithelial alteration can occur as a spontaneous change.

Differential diagnoses: **Larynx, trachea, bronchi and bronchioles squamous metaplasia**; **Laryngeal, tracheal, bronchial, and bronchiolar epithelial regeneration** (i.e., following erosion or ulceration).

Laryngeal, tracheal, bronchial, and bronchiolar adenocarcinomas are malignant neoplasms of the lining surface of those tissues. Tumor patterns may vary, and the tumor cells can range from well differentiated to anaplastic with frequent mitoses. Metastases to the lung can be observed frequently. Refer to **Respiratory System** in Appendix 2 for further information.

Laryngeal, tracheal, bronchial, and bronchiolar benign neuroendocrine cell tumor is composed of basophilic cells with stippled chromatin and eosinophilic, faintly granular cytoplasm that form a nodule that projects into the larynx or airway. Immunohistochemistry for calcitonin gene–related or protein gene product 9.5 may aid in identification. Refer to **Respiratory System** in Appendix 2 for further information.

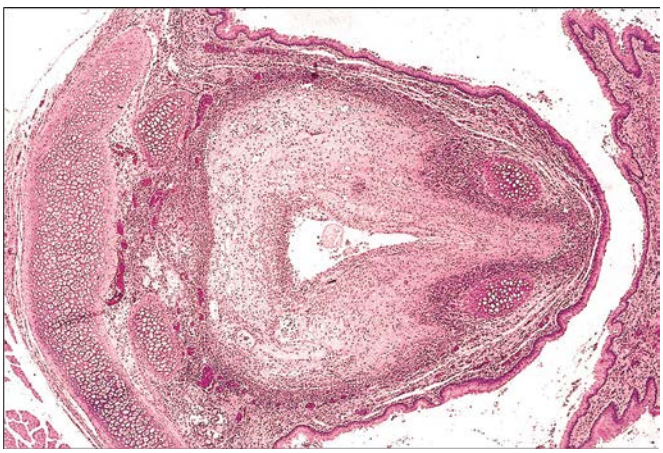
Laryngeal, tracheal, bronchial, and bronchiolar epithelial degeneration is characterized by cytoplasmic blebbing, vacuolation, and deciliation of respiratory epithelium with loss of individual cells and a disruption of the normal architecture of the epithelium. Deciliation should not be confused with regions of normally sparse ciliation in areas of transitional epithelium. Repeated insult to airway epithelium can lead to squamous metaplasia.

Laryngeal, tracheal, bronchial, and bronchiolar epithelial hyperplasia is an increased thickness of the epithelium lining the larynx, bronchi, or bronchioles due to cellular proliferation. In cases of epithelial protrusion, the proliferative lesions must be differentiated from neoplastic growths. Respiratory epithelial hyperplasia is often noted in response to irritants, and associated with other findings such as degeneration, metaplasia, and inflammation. Refer to **Respiratory System** in Appendix 2 for further information.

Laryngeal, tracheal, bronchial, and bronchiolar epithelial hyperplasia with atypia represents hyperplasia containing cells of an abnormal phenotype. Variation of cell or nuclear size and/or shape with bi- or multinucleate forms may be evident. Refer to **Respiratory System** in Appendix 2 for further information.

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Laryngeal, tracheal, bronchial, and bronchiolar epithelial necrosis, erosion, and ulceration represent epithelial cell death which can lead to partial or total loss of the epithelium, including the basement membrane (erosion and ulceration, respectively). The most vulnerable site for these changes in rodents is the base of the epiglottis. Loss of epithelial continuity must be differentiated from artifactual loss of epithelium during processing, or during procedures such as intratracheal dosing or a misdosed oral gavage. Unless peracute, changes occurring in life will be accompanied by an acute inflammatory response. Must be differentiated from autolysis.



Ulceration, larynx, rat, H&E.

Laryngeal, tracheal, bronchial, and bronchiolar epithelial regeneration is characterized by increased cellular basophilia, increased nuclear to cytoplasm ratio, and alteration of normal tissue architecture or differentiation to include a greater proportion of cells that have not yet fully differentiated. Epithelial regeneration following an erosion or ulceration initially involves a thin layer of cells that should not be confused with squamous metaplasia. Regeneration is frequently seen in proximity to areas of degeneration or necrosis, and indicates ongoing repair of the affected epithelium.

Differential diagnoses: **Laryngeal, tracheal, bronchial, and bronchiolar epithelial hyperplasia**; **Laryngeal epithelial alteration**.

Laryngeal, tracheal, bronchial, and bronchiolar inflammation is a common finding in response to inhaled irritants, whether test article–related or due to foreign bodies. In the rodent larynx, the ventral pouch is a frequent site for foreign material to become lodged and induce an inflammatory response. The base of the epiglottis is another common site for inflammation in the rodent larynx. More generally, regions of airflow disruption such as the tracheal bifurcation (carina) and other airway branches are common sites for inflammation due to increased impact of particulates at these locations. The type of inflammation can be categorized by duration (i.e., acute or chronic) defined by the primary cellular response seen. Acute inflammation is characterized by the presence of neutrophils, and may be accompanied by vascular congestion, edema, and exudates. Edema and exudation in the larynx and airways can be fatal if this leads to blockage of the lumen. The presence of eosinophils may indicate an immunologic response. If the primary cellular response is mononuclear, with a variable cell population that may include lymphocytes, macrophages, and plasma cells, then the inflammation is defined as subchronic or chronic. The type of cellular infiltrate may also indicate that the inciting cause is persistent or immunogenic. The presence of a persistent irritant invokes an inflammatory response termed "chronic active" that may progress to granulomatous inflammation. Chronic active inflammation is characterized by the presence of significant granulocytic and mononuclear cell populations comprising the infiltrate, indicating continued stimulation of granulocytes against a background of chronic inflammation, or resolution of the acute phase. Granulomatous inflammation is characterized by the presence of large macrophages with abundant cytoplasm (epithelioid cells), lymphocytes, and plasma cells, and in long-standing lesions, the presence of fibrosis.

Laryngeal, tracheal, bronchial, and bronchiolar inflammatory polyp is a consequence of severe inflammation resulting in the formation of a nonneoplastic inflammatory exophytic mass, consisting of hyperplastic epithelium and abundant, often fibrovascular stroma. Inflammatory polyp formation has been noted in the larynx of rats following inhalation of cobalt sulphate.

Differential diagnoses: **Laryngeal, tracheal, bronchial, and bronchiolar papilloma**; **Laryngeal, tracheal, bronchial, and bronchiolar epithelial hyperplasia with atypia**.

Laryngeal, tracheal, bronchial, and bronchiolar malignant neuroendocrine cell tumor are extremely rare and are composed of basophilic cells with stippled chromatin and eosinophilic, faintly granular cytoplasm that forms a nodule which projects into the laryngeal or airway lumen. Malignant tumors are judged by infiltration and metastasis. Immunohistochemistry for calcitonin gene–related or protein gene product 9.5 may aid in identification. Refer to **Respiratory System** in Appendix 2 for further information.

Laryngeal, tracheal, bronchial, and bronchiolar neuroendocrine cell hyperplasia is a rare form of laryngeal, tracheal, or bronchiolar epithelial hyperplasia. These lesions project into the airways. Confirmation is made by immunohistochemistry identification of calcitonin gene–related peptide or protein gene product 9.5. Refer to **Respiratory System** in Appendix 2 for further information.

Laryngeal, tracheal, bronchial, and bronchiolar papilloma is a benign, exophytic neoplasm of well-differentiated respiratory or squamous epithelium that may distort the airway in

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which it is present. Papillomas must be differentiated from bronchioloalveolar adenomas. Refer to **Respiratory System** in Appendix 2 for further information.

Laryngeal, tracheal, bronchial, and bronchiolar squamous cell carcinoma is a malignant neoplasm arising from the squamous epithelium of the larynx or from a metaplastic squamous epithelium in other locations of the larynx or airways. The carcinomas may be well differentiated, with keratinization or poorly differentiated, nonkeratinizing tumors. Immunohistochemical detection of keratin may help in identifying the tumors. Refer to **Respiratory System** in Appendix 2 for further information.

Larynx, trachea, bronchi, and bronchioles squamous metaplasia is the replacement of the respiratory epithelium normally present at these locations with a squamous epithelium that may be keratinized or nonkeratinized. Refer to **Respiratory System** in Appendix 2 for further information.

LD_{50} and **LC_{50}** are terms for the median lethal dose and median lethal concentration, respectively. They are a measure of the toxicity following application of a compound/drug or a procedure. Technically, it is the dose of an experimental compound, toxin, virus, or radiation at which 50% of the subjects become moribund or die. This is only used in extreme cases when no other measure of safety is available. Variants include LD_{25}, LD_{75}, etc. where the number represents the percent of subjects that will succumb to the agent. Acute toxicity tests in animals to determine LD_{50} values are no longer being conducted to reduce animal use, and in general, approximate values are determined in a few animals to permit dose selection of repeat-dose toxicity testing. Historically, the LD_{50} was used as a benchmark for acute toxicity using this quantitative endpoint and for the classification of toxic substances. Mathematically, the LD_{50} is determined by various methods, the most common being a probit (probability unit)/log-transformation of dose-response. The LD_{50} is no longer required for most regulatory purposes due to the high animal burden for generating an endpoint of questionable relevance within the framework of risk and safety assessment.

LD_{low} (Lethal $Dose_{low}$) is a term used to designate the lowest dose shown to produce lethality in either a single or repeat-dose toxicity study. It is at times used to mitigate risk in the dose escalating portion of Phase 1 clinical trials in cases where the toxicology studies gave little or no indication of toxicity that could be monitored in the presence of a steep dose-lethality response curve.

LDL, LDL-P, and **LDL-C** are acronyms for low-density lipoprotein. See **Low-density lipoproteins** for further information.

Leiomyoma is a benign neoplasm arising from smooth muscle cells. Leiomyoma are usually well-circumscribed nodular tumors. Cytological, histochemical, and immunohistochemical characteristics and ultrastructural features are similar to the ones described for leiomyosarcomas except for the presence of minimal cell polymorphism, a minimal number of mitoses, and the absence of local invasion and metastases. Refer to **Bone, Muscle, and Tooth** in Appendix 2 for further information.

Leiomyoma (gastrointestinal) is a benign intramural tumor derived from the smooth muscle cells of the tunica muscularis. Refer to **Bone**, **Muscle**, **and Tooth**, and **Female Reproductive Tract** in Appendix 2 for further information.

Differential diagnoses: **Leiomyosarcoma**; **Gastrointestinal stromal tumor**; **Schwannoma**; **fibroma/sarcoma**; **Histiocytic sarcoma**.

Leiomyosarcoma is a malignant neoplasm arising from smooth muscle cells. They are characterized by interlacing whorls and bundles of spindle-shaped cells forming criss-cross patterns. Cells with bizarre polygonal shapes with multiple nuclei can also be observed, particularly in the urinary bladder of dogs. Refer to **Bone**, **Muscle**, **and Tooth** and **Female Reproductive Tract** in Appendix 2 for further information.

Leiomyosarcoma (gastrointestinal) is a malignant intramural tumor derived from the smooth muscle cells of the tunica muscularis. Refer to **Gastrointestinal Tract** in Appendix 2 for further information.

Differential diagnoses: **Leiomyoma**; **Gastrointestinal stromal tumor**; **Schwannoma**; **Fibroma/sarcoma**; **Histiocytic sarcoma**.

Lens balloon cells, see the preferred term **Lens fiber degeneration**.

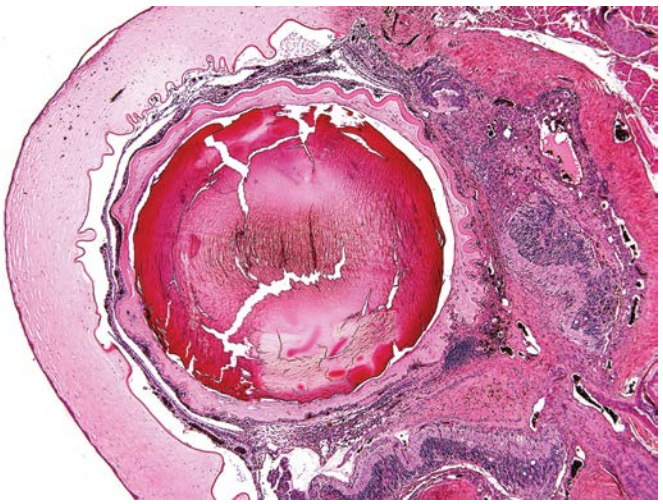
Lens bladder cells, see the preferred term **Lens fiber degeneration**.

Lens calcification, see preferred term **Lens fiber mineralization**.

Lens capsule hypertrophy is focal or diffuse thickening, and often irregular undulations of the capsule. The anterior lens epithelium continues to produce capsule material throughout life, so diffuse hypertrophy of the anterior, but not posterior lens may be a senile change. Focal thickening is usually associated with lens fiber degeneration, inflammation extending from the adjacent extralenticular structures, and trauma, including via intravitreal injections.

Synonym(s): **Lens capsule increased size**.

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Lens capsule hypertrophy with capsule rupture, and iris adhesion, vitreal fibroplasia and retinal atrophy, F344/N rat, H&E. See **Lens epithelial hyperplasia** for an additional illustration. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

Lens capsule increased size, see the preferred term **Lens capsule hypertrophy**.

Lens capsule rupture is a break in the lens capsule and immediate or eventual release of the lens proteins. Rupture occurs most frequently as part of severe and ongoing degeneration of the lens fibers, or may occur secondary to blunt trauma, perilenticular or vitreal inflammation, persistent hyaloid artery, surgery, and intravitreal injections, particularly in rodents due to large a lens relative to intraocular space. See **Lens capsule hypertrophy** for illustration.

Lens dislocation results from stretching and breaking of the lens suspensory zonular ligaments, which causes the lens to fall into the anterior chamber and block the filtration angle, or less frequently, to fall into the posterior segment, as anterior and posterior dislocation, respectively (see Appendix 3 for additional information). Sequelae include damage to the retina and cataracts from posterior dislocation, iris adhesions, narrowing of the filtration angle, corneal endothelial atrophy, lens fibrous metaplasia, and vitreal fibrosis and hemorrhage. Complete ligament breakage results in lens detachment. Dislocation occurs as a hereditary ligament deficiency, spontaneously with glaucoma, inflammation, neoplasia, and after surgery and trauma including intraocular injections. Dislocation is a frequent artifact of trimming and sectioning of the globe.

Synonym(s): **Lens luxation**; **lens displacement**.

Lens displacement, see the preferred term **Lens dislocation**.

Lens dystrophic calcification, see the preferred term **Lens fiber mineralization**.

Lens dystrophic mineralization, see the preferred term **Lens fiber mineralization**.

Lens epithelial cellular transdifferentiation, see the preferred term **Lens epithelial fibroplasia**.

Lens epithelial fibroplasia consists of transformation of anterior lens epithelium to spindloid (myofibroblasts) cells that deposit linear arrays of eosinophilic collagenous matrix that replace injured lens epithelium, and subjacent lens fibers with fibrous tissue. Lens epithelial hyperplasia and secretion of a new lens capsule over the affected area may also be present. See **Iris adhesion** for illustration.

Differential diagnoses: **Lens epithelial hyperplasia**; **Fibrosis**.

Synonym(s): **Lens epithelial fibrous metaplasia**; **lens epithelium cellular transdifferentiation**.

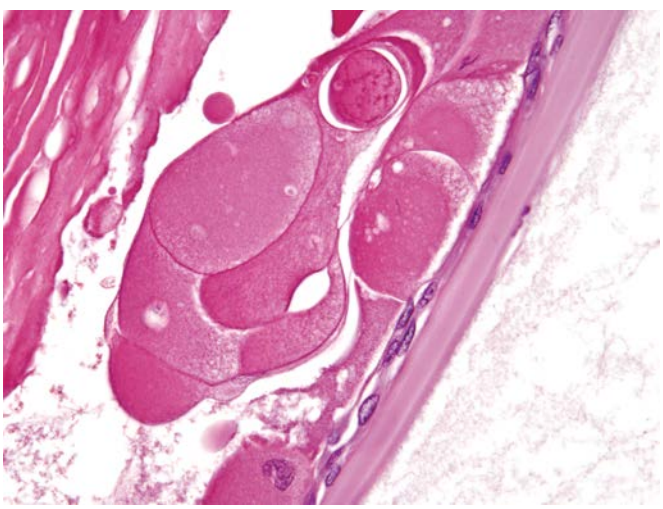
Lens epithelial fibrous metaplasia, see the preferred term **Lens epithelial fibroplasia**.

Lens epithelial hyperplasia is proliferation of a single layer of the anterior lenticular epithelium to form focal or multifocal nodules under the lens capsule that may extend to the posterior lens capsule. Injury to the lens may result in lens epithelial hyperplasia or transformation to fibroblasts. Refer to **Special Senses** in Appendix 2 for further information.

Lens epithelial hypertrophy consists of enlarged anterior epithelial cells, often associated with adjacent lens fiber swelling as a result of injury or abnormal metabolism.

Differential diagnosis: **Lens vacuolation**.

Synonym(s): **Lens epithelium increased size**.



Lens epithelial hypertrophy with lens fiber degeneration, F344/N rat, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

Lens epithelial necrosis is irreversible cell injury to the anterior epithelial cells of the lens which results in single cell,

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focal, or diffuse loss of cell detail, the presence of cellular debris, inflammation, and the drop-out of cells. This change is frequently associated with other changes in the lens capsule, epithelium, and fibers and can occur following administration of chemotherapeutics and radiomimetics.

Lens epithelium increased size, see the preferred term **lens epithelial hypertrophy**.

Lens fiber cleft formation, see the preferred term **Lens fiber degeneration**.

Lens fiber degeneration consists of enlarged, pale and irregular shapes and disorganized lens fiber arrays due to metabolic changes that may manifest as swelling, clefts, fragmentation, and liquefaction. Initial acidification causes fluid loss, cell shrinkage, and formation of clefts consisting of spaces between rounded lens fibers with an accumulation of proteinaceous fluid. Osmotic changes induce swelling that consists of enlarged, pale and disorganized lens fibers with those containing abnormally retained nuclei sometimes called balloon or bladder cells. Morgagnian globules are an extreme form of swelling that results in loss of nuclei and coagulation of eosinophilic balls or globules of protein. Fragmentation consists of swollen, membrane-bound fragments, and liquefaction is identified by proteinaceous fluid within the lens cortex as small pockets or larger areas of fluid that replaces lens fibers. Additional changes include cytoplasmic granularity, vacuolation, separation and mineralization of lens fibers, lens epithelial (hyperplasia, hypertrophy, and fibroplasia), capsular (hypertrophy and rupture) changes, and inflammation that is typical of a clinically observed cataract.

Synonym(s): **Lens fiber swelling**; **lens fiber cleft formation**; **balloon cell**; **bladder cell**; **Morgagnian globule**; **lens fiber fragmentation**; **lens fiber liquefaction**; **cataract**.



Lens fiber degeneration with vacuolation, rat, H&E. See **Lens epithelial hypertrophy** and **Iris adhesion** for additional illustrations. (Image courtesy of Teixeira, L. University of Wisconsin.)

Lens fiber fragmentation, see the preferred term **Lens fiber degeneration**.

Lens fiber hypertrophy consists of swelling of individual lens fibers with variable eosinophilic staining or numerous enlarged cells with a foamy cytoplasm ("bladder" or "balloon" cells). Causes include hyperosmotic conditions with passive diffusion of fluids into the cells from increased glucose or other simple sugars or other agents, and drugs such as opiates, opioids, and phenothiazine. If the substance is not metabolized by the lens fibers, the changes may not reverse, and may progress to lens fiber degeneration.

Differential diagnoses: **Lens fiber swelling**; **Lens fiber degeneration**.

Lens fiber liquefaction, see the preferred term **Lens fiber degeneration**.

Lens fiber mineralization is characterized by basophilic intracellular granules or crystalline material in sites of lens fiber degeneration. See **Iris adhesion** for the illustration. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

Synonym(s): **Lens calcification**; **lens dystrophic calcification**; **lens dystrophic mineralization**.

Lens fiber swelling, see the preferred term **Lens fiber degeneration**.

Lens inflammation consists of focal or diffuse inflammatory cells (granulocytes or heterophils [rabbit], macrophages, lymphocytes, multinucleated giant cells, and plasma cells) in the lens. Lenticular inflammation is frequently neutrophilic or granulomatous that occurs after lens fiber degeneration, lens epithelial changes, or rupture of the lens capsule and extension of inflammation from the surrounding tissues. Trauma including intraocular injections, injury, and infectious diseases are common causes. Iatrogenic damage to the lens capsule during aseptically performed intravitreal injections or implants do not appear to induce inflammation in rabbits.

Synonym(s): **Phacoclastic uveitis**.

Lens luxation, see the preferred term **Lens dislocation**.

Lens malformation, see the preferred term **Optic fissure malformation**.

Lens opacity is a nonspecific clinical finding of a cloudy area on or in the lens. Multiple etiologies (anomalies, genetic abnormalities, trauma, degeneration, edema, fibrosis, and inflammation) can cause lenticular opacifications and translate into a variety of histologic changes in the lens and on the lens capsule.

Lens phospholipidosis, see the preferred term **Lens vacuolation**.

Lens vacuolation consists of clear or foamy, round to oval cytoplasmic spaces of variable size and number in the anterior lens epithelium or lens fibers, as well as clefting

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between fibers, as a result of injury and metabolic changes. Vacuolation is usually associated with cytoplasmic inclusions that may represent lysosomal accumulation of molecules or drugs or metabolites, including those that cause phospholipidosis. Transmission electron microscopy to identify lamellar inclusions or MALDI imaging mass spectrometry to measure the analytes is required to identify the vacuole contents. Vacuoles may also be present in other ocular compartments (see **Corneal vacuolation**; **Ciliary body epithelial cytoplasmic vacuolation**; **Iris epithelial cytoplasmic vacuolation**; **Retinal cytoplasmic vacuolation**; **Retinal extracellular vacuolation**; **Retinal pigment epithelium vacuolation**). Vacuoles may also be an artifact from delays in fixation. See **Lens fiber degeneration** for the illustration. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

Synonym(s): **Lens epithelial hypertrophy**; **lens fiber hypertrophy**; **lens fiber degeneration**; **lens phospholipidosis**.

Leptomeninges are the combination of the pia mater on the surface of the brain, which follows all the contours, and the arachnoid mater that holds and forms a barrier between the cerebrospinal fluid (CSF) and external structures.

Leukemia, NOS (not otherwise specified) is the general term for a white blood cell neoplasm which leads to a high white blood cell count in the peripheral blood. Refer to **Hematopoietic System** in Appendix 2 for further information.

Leukoencephalitis is inflammation involving the white matter (axons and myelin) of the brain.

Leukoencephalomalacia is degeneration of the white matter (axons and myelin) of the brain.

Leukoencephalopathy, see the preferred term **Intramyelinic edema**.

Leydig (interstitial) cells are polyhedral, and reside in the interstitium of the testis, outside the blood-testis barrier. They have an ovoid, centrally located nucleus and moderate amounts of eosinophilic, finely vacuolated cytoplasm, rich in smooth endoplasmic reticulum. Leydig cells (LC) are the major site of testosterone synthesis in response to luteinizing hormone (LH). The size and number of LC are species-dependent. They are larger and more numerous in the mouse than the rat, where they make up 35% of the mouse testis interstitium compared to 17% of the rat testis interstitium. They comprise up to 50% of the testis interstitium in the pig.

Leydig cell adenoma is a benign tumor of the testes observed spontaneously in the aging rodent but may also be induced by xenobiotics such those that increase luteinizing hormone (LH) levels or hyperestrogenic compounds. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Leydig cell adenoma in the epididymis is a rare benign tumor in B6C3F1 mice composed of nodules or sheets of Leydig cells. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Leydig cell atrophy is characterized by reduced cell size and cytoplasmic volume of the Leydig cell (LC). LCs can be inhibited by chronic estrogen or testosterone administration, both of which inhibit the hypothalamic-pituitary axis and production of LH. Direct LH receptor inhibition on the LC could also result in atrophy. LC atrophy may be difficult to diagnose unless steroidogenesis has been profoundly affected. Ancillary hallmarks include decreased accessory sex gland and epididymal organ weights, due to their androgen dependency, hypertrophy of the gonadotropin-secreting cells in the pituitary gland, and mammary gland atrophy. Germ cell degeneration in Stages VII and VIII seminiferous tubules, with decreased numbers of elongating spermatids and spermatid retention, will often accompany LC atrophy.

Synonym(s): **Leydig (interstitial) cells, decreased numbers/size**.

Leydig cell carcinoma in the testis is an uncommon malignant tumor of Leydig cells and is also luteinizing hormone (LH)- or estrogen-dependent. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Leydig cell hyperplasia is a focal, multifocal, or diffuse change characterized by an increase in the number and size of testicular Leydig cells corresponding to a diameter of smaller than or equal to three seminiferous tubules. Usually occurs in response to an imbalance in luteinizing hormone (LH). Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Differential diagnosis: **Leydig cell hypertrophy**.

Synonym(s): **Interstitial cell hyperplasia**.

Leydig cell hyperplasia, functional occurs as a diffuse increase in the number of testicular Leydig cells and is a physiological adaptive response to hormone imbalances. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

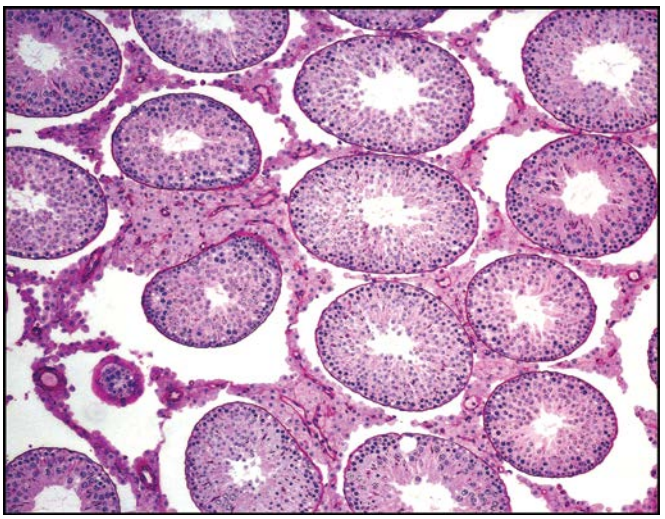
Leydig cell hypertrophy is a focal, multifocal, or diffuse change characterized by enlarged, sometimes vacuolated, Leydig cells (LCs) between seminiferous tubules. LC hypertrophy is often seen in conjunction with LC hyperplasia. Normal LCs of mice are generally larger and have a more vacuolated appearance than those of rats. Different mechanisms in negative feedback for gonadotropin-releasing hormone (GnRH) release between dog, primates, and rat are represented by varying responses of LCs to administration of aromatase inhibitors such as formestane and letrozole, which block the conversion of androgens to estrogens. Due to the importance of estrogens as the major negative feedback stimulus in dogs (and primates), aromatase inhibitors administered to dogs result in LC hypertrophy/hyperplasia. In contrast, rats

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depend on testosterone and dihydrotestosterone for negative feedback to the hypothalamus. See **Leydig cell hyperplasia** for further information.

Differential diagnosis: **Leydig cell hyperplasia**.

Synonym(s): **Interstitial cell hypertrophy**.



Leydig cell hypertrophy, testis, rat, H&E.

Leydig cell necrosis is a primary, xenobiotic-induced change, or may be secondary to an ischemic process within the testis. Histologically, Leydig cell (LC) necrosis is characterized by chromatin clumping and nuclear margination, which may be accompanied by phagocytosis of LC debris by testicular macrophages. LC necrosis with secondary germ cell death, and atrophy of accessory sex organs with castrate levels of testosterone have been described in mature rats 4 days following administration of the alkylating agent ethane dimethane sulfonate.

Leydig (interstitial) cells, decreased numbers/size, see the preferred term **Leydig cell atrophy**.

Leydig cell tumor, benign, see the preferred term **Leydig cell adenoma**.

Leydig cell vacuolation is characterized by enlarged, pale-staining interstitial cells with foamy vacuolation of the cytoplasm, and usually results from xenobiotic-induced disturbance of steroidogenesis. Normal Leydig cells (LC) of mice are generally larger and have a more vacuolated appearance than those of rats, and LC vacuolation has been described in mice administered ethinyl estradiol. Testicular macrophages can also become vacuolated, independent of interstitial cells. The periodic acid-Schiff (PAS) method will stain macrophages, but not interstitial cells.

Synonym(s): **Interstitial cell vacuolation**.

LGL-NK lymphoma, see the preferred term **Lymphoma, LGL (large granular cell) leukemia**.

LH is an acronym for luteinizing hormone. See **Luteinizing hormone (LH)** and **Female sex hormones** for further information.

Light-induced photoreceptor degeneration, see the preferred term **Retina light-induced atrophy**.

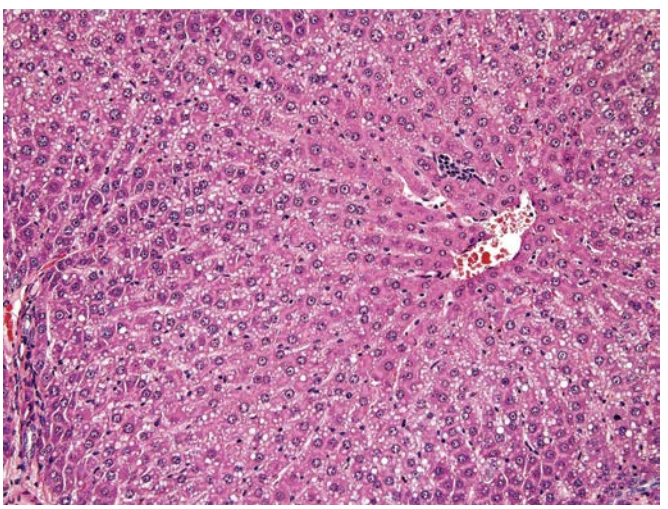
Light-induced retinopathy, see the preferred term **Retina light-induced atrophy**.

Linear extrapolation represents the drawing of a straight line through a series of data points generated by observational means (typically quantitative) on an *x*-*y* set of coordinates on a graph, extended to intersect either the *x* or *y* axis for purposes of projecting a data point(s) not represented by the range of data producing the straight line.

Linear retinopathy, see the preferred term **Retinal rosette**.

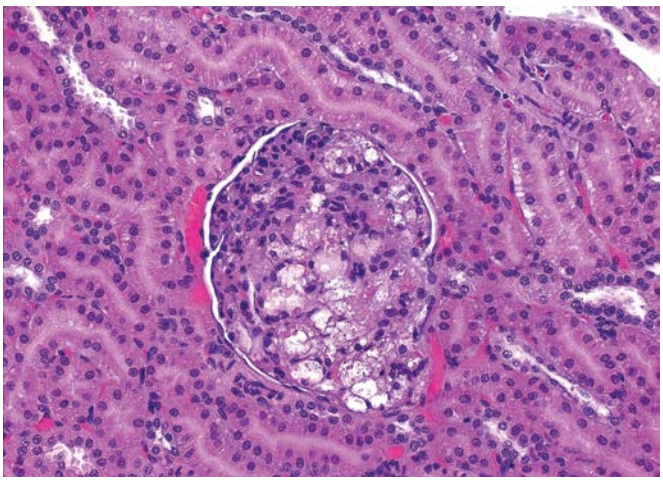
Lipid accumulation is an intracellular accumulation of variably sized, clear or foamy vacuoles. Depending on the cell affected, the lipid accumulation may displace zymogen granules or mucinous secretions. In the liver, the vacuoles may be small and numerous (microvesicular vacuolation) or coalesce into a single or a few large vacuoles (macrovesicular vacuolation). The latter may result in nuclear displacement. Larger vacuoles generally have distinct, well-defined borders while smaller, numerous vacuoles appear less distinct and tend to have a foamy appearance. Confirmation of lipid within vacuoles is normally not possible on examination of hematoxylin and eosin (H&E)-stained slides and requires staining with oil red O or Sudan Black using frozen sections to confirm. Isoprenaline and oxfenicine have been shown to produce lipid droplet accumulation in rat myocardial cells.

Synonym(s): **Fatty change**; **lipidosis**; **steatosis**.



Lipid accumulation in the liver of a rat, H&E. Note the formation of numerous small clear lipid vacuoles within hepatocytes. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

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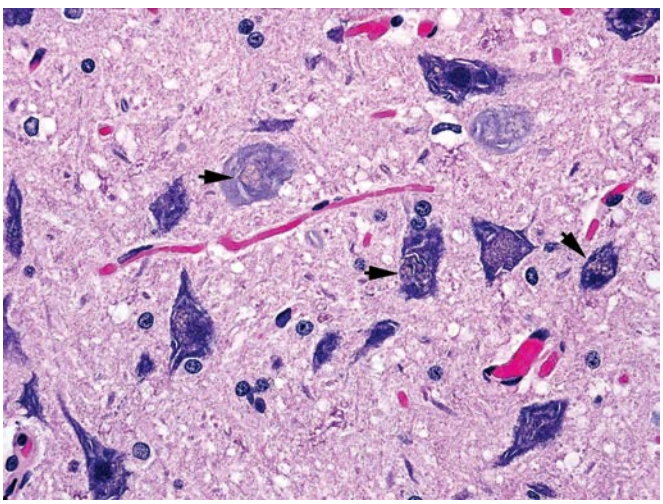


Lipid accumulation (lipidosis) in the kidney of a dog, H&E. The glomerulus has a foamy appearance due to the presence of multiple variably sized clear spaces (lipid).

Lipidosis, see the preferred terms **Lipid accumulation** and **Fatty change**.

Lipoatrophy, see the preferred terms **Adipose tissue atrophy** and **Mucoid or serous atrophy of adipose tissue**.

Lipofuscin accumulation is an intracellular aggregation of dark yellow to brown granular cellular oxidative molecules and has been described as wear and tear or aging pigment. Lipofuscin is formed from autophagosomal lysosomes and is composed of polymers of lipid/phospholipid complexed with proteins, carbohydrates, and metal residues (iron, aluminum, calcium). Spontaneous lipofuscin accumulation may be age related and has a predilection for the adrenal cortex, renal tubular epithelium, thyroid follicular cells, and the central nervous system. However, lipofuscin has been seen in younger animal tissues, such as 8-week-old rodents, where the pigment's intracellular presence reflects increased metabolic/oxidative capacity and not necessarily the postmitotic age of the cells. Lipofuscin accumulation has been reported in myocytes of rats fed Brown FK (a food coloring agent), and in humans dosed with chloroquine. Lipofuscin autofluoresces, and stains with various special stains such as periodic acid-Schiff, oil red O, Luxol fast blue, Sudan black B, and Ziehl-Nielsen. It is important to remember that other oxidative wear-and-tear pigments such as ceroid will have similar microscopic appearance and stain similarities as described above. Accurate distinction of lipofuscin from ceroid will require the demonstration of ceroid-related molecules such as agglutinin and/or subunit c of mitochondrial ATPase. See **Ceroid** and **Wear-and-tear pigment** for further information.



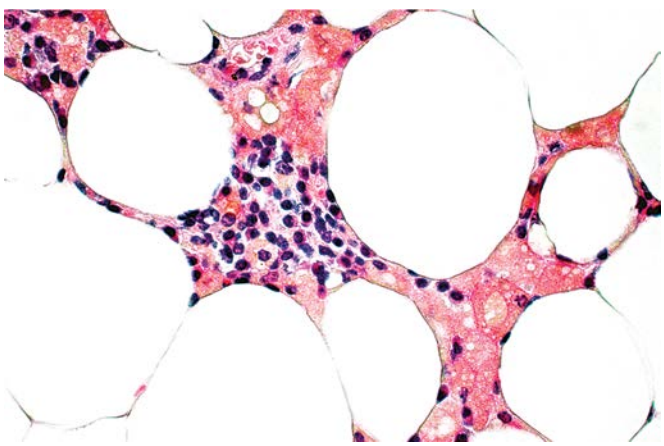
Lipofuscin accumulation in the brain of a rat, H&E. Accumulation of brown granular pigment within neurons (arrows). (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

Lipofuscinosis, see the preferred term **Lipofuscin accumulation**.

Lipogranulomatous inflammation is characterized by the presence of inflammatory cells generally consisting of multinucleate giant cells, foamy macrophages (containing cytoplasmic lipid vacuoles), neutrophils, cholesterol clefts, and new blood vessel formation. Lipogranulomatous inflammation is generally due to the introduction of a foreign lipid material or due to injury to adipose tissue.

Differential diagnosis: **Liposarcoma**.

Synonym(s): **Obesity-associated inflammation**; **steatitis**.



Mesenteric fat from a C67B1 mouse fed a high fat diet. There is a granulomatous inflammatory process in the fat with clusters of macrophages with lipid vacuoles and brown lipofuscin pigment (H&E). (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Greaves, P. et al. 2013. *J. Toxicol. Pathol.* 26:1S–26S.)

Lipoma is a benign neoplasm arising from white adipose cells. The tumor is usually identified macroscopically as a white mass. The neoplastic cells resemble mature adipocytes with one or a few large vacuoles in the cytoplasm that push the nucleus to one side of the cell. There is very little stroma in lipomas, usually limited to fine collagenous strands

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separating tumor lobules. Refer to **Bone, Muscle, and Tooth** in Appendix 2 for further information.

Lipomatous refers to the features of a lipoma (a benign neoplasm of adipocytes). It is not the same as adipocyte accumulation. See also **Adipocyte accumulation**; **Fatty infiltration** for further information.

Lipomatous hamartoma is a benign focal malformation characterized by adipose tissue growing as a disorganized mass. See **Hamartoma** for further information.

Lipoproteins are endogenous molecules comprised of lipids (fats) and proteins that allow for the transport of hydrophobic lipids as soluble entities though the bloodstream. They are the primary components of membranes interacting with both lipid- and aqueous-soluble substances required for normal cell function. Two major forms include low-density lipoproteins and high-density lipoproteins. See **Low-density lipoproteins** and **High-density lipoproteins** for further information.

Liposarcoma is a malignant neoplasm arising from white adipocytes. The neoplastic adipocytes or lipoblasts are round or polygonal, have one or a few large or multiple small cytoplasmic vacuoles with a single centrally placed or eccentric nucleus with dense chromatin and an irregular nuclear envelope compared to mature non-neoplastic adipocytes. Refer to **Bone, Muscle, and Tooth** in Appendix 2 for further information.

Liquefactive necrosis is used to describe an area of cell death in which morphologic details of the dead cells are lost. Under conditions of infection or increased inflammation, or within the central nervous system, liquefactive necrosis can occur characterized by complete enzymatic degeneration of cellular components resulting in an amorphous, empty space in place of what was once healthy tissue. There is often a large influx of neutrophils, either via enzyme release or as a consequence of DAMP-related chemoattraction. In the brain, hypoxia-related necrosis occurs as liquefactive necrosis, unlike other tissues where hypoxia-mediated necrosis is frequently coagulative-type necrosis. The pathogenesis of liquefaction in the brain is not well understood but does not appear to require the same amount of enzyme digestion that is necessary in other tissues. The end result is the transformation of the dead tissue into a liquid, viscous mass. Liquefactive necrosis is grossly visible as tan, fluid-filled spaces, while coagulative necrosis retains a firm consistency. See **Coagulative necrosis** for further information.

Liver cell carcinoma, see the preferred term **Hepatocellular carcinoma**.

Liver damage is a generic term for any inflammatory or degenerative changes in hepatocyte, biliary epithelium, resident macrophages (Kupffer cells), or vasculature observed microscopically or projected indirectly by measuring changes in circulating enzymes such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT), alkaline phosphatase (ALP), sorbitol dehydrogenase (SDH), or other biomarkers such as serum bilirubin (total or conjugated forms) considered reflective of increased cellular release from a compromised or dysfunctional liver.

Liver enzymes (in blood/serum) is a general term referring to the measurement of serum or plasma levels of enzymes with a high concentration in the liver and readily released upon hepatocellular or biliary epithelial injury. These include but are not limited to alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT), alkaline phosphatase (ALP), sorbitol dehydrogenase (SDH), glutamate dehydrogenase (GDH), arginine-succinate lyase (ASAL), 5′-nucleotidase, and at times, lactate dehydrogenase (LDH). Although sensitive to liver injury, only ALT, SDH, GDH, 5′-nucleotidase, and ASAL are generally considered mostly "liver specific" due to the high concentrations and panlobular distribution, and rapid release into the blood stream upon cellular stress or toxicity. In standard toxicology study panels, serum ALT, AST, ALP, and LDH activities are typically included, with GGT added for non-rodents and SDH or GDH added for the minipig.

Liver function test (LFT) is a general term that refers to assays that measure endpoints related to normal liver functional or anatomic integrity, typically done in serum, plasma, or less frequently in research models, bile. LFTs may include clinical chemistry measurements of serum liver enzymes, bilirubin, protein, albumin, globulins, and indirect measurement of clotting factors (e.g., prothrombin time). Although referred to as "liver function tests," these assays measure changes occurring in the liver as a likely result of biochemical, metabolic, degenerative, or hypertrophic alterations that may not reflect the ability of the liver to function normally.

Liver, gallbladder, exocrine pancreas, Anatomy and Histology, see Appendix 3 for further information.

Liver toxicity an alteration in the structure or function of the liver as a result of an interaction of a drug or chemical with the hepatocyte, resident liver macrophages (Kupffer cells) or biliary epithelium resulting in a degenerative or pathological condition that, if severe enough, would be considered adverse. Liver toxicity may be direct or indirect, reversible or irreversible, species-specific, and dependent upon the general nutritional and immunological state of the animal or human subject. See **Adverse effects** for further information.

LOAEL is an acronym for lowest observed adverse effect level. See **Lowest observed adverse effect level** for further information.

Local effect is an action of a drug or chemical in a defined area of application or exposure (e.g., the eye, skin,

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gastrointestinal tract, or trachea/lung) from agents administered topically to the eyes or skin or via the oral or inhalation routes, respectively.

Local lymph node assay (LLNA), also referred to as the murine LLNA, is a test conducted in mice to assess the sensitization potential of compounds, described in OECD test number 429. Solutions of the compound or topical drug formulations are applied to mouse ears to achieve exposure in local tissues and draining lymph. A dose of tritiated thymidine or bromodeoxyuridine may also be applied to assess cell proliferation as measured by the increase in the rate of tracer incorporation (stimulation index [SI]). After application, the draining lymph node is removed and the weight and cell proliferation rate are determined. If the SI is increased by a factor greater than 3, the compound is deemed to be a skin sensitizer.

Locomotor behavior is an observable movement or activity involving voluntary muscles in response to an outside stimulus. For pharmacological screenings, the activity should not require extensive learning or conditioning so that a large number of responses can be quickly and easily evaluated. These types of evaluations can be a startle response to a sudden noise, avoidance of a noxious odor, or the seeking of shelter or warmth from low temperature. These are generally basic responses that are highly predictable and can be used for predicting efficacy of a drug class or assessing CNS effects in safety pharmacology studies.

LOEL is an acronym for lowest observed effect level. See **Lowest observed effect level** for further information.

Low-density lipoproteins (LDL, LDL-P, LDL-C) are endogenous molecules found free in the circulation that are comprised of lipids (fats) and protein. They are also known as "bad cholesterol." LDL-P is low-density lipoprotein particles associated with the increased risk of atherosclerosis; LDL-C is low-density lipoprotein cholesterol, which is used as a surrogate marker to estimate the cholesterol content in LDL-P. LDLs function to transport cholesterol from the liver to tissues. High plasma concentrations of LDL-cholesterol are associated with increased risk of heart disease and atheromatous plaques.

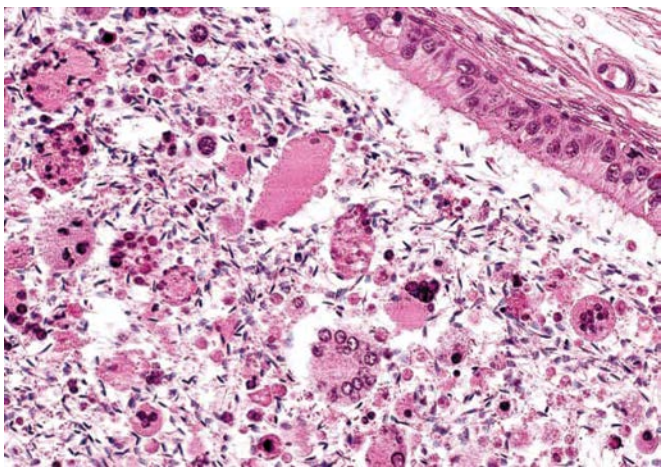
Synonym(s): **β-lipoprotein**.

Lower urinary tract is comprised of the renal pelvis, ureters, urinary bladder, and urethra, and is the excretory pathway of urine from the kidneys. The lining epithelium of all three tissues is urothelium, also known as transitional epithelium. The urothelium is generally quiescent but may become rapidly hyperplastic upon stimulation. The urothelial surface is distinguished by a single layer of large, flattened cells known as umbrella cells. Umbrella cells have unique cellular structures referred to as asymmetric unit membrane (AUM) plaques, which along with other cell vesicles undergo configurational changes as needed during bladder distension or contraction. Beneath the urothelium lie the submucosal and smooth muscle layers comprising the majority of the bladder wall.

Lowest observed adverse effect level (LOAEL) is determined in a toxicology study. Like the NOAEL (no observed adverse effect level), this is a species-specific, dose-response designation, which is also route and level/duration of exposure dependent. The LOAEL can be valuable in preclinical safety evaluation in relation to the NOAEL when considering dose escalation in human trials beyond the NOAEL (or when a NOAEL cannot be determined), especially if there are human-relevant biomarkers that can be considered premonitory for the types of adverse effects occurring at the LOAEL. These situations may arise with drugs or chemicals exhibiting a steep dose-response curve for adverse effects in animal studies, in support, for example, of human trials for a disease state with high morbidity and few therapeutic options.

Lowest observed effect level (LOEL) is the lowest dose or concentration delivered or measured that results in a biological or biophysical effect.

Luminal cell debris refers to sloughed cells in the lumen of a tubular organ. Typically, the sloughed cells are degenerating cells of the epithelial lining of this organ or of the "upstream" organ; degenerating germ cells in the testes can be seen as luminal cellular debris in both the testes and the epididymides.



Luminal cell debris in the epididymis of a dog, H&E. The debris is composed of degenerating cells that are likely sloughed germ cells from the testes. (Reproduced with the permission Germann, P. and Morawietz, G. (eds). *Toxicopathology Case Collection CD-ROM. European Society of Toxicologic Pathology*. ISBN: 3-9522681-1-9. https://www.eurotox-path.org/publications/form_cdrom.php?id=casecoll.)

Lung (alveolar) histiocytosis, see the preferred term **Pulmonary alveolar macrophage aggregation**.

Lung toxicity is an alteration in the structure or function of the lung as a result of an interaction of a drug or chemical with cells or tissues within the lower respiratory tract, including the bronchus, bronchioles, alveoli, pneumocytes,

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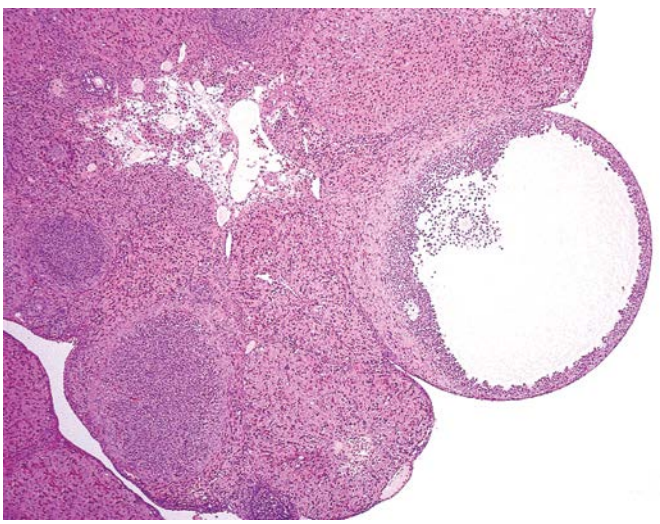
vasculature, or resident alveolar macrophages, resulting in a degenerative or pathological condition that if severe enough, would be considered adverse. Lung toxicity may occur through inhaled drugs, chemicals, or particles, or as a result of systemically available chemicals that affect the lung (and possibly other tissues) due to target or off-target binding, preferential uptake into the lung, and/or metabolism to reactive species. Lung toxicity may be reversible or irreversible, species-specific, and dependent upon the physical state of the inhaled material and/or general nutritional and immunological state of the subject. See **Adverse effect** for further information.

Luteal cyst is a variably sized, usually fluid-filled cyst derived from ovulatory follicles. It is lined by one or more layers of granulosa luteal and/or theca lutein cells. Luteal cysts may serve as a source of noncyclic progesterone, and are uncommon in rodents, dogs, and the nonhuman primate (NHP). Luteal cysts must be distinguished from a luteinized cystic follicle, which arise in a nonovulatory Graafian follicle and CL that may not fill normally and appear cyst-like during estrous cycling. Corpora lutea cysts can be spontaneous or xenobiotic-induced. In rats, progesterone receptor antagonists induce luteal cysts.

Synonym(s): **Cystic corpora lutea**.

Luteinized cystic follicle, see the preferred term **Luteinized follicle**.

Luteinized follicle is a nonovulatory Graafian follicle in which all or groups of the granulosa cells have become luteinized (i.e., enlarged with cytoplasmic lipid accumulation). The follicle may be larger than a normal Graafian follicle, and with a cystic center that can be filled with blood or fluid. A degenerate oocyte may sometimes be visible within the cavity. Luteinized follicles occur frequently in aging females of multiple species and may result from dysregulation of gonadotropins. Luteinized follicles can also result from treatment with xenobiotics.



Cystic luteinized follicle, ovary, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Dixon, D. et al. 2014. *J. Toxicol. Pathol.* 26 (3 Suppl):1S–107S.)

Synonym(s): **Luteinized nonovulatory follicle**; **luteinized unruptured follicle**; **luteinized cystic follicle**.

Luteinized nonovulatory follicle, see the preferred term **Luteinized follicle**.

Luteinized unruptured follicle, see the preferred term **Luteinized follicle**.

Luteinizing hormone (LH) is one of the gonadotropic hormones (i.e., FSH and LH). LH is produced by the anterior pituitary gland. In females, LH triggers ovulation and stimulates the secretion of progesterone by the corpora lutea. In conjunction with FSH, LH controls the secretion of estrogen from ovarian follicles. In males, LH stimulates the production of testosterone by the Leydig cells (interstitial cells) of the testes. In conjunction with FSH, LH participates in the maturation of spermatozoa. See **Interstitial cell–stimulating hormone (ICSH)** and **Female reproductive hormones** for further information.

Synonym(s): **Lutropin, lutrophin**.

Luteinizing hormone–releasing hormone (LHRH), see the preferred term **Gondadotropin-releasing hormone**.

Luteolysis is the structural and functional degradation of the ovarian corpus luteum (CL) which occurs at the end of the luteal phase of both the estrous and menstrual cycles in the absence of pregnancy. Prolactin contributes to luteolysis during proestrus in nonpregnant, cycling female rodents. In most domestic animals, prostaglandin F2alpha (PGF2α) and oxytocin are postulated to drive luteolysis. In primates, decreasing responsiveness to luteinizing hormone is also thought to contribute to luteolysis.

Differential diagnosis: **Corpora lutea degeneration**.

Synonym(s): **Corpora lutea atresia**.

Luteoma is a type of sex cord/stromal ovarian tumor composed predominantly of highly luteinized cells with abundant pale, or vacuolated cytoplasm and distinct cell boundaries. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Luteotroph cell, see the preferred term **Pituitary acidophil cell**.

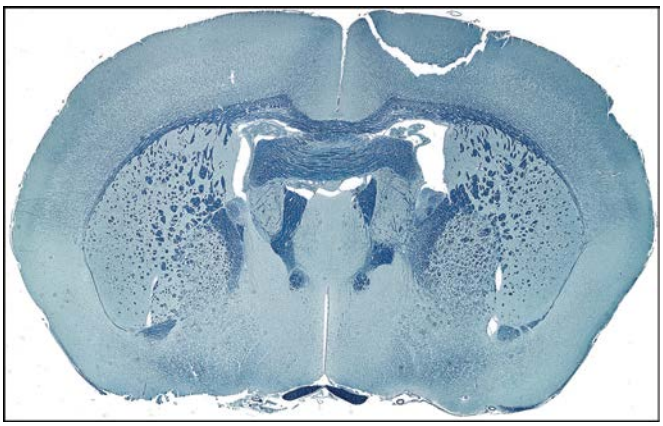
Luteotropin, see the preferred term **Prolactin**.

Lutrophin, see the preferred term **Luteinizing hormone**.

Lutropin, see the preferred term **Luteinizing hormone**.

Luxol fast blue is a stain for myelin. See **Demyelination** for further information.

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Myelin staining in a coronal section of normal brain. The darkest blue areas (white matter) have the greatest proportion of myelin. Rat. Luxol fast blue.

Lymph is the fluid that circulates through the lymphatic system comprised of lymphatic vessels emptying interstitial fluid into lymph nodes prior to mixing with venous blood.

Lymphangiectasis is a widening or dilatation of the extranodal lymphatic vessels. This term is applied to lymphatic vessels external to the lymph node. Within lymph nodes, lymphatic vessels are referred to as sinuses or sinusoids. Dilation or hyperplasia of blood vessels is a distinct lesion primarily seen in the medullary cords of some strains of aging rats and mice. These vessels may sometimes resemble lymphatics due to the absence of red blood cells within the lumen of vessels.

Lymphangioma is a rare, benign tumor originating from the lymphatic endothelial cells. They are usually well-defined and demarcated from the normal parenchyma. Morphologically, spaces or channels that are devoid of blood are lined by a single layer of well-differentiated endothelial cells, which are often slightly hypertrophied with hyperchromatic nuclei. Refer to **Cardiovascular System** in Appendix 2 for further information.

Lymphangiosarcoma is a rare, invasive malignant tumor arising from the lymphatic endothelium that is generally associated with lymphedema. Neoplastic spindle-shaped cells surround slits or channels that are devoid of blood and invade surrounding tissue, often following fascial planes. Moderate pleomorphism and/or atypia of the neoplastic cells may be present. Refer to **Cardiovascular System** in Appendix 2 for further information.

Lymph node capsular fibrosis is increased collagen and connective tissue in the capsule of the lymph node in response to chronic inflammation. Fibroblasts and other inflammatory cells may be present during active inflammation but may be absent after inflammation is resolved and remodeling has occurred. Fibrosis may distort the normal architecture and function if severe enough. Caution should be used when identifying this finding, as artifact from tangential sections of the capsule should also be considered.

Lymph node dendritic cell hyperplasia is characterized by an increased number or prominence of interdigitating cells within T-cell zones of the paracortex of lymph nodes that is often accompanied by an expanded paracortex. Dendritic cells are antigen presenting cells within the lymphoid tissue. Refer to **Lymphoid System** in Appendix 2 for further information.

Lymph node inflammation is the presence of an inflammatory process within the lymph node. Further characterization of the type of inflammatory process is required. Time frame (e.g., acute, chronic), distribution (e.g., focal, multifocal, diffuse) and predominant cell type or process (e.g., neutrophilic, granulomatous, pyogranulomatous) is encouraged. Lymph nodes drain distal sites of inflammation and the transit of inflammatory cells through lymph nodes must be distinguished from true inflammation of the lymph node proper.

Lymph node plasma cell hyperplasia is characterized by increased numbers of plasma cells usually located within medullary cords of lymph nodes but can potentially extend into the deeper paracortex. Refer to **Lymphoid System** in Appendix 2 for further information.

Lymph node reticular cell hyperplasia is characterized by increased numbers or prominence of fibroblastic reticular cells (FRC) cells of the lymph node. They have pale cytoplasm and irregular-shaped nuclei, and are difficult to see in standard hematoxylin and eosin (H&E)-stained sections. Increased FRC and reticulin fibers should be differentiated from collagen fibrosis, and scarring of the lymph node. Refer to **Lymphoid System** in Appendix 2 for further information.

Lymph nodes are discrete encapsulated secondary lymphoid organs found throughout the body. Their organized structure consists of an outer cortex, which contains multiple lymphoid follicles made up primarily of B cells with lesser numbers of antigen-presenting cells and T cells, and an inner medulla, which consists of cords containing largely plasma cells, and sinuses lined by macrophages and fibroblastic reticular cells (FRCs). In between the cortex and medulla is the paracortex, which consists almost entirely of T lymphocytes. Afferent lymphatic vessels drain distal tissues transporting extracellular fluids, leukocytes, antigen-presenting cells, and byproducts of inflammation to proximal lymph nodes. Lymph enters the lymph node via afferent lymphatics that pierce the capsule and empty into the subcapsular sinus. Paracortical sinuses then traverse the cortex and paracortex. Medullary sinuses converge in the hilus, exiting the lymph node via efferent lymphatic vessels. Fixed-tissue macrophages and FRCs line sinuses, phagocytize particulate matter, and secrete cytokines. Lymph nodes dramatically change in size and morphology

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in response to antigenic and proinflammatory stimulation. Antigen-presenting cells (APCs) arrive from distal sites, move to follicles in the cortex to encounter B cells and to the deep cortical unit of the paracortex to encounter T cells. Follicles remodel from primary to secondary follicles and paracortical areas expand. Lymphocyte trafficking originates with egress of lymphocytes from cortical and paracortical zones into sinuses exiting the lymph node, eventually rejoining circulation via the thoracic duct. Lymphocytes exit circulation, surveille tissues via migration, home to sites of inflammation, colonize other lymphoid organs as well as return to the lymph node of origin. Lymphocyte reentry to the lymph node occurs via lymphatic drainage or via circulation by transmigration across high endothelial venules (HEV), which are postcapillary venules with distinct endothelial cell morphology where the endothelium expresses unique surface proteins directing lymphocyte homing. See Appendix 3 for further information.

Lymph node sinus dilation is the condition of widening or opening of the sinus cavity space within the lymph node. Sinuses are cavities by which lymph drains through the lymph node. Lymph node sinuses are described by anatomic location as subcapsular, paracortical or transverse, and medullary. Sinuses are crossed by fine reticular fibers that are not typically seen in standard tissue sections and are lined by macrophages and flattened fibroblastic reticular cells (FRC) that serve to remove particular matter including red blood cells and inflammatory debris. Dilated sinuses may contain eosinophilic proteinaceous fluid (lymph), intact cells (e.g., lymphocytes, erythrocytes) and cellular debris.

Lymph node intrasinusoidal erythrocytes are red blood cells present within the lymph node sinuses. When hemorrhage occurs in tissues distal to the lymph node, extravascular erythrocytes may exit the immediate area by lymphatic drainage. Red blood cells arrive at the draining lymph node and are then visualized within sinuses. As time elapses, erythrocytes are engulfed by phagocytic cells (erythrophagocytosis) and then later degraded resulting in macrophages containing iron pigments within vacuoles. See **Pigmented macrophage** for further information.

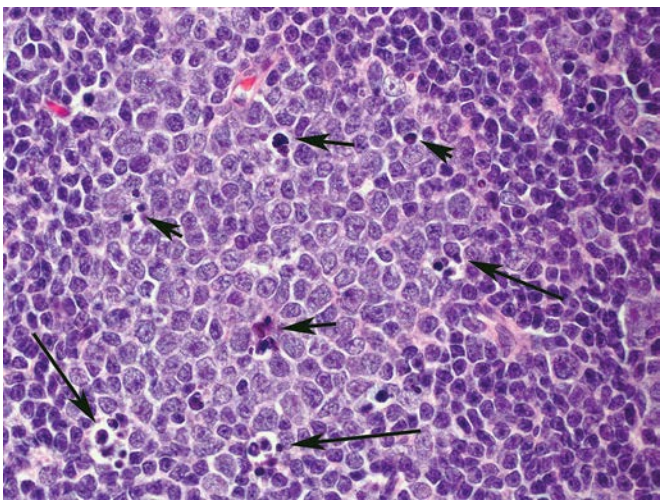
Lymphoblastic lymphoma is characterized by lymphoid cells that are medium to large in size with a high nuclear to cytoplasmic ratio, high mitotic index, and are of T- or B-cell origin. Refer to **Hematopoietic System** in Appendix 2 for further information.

Lymphoblasts are large lymphocytes (~10–20 μm in diameter) with abundant, lightly basophilic cytoplasm, and an eccentric round to reniform (kidney-shaped) nucleus that contains 1–2 small round nucleoli. They correspond to the proliferative lymphoid pool that originates from either hematopoietic stem cells or blastogenesis following clonal expansion of a small lymphocyte after antigenic stimulation. They are found in the bone marrow, lymphoid tissues, and rarely in the peripheral blood. They eventually develop into small lymphocytes or plasma cells.

Lymphocytic lymphoma is characterized by tumor cells that are well differentiated, small to medium-sized lymphocytes of T- or B-cell origin, morphologically similar to the normal circulating lymphocytes. Refer to **Hematopoietic System** in Appendix 2 for further information.

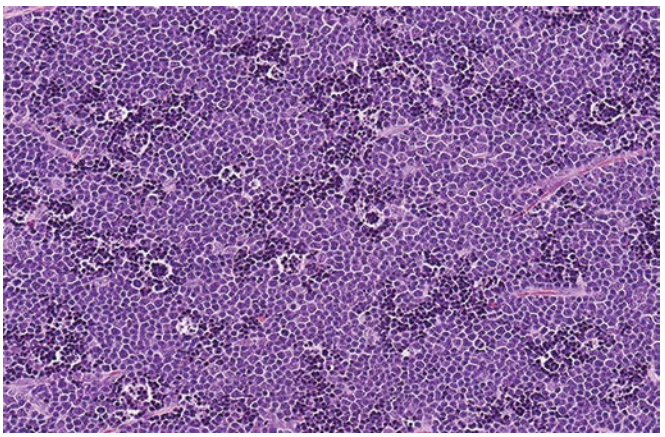
Lymphoepithelium, see the preferred term **Follicle-associated epithelium**.

Lymphoid apoptosis is commonly referred to as "programmed cell death" because it is mediated by an energy-dependent intracellular genetic program. In the lymphoid system it is found as an end stage of normal cellular processes and can also be the result of toxicological insult. Apoptosis has a very distinct morphological appearance upon light microscopy, characterized by cell shrinkage and nuclear pyknosis. The cells are smaller in size, the cytoplasm is dense, and the organelles appear more compact. Nuclear pyknosis is the result of chromatin condensation and is the most characteristic feature of apoptosis. Generally, single cells are affected. Transmission electron microscopy (TEM) can illustrate the subcellular features of apoptosis. In the early stages there is peripheralization of chromatin. In the later stages, the chromatin becomes more electron-dense and rounds up in the center of the cell. Plasma membrane blebbing and karyorhexis occurs with separation of cell fragments into apoptotic bodies that are engulfed by macrophages. These macrophages are called tingible body macrophages. Examples of normal apoptosis in lymphoid organs include clonal selection of B cells in reactive germinal centers of lymphoid follicles and central tolerance in the thymus and bone marrow. In germinal centers, apoptosis is involved in both positive and negative selection of B cells after stimulation by various antigens.

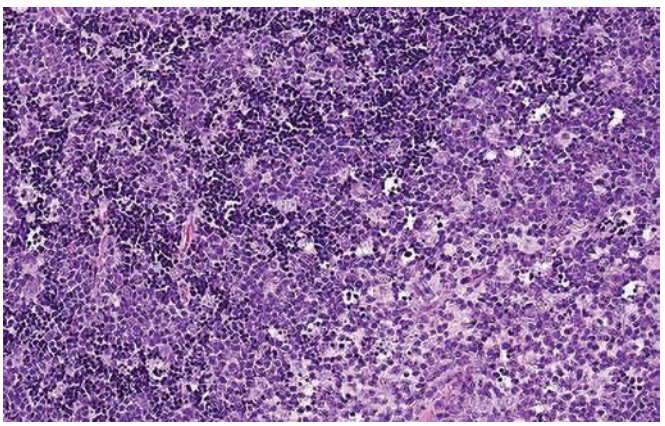


B-cell apoptosis in a reactive germinal center from a rat mesenteric lymph node. There are apoptotic cells (short arrows) and tingible body macrophages (long arrows) within a germinal center.

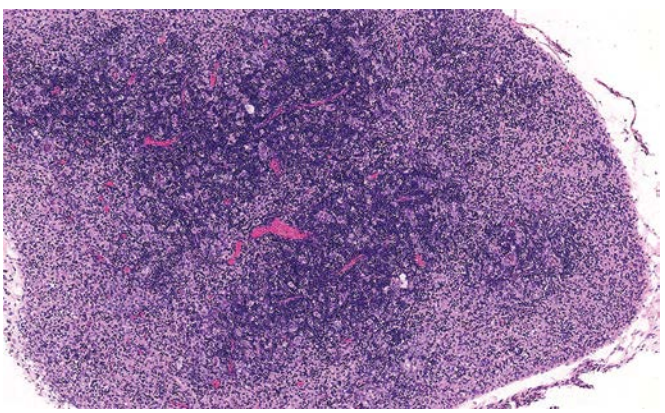
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Apoptosis of cortical lymphocytes in a 3-month-old Sprague Dawley rat treated once with 0.5 mg/kg dexamethasone and necropsied 6 hours later.



More severe apoptosis of cortical lymphocytes in a 3-month-old Sprague Dawley rat treated once with 1.0 mg/kg dexamethasone and necropsied 6 hours later. Fewer apoptotic lymphocytes occur in the medullary region (right side of image).



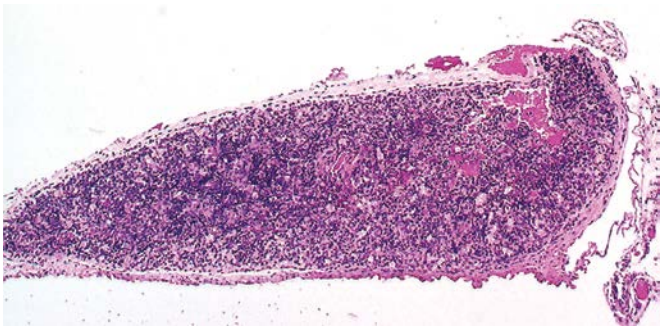
Massive thymocyte apoptosis in a B6C3F1 mouse treated with methylene blue. The majority of cortical lymphocytes are destroyed, with paler reticular epithelial cells remaining. The central medullary regions contain the darker lymphocytes.

After exposure to an antigen, activated B cells that fail to undergo germinal center differentiation do not persist as effective memory B cells, and are rapidly and negatively selected against via apoptosis.

Lymphoid atrophy is loss of lymphocytes in one or more lymphoid compartments which can result in small size and lower organ weight for lymphoid tissues, and also cause functional immunosuppression. Atrophy may also be follicular when the entire lymphoid follicle is lost. This is a common and often reversible finding in toxicology studies that may be the direct result of necrosis, apoptosis, or inhibition of proliferation of lymphocytes, or result from apoptotic loss of lymphocytes secondary to release of endogenous corticosteroids when related to stress or exogenous (administered).

Differential diagnosis: **Thymic involution, age-related** (i.e., physiologic involution may be difficult to differentiate from atrophy).

Synonym(s): **Lymphoid depletion**; **lymphoid hypocellularity**.



Marked lymphoid atrophy from experimental adriamycin administration in a C57BL/6 mouse.

Lymphoid depletion, see the preferred term **Lymphoid atrophy**.

Lymphoid follicles are found in secondary lymphoid tissues, including the spleen, lymph nodes, and mucosa-associated lymphoid tissue (MALT). Lymphoid follicles are made up primarily of a central zone consisting of B cells with fewer numbers of antigen presenting cells throughout, and T cells along the periphery. Lymphoid follicles are defined as primary prior to antigenic stimulation, and secondary following antigenic stimulation with formation of a central germinal center. Follicular morphology is best illustrated in the spleen, where the innermost portion of the lymphoid follicle contains B lymphocytes (CD20+) and is divided into a central region termed the germinal center. This central germinal center contains proliferating and differentiating B lymphocytes and is surrounded by concentric zones of more mature B lymphocytes starting with (from innermost to outermost) the mantle zone, the inner marginal zone, a band of smooth muscle actin (SMA)+ myofibroblasts (MF), and the outer marginal zone that lies outside the SMA+ band of MF. Immediately outside the B lymphocytes of the central lymphoid follicle is the central splenic arteriole, which is surrounded by the periarteriolar lymphoid sheath (PALS), consisting of primarily $CD3^+$ T cells.

In lymph nodes, the lymphoid follicular structure is simplified compared to follicles in the spleen. The lymph node consists of an outer cortex, which contains multiple lymphoid

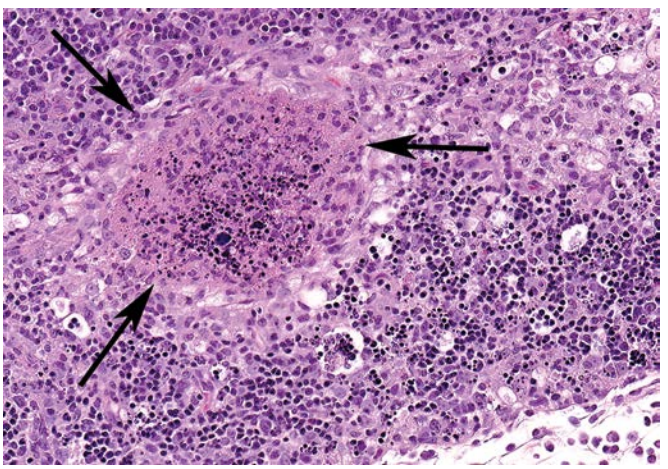
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follicles made up primarily of B lymphocytes, an inner medulla, which consists of cords that largely contain plasma cells, and sinuses containing macrophages, fibroblastic reticular cells (FRCs), and other leukocytes. In between the cortex and medulla is the paracortex, which consists almost entirely of T lymphocytes. See Appendix 3 for further information.

Lymphoid hyperplasia is characterized by increased numbers of lymphocytes or an increase in size or prominence of lymphoid compartments within lymphoid tissues. Modifiers may be added to specify the location or compartment involved (e.g., follicular hyperplasia, paracortical hyperplasia, medullary hyperplasia). Refer to **Lymphoid System** in Appendix 2 for further information.

Lymphoid hypocellularity, see the preferred term **Lymphoid atrophy**.

Lymphoid necrosis can occur in all lymphoid organs and involves B lymphocytes more often than T lymphocytes. It is usually caused by factors external to the cell or tissue (e.g., infection, toxins, or trauma) that are severe enough to result in the unregulated digestion of cellular components. Unlike apoptosis, there is loss of cell membrane integrity with a subsequent uncontrolled release of cellular components into the extracellular space, with activation of proinflammatory mediators and recruitment of inflammatory cells. Lymphocyte necrosis can also result when lymphocyte apoptosis is so severe that cellular components, such as caspases, necessary for apoptosis are depreciated, thus converting an apoptotic phenotype to a necrotic one.



Massive dexamethasone-induced apoptosis in a Sprague Dawley rat that led to consumption of apoptotic factors (such as caspases) and resulted in a focal necrotic phenotype (arrows).

Lymphoid neogenesis, see the preferred term **Tertiary lymphoid structure**.

Lymphoid system, Anatomy and Histology, see Appendix 3 for further information.

Lymphoid tissue refers to all of the tissues and organs that comprise the lymphoid system. Broadly, lymphoid tissue can be divided into primary lymphoid tissues, those where T and B lymphocytes originate and develop, and secondary lymphoid tissues, where T and B lymphocytes mature and become activated. The primary lymphoid tissues are the thymus, where T cells develop, the bone marrow in mammals and bursa of Fabricius in birds, where B cells develop (B lymphocytes are named for the avian bursa of Fabricius). Secondary lymphoid tissues are numerous, and include the lymph nodes, the spleen, and all the various mucosa-associated lymphoid tissues (MALT), which are organized lymphoid tissues that are found in the subepithelial locations of mucosal surfaces, such as the gastrointestinal (GI) tract, respiratory tract, and conjunctiva. Tonsils are particularly large and well-developed examples of MALT in the oral cavity. Lymphatic vessels are found throughout the body and connect peripheral tissues to lymph nodes, which function to respond to tissue-based pathogens. The spleen functions to respond to blood-borne pathogens. Pathogens come in contact with the immune system in mucocutaneous epithelial tissues such as skin, the GI tract, and respiratory tract, where dendritic cells recognize the pathogen and present antigens to cells in lymphoid tissues, thus initiating both cell-mediated and humoral immune responses. Naïve mature lymphocytes traffic or recirculate throughout the body, leaving the circulation via specialized postcapillary venules termed high endothelial venules (HEV) in lymph nodes and MALT, and return to the circulation via lymphatics and the thoracic duct. HEV are lined by tall cuboidal endothelial cells and are predominantly found in the paracortex or T lymphocyte zone but are also found to a lesser extent in the cortex, or B lymphocyte zone. Lymphocyte trafficking is not random; rather, lymphocytes home to specific locations using surface homing receptors that are specific for tissue-specific molecules termed vascular addressins on endothelial cell surfaces. For example, homing to mucosal tissues occurs via $\alpha 4\beta 7$ integrin on lymphocytes and mucosal addressin cell adhesion molecule-1 (MAdCAM-1) on HEV of mucosal tissues, while homing to peripheral lymphoid tissues occurs via L-selectin on lymphocytes and glycosylation-dependent cell adhesion molecule-1 (GlyCAM-1) on HEV of peripheral lymph nodes or CD34 on peripheral endothelial cells.

Lymphoid tissue, increased cellularity, see the preferred term **Lymphoid hyperplasia**.

Lymphoma is a malignant, systemic lymphoid tumor which is often leukemic (i.e., circulating neoplastic lymphoid cells in the blood). Refer to **Hematopoietic System** in Appendix 2 for further information.

Lymphoma, cutaneous, see the preferred term **Lymphoma, epitheliotrophic (canine)**.

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Lymphoma, epitheliotrophic (canine) is a spontaneous neoplasm of skin and mucous membranes that occurs in old dogs (mean age 11 years), where the neoplastic lymphocytic infiltrate demonstrates very prominent epitheliotropism, and are all of T-cell origin. Refer to **Skin** in Appendix 2 for further information.

Lymphoma, extranodal marginal zone B cell, see the preferred term **Mucosa-associated lymphoid tissue lymphoma**.

Lymphoma, follicular center cell is a form of lymphoma with multiple nodules or follicle-like structures that are evident at low microscopic magnifications. It can occur in both lymph nodes and spleen and is characterized by a proliferation of diffuse sheets of pleomorphic cells of B lymphocyte origin that invade and efface normal lymphoid architecture. Refer to **Lymphoid System** in Appendix 2 for further information.

Lymphoma, thymic is a malignant neoplasm composed of sheets of neoplastic homogeneous lymphocytes. This neoplasm originates in the thymus, is of T-cell origin, and may spread to the surrounding tissues and organs such as the liver, spleen, and lymph nodes. Refer to **Lymphoid System** in Appendix 2 for further information.

Lymphoneogenesis, see the preferred term **Tertiary lymphoid structure**.

Lymphopenia is characterized by decreased lymphocyte counts in the peripheral blood due to retention of lymphocytes within lymphoid organs and increased lysis.

Lymphosarcoma, see the preferred term **Lymphoma**.

Lysosomal lamellar body is a structure observed within a lysosome, a cytoplasmic organelle that digests damaged cellular membranes and organelles. During normal cellular processing, lysosomes frequently contain multilayered, loose, small whorls (lamellar bodies) on ultrastructural examination. See **Multilamellar bodies** for further information.

Lysosomal storage disease is a category of storage disorders characterized by intracellular accumulation of endogenous material, particularly within lysosomes. This accumulation results from defects in various mechanisms involved in lysosomal function (e.g., abnormal processing, degradation, transport). Dysfunction of these mechanisms can be due to inherited defects and result in tissue damage or dysfunction in a variety of organ systems. See **Multilamellar bodies** for further information.

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M

MABEL is an acronym for the minimal anticipated biological effect level. It is used mainly for biopharmaceutical drug candidates to determine a safe starting dose for Phase 1 trials at which no pharmacological effects are to be expected. The MABEL is derived from animal pharmacology and pharmacokinetic data, using physiological-based modeling for cross-species extrapolation to determine the human equivalent dose.

Macrophage hyperplasia is a benign and local increase in the number of macrophages that occurs by proliferation of tissue-resident macrophages within lymphoid and non-lymphoid tissues and in body cavities. Refer to **Lymphoid System** in Appendix 2 for further information.

Macrophage vacuolation describes the occurrence of fine, variably sized clear spaces within the cytoplasm of macrophages. They may be observed in the sinusoids of lymph nodes, choroid plexus of the brain, and red pulp to marginal zone of the spleen. The vacuoles may represent lysosomal accumulation of phospholipids, as is observed with certain cationic amphophilic drugs. Some lipid-containing or pegylated xenobiotics can increase the incidence of macrophage vacuolation. When macrophage vacuolation is largely related to the vehicle, incidence and/or severity might increase with higher dose volumes. In such cases, an apparent dose response should take into consideration dose volumes and/or excipient concentrations. See **Cellular vacuolation** for further information.

Macrovesicular vacuolation, see **Lipid accumulation** for further information.

Macule is a clinical veterinary or medical dermatology term. It is a circumscribed, focal discoloration of the skin. The discoloration can be of any origin (e.g., blood extravasation, skin pigment accumulation). A macule is neither depressed nor elevated. The diameter of a macule does not exceed 1 cm. A change in discoloration greater than 1 cm in diameter is usually called a patch.

MAD (multiple ascending dose study) is a study similar in design to a SAD (single ascending dose) study but the subjects receive multiple doses of study drug or placebo. See **Clinical Trial Phase I** for further information.

Magakaryocytic myelosis, see the preferred term **Megakaryocytic leukemia**.

Magnusson-Kligman maximization test is an in vivo test conducted in guinea pigs to screen for human skin sensitizing agents. The test material is injected intradermally along with an adjuvant, and then a challenge dose is administered at a lower concentration after a given duration. The test is described in OECD guideline 406 but has largely been replaced by the local lymph node assay. See **Local lymph node assay** for further information.

MALDI an abbreviation for matrix-assisted laser desorption ionization, a mild form of ionization used in mass spectrometry of large molecules, particularly peptides and proteins. These large molecules may then be separated by time of flight mass spectrometry (MALDI-TOF-MS).

Male reproductive tract feminization results from a disruption in normal endocrine homeostasis due to a variety of xenobiotic classes. These xenobiotics may mimic or block actions of natural hormones and their receptors and alter the normal regulatory function of the hypothalamic-pituitary-testis (HPT) axis. Specific causative agents include bisphenol A (BPA), phthalate esters, polychlorinated biphenyls (PCBs), dichlorodiphenyltrichloroethane (DDT), dioxin and certain pesticides, estrogenic xenobiotics including selective estrogen receptor modulating drugs (SERMs) such as tamoxifen and idoxifene, estrogenic effluents found in sewage, and genetic mutations resulting in androgen insensitivity (Tfm/y) in rodents. The effects of exposure vary depending on the age and species of the test animal. In utero exposure can produce hypoplasia of the testes, epididymides, and/or accessory sex organs, cryptorchidism, underdeveloped scrotal size, shortened anogenital distance (AGD), disruption of the blood-testis barrier (BTB), and sperm parameter alterations. Postnatal, pubertal, and adult animal exposures can result in inhibited gonadal maturation, Leydig and/or Sertoli cell dysfunction, Leydig cell atrophy, depletion of various germ cell subpopulations, epididymal epithelial atrophy and/or apoptosis (the latter of occurs particularly in the caput epididymis), decreased prostate size and weight with epithelial squamous metaplasia and increased prostatic fibromuscular stroma, and an overall decrease in accessory organ secretions.

Differential diagnoses: Testicular atrophy; **Cryptorchidism**.
Synonym(s): **Pseudohermaphrodite**.

Male sex hormones consist of testosterone, dihydrotestosterone, estradiol, FSH, LH, and prolactin. Testosterone, secreted by the Leydig cells (LC), is responsible for cranial Wolffian differentiation to the epididymis, central part differentiation to the vas deferens, and caudal part differentiation to the seminal vesicles and the ejaculatory duct, as well as spermatogenesis within the testis. Testosterone is transported into the peripheral circulation and into the seminiferous tubule fluid and metabolized to dihydrotestosterone by 5α-reductase, and

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to estradiol by aromatase. Dihydrotestosterone is responsible for the development of the prostate and external genitalia, and is the main androgen regulating epididymal and accessory sex organ function. Estradiol has important regulatory functions in the efferent ducts and epididymis. Luteinizing hormone (LH) provides the major stimulus for testosterone production. In dogs and nonhuman primates, a pulse of LH is closely followed by a pulse of testosterone. In rats, several LH pulses may elicit no rise in testosterone, or there may be a significant delay before a testosterone pulse occurs. Follicle-stimulating hormone (FSH) acts on Sertoli cells (SC), regulating several cellular processes including inhibin secretion, which negatively feeds back to the hypothalamus and pituitary. The action of FSH on immature and mature animals is profoundly different. FSH is often considered to be the hormone of puberty, as rising levels of FSH act as a trigger for testicular growth, junction formation between adjacent SC, androgen-binding protein secretion from the SC, and spermatogenesis initiation. Prolactin secreted from the pituitary gland modulates LH receptor number/sensitivity on LC, and therefore has a regulatory role in the secretion of testosterone. In the rat, prolactin permits LH-stimulated testosterone secretion by increasing the number of LH receptors on the LC. LC of other species do not have prolactin receptors, which has important implications in the evaluation of species-specificity/sensitivity to xenobiotic-induced LC tumors.

M

Malformation is a fetal abnormality which is a permanent change that is likely to adversely affect survival, development, or function of the offspring.

Malignancy is often defined by cellular features of neoplastic (tumor) cells. Morphologically, malignant cells are characterized by a large nucleus, often having an irregular size and shape, prominent nucleoli, and decreased dark or pale, poorly staining cytoplasm. The nucleus of neoplastic cells can have increased volume with a subsequent increased nuclear:cytoplasmic ratio, abnormal shape and density, and occasionally be markedly enlarged (karyomegaly) or have increased numbers of nuclei (multinucleated). Mitoses, including atypical mitotic figures, are common in malignant cells. See **Neoplasia** and **Tumor differentiation** for further information.

Malignant cell epithelioma, see the preferred term **Renal tubular carcinoma**.

Malignant cholangioma, see the preferred term **Cholangiocarcinoma**.

Malignant hemangioendothelioma, see the preferred term **Hepatic hemangiosarcoma**.

Malignant hepatoma, see the preferred term **Hepatocellular carcinoma**.

Malignant mesenchymoma, see the preferred the term **Mixed sarcoma**.

Mallory bodies are cytoplasmic inclusions that appear as clumps of hyaline, eosinophilic material within hepatocytes. They have recently been renamed Mallory-Denk bodies. Mallory (1911) first described them in association with alcoholic hepatitis in humans. Denk et al. (1975) described them in association with griseofulvin (an antifungal drug) toxicity in mice. They are composed of cytokeratins (CK8 and CK18) along with other peptides and proteins such as ubiquitin and p62, both involved in proteasomal degradation pathways. As such, it is hypothesized that Mallory bodies result from intracellular stress. The cytokeratin in Mallory-Denk bodies can be labeled by immunohistochemistry.

References

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Mallory, F. 1911. Cirrhosis of the liver. Five different types of lesions from which it may arise. *Bul. Johns Hopkins Hosp.* 22: 69–75.

Mammalian cell mutation test is an in vitro test for the induction of mutations using mammalian cells as test system and a biochemical cell function as the genetic endpoint See **Eukaryotic mutagenicity tests** for further information.

Mammalian cell transformation assays are tests for the formation of a cancerous cell from a noncancerous cell. These assays often use morphological parameters such as cell colony appearance or the ability to grow without a solid support matrix. This endpoint is not genetically well defined but is associated with features that resemble tumor cells in vivo. The most commonly used transformation assay uses Syrian hamster embryo (SHE) cells. Cell transformation assays are not widely used in drug development.

Mammary adenosquamous carcinoma is a neoplasm in mice characterized by a mixed glandular and squamous phenotype whereby the squamous component composes at least 25% of the neoplasm. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Mammary carcinosarcoma, see the preferred term **Mammary tumor, mixed**.

Mammary gland adenocarcinoma is a malignant neoplasm of the mammary gland characterized by an infiltrative mass with epithelial pleomorphism and atypia. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Mammary gland adenocarcinoma arising in fibroadenoma is a rat-specific tumor in which focal areas of adenocarcinomatous differentiation are observed within a fibroadenoma. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

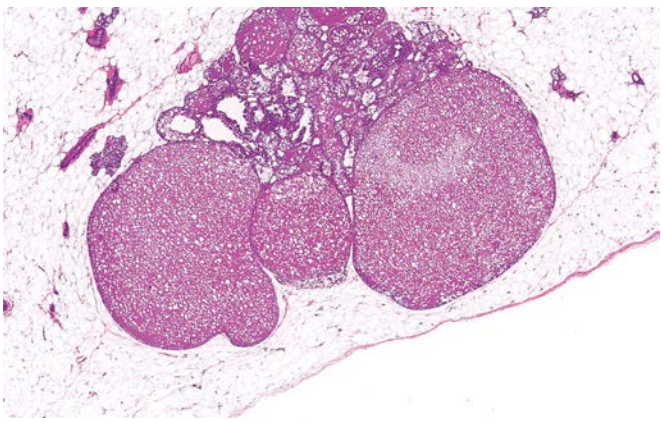
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Mammary gland adenoma is a benign neoplasm of the mammary gland characterized by a well-demarcated and compressive area composed of dense, generally well-differentiated alveolar and tubular epithelium. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Mammary gland ductal hyperplasia is characterized in the female by the presence of extralobular ducts with a stratified epithelium (usually 3 or more layers). Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Mammary gland, duct/alveolus, dilation is characterized by the distension of single or groups of alveoli and/or ducts with or without alveolar/ductal epithelial hypertrophy or hyperplasia. The dilated alveolus or duct may vary in diameter and contain secretions, cellular debris and/or mineral.

Synonym(s): **Mammary gland, duct/alveolus, ectasia**; **mammary gland, duct/alveolus, galactocele**.



Marked dilation (ectasia) of mammary gland duct, H&E. (Reproduced with permission of Society of Toxicologic Pathology from Rudmann, D. et al. 2012. *Toxicol. Pathol.* 40:7S–39S.)

Mammary gland, duct/alveolus, ectasia, see the preferred term **Mammary gland, duct/alveolus, dilation**.

Mammary gland, duct/alveolus, galactocele, see the preferred term **Mammary gland, duct/alveolus**, **dilation**.

Mammary gland fibroadenoma is a benign neoplasm composed of a mixture of predominantly fibrous connective tissue with variable numbers of epithelial cells, forming ducts or acini. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Mammary gland hyperplasia, **lobuloalveolar**, see the preferred term **Mammary gland lobular hyperplasia**.

Mammary gland hyperplastic alveolar nodule (HAN) is a form of mammary lobular hyperplasia that occurs in high incidence in mice harboring mouse mammary tumor virus (MMTV). Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Mammary gland inflammation is comprised of leukocytic infiltrates in the mammary gland in conjunction with evidence of tissue damage and/or repair, vascular congestion, edema, exudates, fibrosis/fibroplasia, all depending on the chronicity of the response and the inciting event. It may have an infectious or noninfectious origin, and an infectious origin is most often observed during weaning or pseudopregnancy. While uncommon in rodents, infection by the bacterium *Pasteurella pneumotropica* should be ruled out. Regenerative, hyperplastic, and/or metaplastic changes in the affected epithelium and fibroplasia may also be present.

Synonym(s): **Mastitis**.

Mammary gland lobular hyperplasia is characterized by focal or diffuse epithelial proliferation in the acini of the mammary gland with physiologic (lactation) or pathologic origins. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Mammary gland pseudopregnancy, see the preferred term **Mammary gland lobular hyperplasia**.

Mammary tumor, **mixed** is a neoplasm of the dog mammary gland that is composed of at least an epithelial and a mesenchymal (myoepithelial) component with a fibrous stroma and foci of cartilage, bone, and/or adipose tissue. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

M

Mammotroph cell, see the preferred term **Pituitary acidophil cell**.

MAO is an abbreviation for monoamine oxidase. See **Monoamine oxidase** for further information.

Marginal zone lymphoma is a lymphoma originating from the marginal zone in the spleen in which the marginal zone expands and leads to coalescing of the white pulp. Refer to **Hematopoietic System** in Appendix 2 for further information.

Marker enzymes are considered specific to a cellular type, component, or organelle, and are typically measured in the serum, but also in in vitro assays. Marker enzymes allow characterization of the integrity of a subcellular compartment by measuring the levels or activity of the enzyme compared to other isoforms or enzymes found in other parts of the cell. Overall, they serve as indicators of tissue integrity and function. Examples include succinate dehydrogenase in mitochondria, acid phosphatase in lysosomes, and creatine phosphokinase isozymes to differentiate sources from heart, skeletal muscle, and brain/lungs. See **Biomarkers** for further information.

Marmoset wasting syndrome is one of the leading causes of morbidity and mortality in captive marmosets. The etiology, pathogenesis, and disease spectrum are poorly defined, with several case-definitions reported in the literature. The

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only consistent clinical sign is chronic weight loss; however, alopecia and diarrhea are also typically noted. Other clinical criteria have included weakness and muscle loss leading to hind limb weakness and/or paralysis. Clinical pathology findings are variable and may include anemia, decreases in albumin or total protein, and variable elevation in liver enzymes, and in some cases increases in calprotectin, white cell counts, and/or muscle creatine kinase (CK) are also noted. Histologically, variable mononuclear-to-mixed, chronic-active colitis, and/or typhlitis are often seen (although not in all instances), and there is a question as to the primacy of this finding in the overall syndrome, given the ubiquity of colitis in captive callitrichids, not all of whom succumb to the wasting syndrome. Glucocorticoids are useful in treating signs associated with this syndrome.

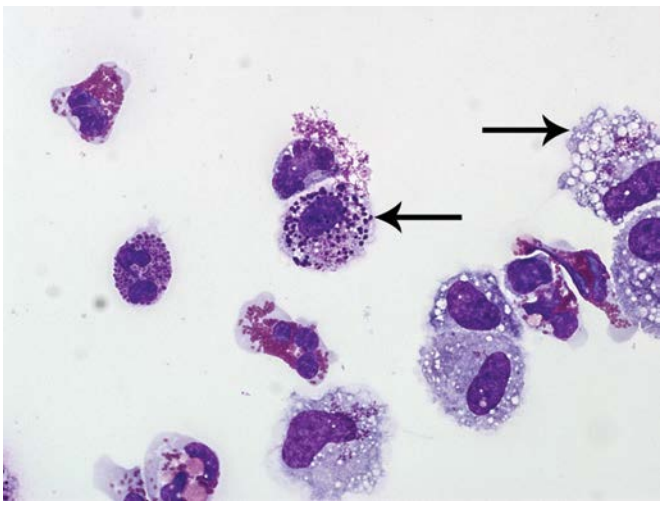
Masson hemangioma, see the preferred term **Papillary endothelial hyperplasia**.

Mast cell hyperplasia is a nonneoplastic proliferation of mature mast cells, as within the site of origin of an allergic reaction or parasitic infections. This should be differentiated from mast cell tumor. Refer to **Skin** in Appendix 2 for further information.

Mast cell leukemia is a malignant mast cell tumor in bone marrow showing atypical mast cells (a type of granulocyte derived from the myeloid stem cell that is a part of the immune and neuroimmune systems and contains many granules rich in histamine and heparin) in the peripheral blood. Mast cell accumulations/nodules are present in hematopoietic and/or lymphoid tissues. Refer to **Hematopoietic System** in Appendix 2 for further information.

Mast cells are granulocytes that are derived from CD34+ bone marrow myeloid precursor cells, similarly to basophils. Basophils exit bone marrow fully differentiated, while mast cells leave in an immature state, circulate in blood, and differentiate and mature in situ in tissues. Mast cells are most common in loose connective tissue but may also be present in other tissues. Mast cells are heterogeneous in morphology and function. They characteristically have an ovoid, nonsegmented nucleus, and cytoplasm containing variable amounts of prominent granules that stain metachromatically with Toluidine blue. Degranulation can occur via multiple mechanisms. Importantly, degranulation occurs in response to allergen-mediated cross-linking of IgE that is bound to mast cells via FcεRI. These cells can release a variety of bioactive chemicals, either preformed or newly synthesized. Preformed mediators from granules include serine proteases, such as tryptase and chymase, histamine, serotonin, and proteoglycans, mainly heparin. Newly formed lipid mediators (e.g., eicosanoids) include thromboxane, prostaglandin D2, leukotriene C4, and platelet-activating factor. Cytokines also may be produced, including eosinophil chemotactic factor and TNFα. Special stain histochemistry such as chloroacetate esterase (CAE) or IHC for c-kit (CD117) may be used to differentiate mast cells from basophils. Mast cells are positive for both CAE and c-kit, while basophils are negative for both stains.

Mast cells have a round nucleus with numerous metachromatic granules, is ~10–15 μm in diameter, and stains magenta to purple with Romanowsky, May-Grünwald Giemsa, and toluidine blue stains. Mast cell proliferation and differentiation is stimulated primarily by SCF where it acts as a chemotactic agent, but also by cytokines including IL-3, IL-4, IL-9, IL-10, and IL-13. Committed mast cell precursors leave the bone marrow during development and migrate into tissues where they can live for weeks to months. They do not usually circulate in peripheral blood but are found in the skin and mucosal tissues in health, and are a major effector cell of immediate hypersensitivity (anaphylactic) reactions and allergic diseases. When activated, they release potent inflammatory mediators including histamine, proteases, chemotactic factors, cytokines, and metabolites of arachidonic acid. Activation involves cross-linking of antigen and IgE bound to the FcξRI of mast cells resulting in degranulation and increased vascular permeability, smooth muscle contraction, and mucus secretion. They are an innate immune cell that can rapidly detect invading microorganisms such as bacteria, parasites, and viruses through Toll-like receptor recognition. They also display adaptive immunity through antigen presentation via MHCI and MHCII complexes and can directly activate T lymphocytes through the release of TNF-α. Cutaneous mast cell tumors (cutaneous mastocytosis) have been reported in laboratory animal species, and can be benign or neoplastic.



Mast cells, bronchoalveolar lavage fluid, monkey.

Mast cell sarcoma is comprised of atypical often pleomorphic mast cells and may be hypogranular. Due to hypogranularity, it is often difficult to distinguish from other sarcomas without special stains. Refer to **Hematopoietic System** in Appendix 2 for further information.

Mast cell tumor is the neoplastic proliferation of mast cells and must be differentiated from mast cell hyperplasia, as most of these tumors present easily recognizable neoplastic

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mast cells including a round shape, central to paracentral nucleus, and lightly blue cytoplastic granules. It is a relatively frequent skin tumor in dogs (is less frequent in other laboratory animal species such as rodents and macaques). Paraneoplastic syndromes involving skin, gastrointestinal, or systemic paraneoplastic syndromes can be associated with this tumor. Refer to **Skin** in Appendix 2 for further information.

Differential diagnosis: **Mast cell hyperplasia**.

Mastitis, see the preferred term **Mammary gland inflammation**.

Mastocytoma, see the preferred term **Mast cell tumor**.

Mastocytoma, benign is a single nodule comprised of well-differentiated cells (benign tumor), while mastocytosis (malignant tumor) consists of multiple sites that are more infiltrative. Refer to **Hematopoietic System** in Appendix 2 for further information.

Mastocytoma, malignant are mast cell tumors in which multiple sites are involved and a more infiltrative growth pattern exists. The tumor may show an infiltrative growth pattern and has no bone marrow involvement (i.e., malignant tumor). Refer to **Hematopoietic System** in Appendix 2 for further information.

Mastocytosis, see the preferred term **Mastocytoma, malignant**.

Maternal toxicity represents adverse events caused by a substance (e.g., chemical, drug), a pathogen (e.g., microorganism, virus) or any other agent (e.g., radiation) that could affect a pregnant female. Generally, the highest dose level in an embryofetal toxicity study should show signs of maternal toxicity.

Mating index (%) is the percentage of cohabited animal pairs that mate, or number mated or inseminated/number paired $\times$ 100.

Maximum tolerated dose (MTD) is the highest dose in a toxicology/tolerability study that does not result in moribundity/death or in severe clinical signs including gastrointestinal intolerance and/or body weight losses that would impact the ability of the animal to humanely receive or survive continued dosing. A dose level producing obvious pain or discomfort that cannot be ameliorated or attenuated is not considered a tolerated dose.

Mean corpuscular hemoglobin (MCH) is a red blood cell index that represents the average weight (mass) of hemoglobin in the average red blood cell and is calculated using the following formula:

$$\text{MCH} = \frac{\text{Hemoglobin (g/L)} \times 10}{\text{RBC} (\times 10^{12}/\text{L})}$$

The reporting unit for MCH is in picograms (pg). The reference range for the MCH in humans is approximately 26–34 pg, and values in veterinary species is fairly consistent to this range. MCH values usually rise or fall in the same direction of change as the MCV. False elevation of the MCH may occur in the presence of hyperlipidemia or leukocytosis because increased turbidity may falsely elevate the hemoglobin concentration. Failure to lyse red blood cells may occur in disease states such as hemoglobinopathies and contribute to falsely decreased MCH values. MCH is the most stable of the RBC indices since hemoglobin and red blood cell count are also relatively stable over short periods of time (i.e., 72 hours).

Mean corpuscular hemoglobin concentration (MCHC) represents the average concentration of hemoglobin in all the red blood cell. MCHC is calculated with the following formula:

$$\text{MCHC} = \frac{\text{Hemoglobin(g/L)} \times 100}{\text{Hematocrit (\%)}}$$

Reporting units for MCHA is grams/deciliter (g/dL). The reference range for MCHC is approximately 32–36 g/dL in humans and varies only slightly among species and due to red blood cell (RBC) size. Most veterinary species tend to have a slightly lower MCHC reference range than humans. Low MCHC values are typically associated with hypochromic RBCs associated with iron deficiency or decreased hemoglobin production. Hyperchromic conditions and MCHC values above the maximum threshold of hemoglobin content are always considered an artifact. MCHC is a calculated parameter, so it is dependent on the accuracy of hemoglobin and hematocrit. Since hematocrit is also a calculated parameter on most automated hematology analyzers, false increases or decreases in MCV or RBC will falsely change the MCHC value. Hyperlipidemia, hemolysis, Heinz bodies, and excess EDTA can be associated with a falsely increased MCHC. The MCHC parameter is not stable. It can either increase due to hemolysis of RBC or decrease due to swelling of RBC with storage.

Mean corpuscular volume (MCV) represents the average volume of the red blood cell. MCV is typically measured directly with automated hematology analyzers but it can also be calculated using the following formula:

$$\text{MCV} = \frac{\text{Hematocrit (\%)} \times 10}{\text{RBC} (\times 10^{12}/\text{L})}$$

MCV is a useful measure in the classification of anemias. Red blood cells may be classified as microcytic, normocytic, or macrocytic based on MCV results. Low MCV values are often associated with iron deficiency anemia, lead poisoning, or hemoglobinopathies. Macrocytic anemias have high MCV values and are more typically associated with chemotherapy, folate deficiency, or B_{12} deficiency. Reporting units for MCV are expressed in femtoliters (fL). The reference range for MCV is 80–100 fL in humans, but the reference range

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for MCV is species-dependent and varies widely among species. For example, the MCV in goats can be as low as 15 fL, whereas the MCV in some avian species can exceed 300 fL. False elevations in MCV are associated with warm or cold agglutinins or in old samples due to swelling of red blood cells. When liquid EDTA anticoagulants are used, underfilling the tube may cause red blood cells to shrink due to osmotic effects (dehydration of red blood cells) resulting in a falsely decreased MCV value. MCV is not a stable parameter and increases due to red cell swelling upon storage.

Mean platelet component (MPC) represents the mean refractive index of platelets, and is an indication of platelet density. It is expressed in grams per deciliter (g/dL) and is reduced when platelets degranulate. MPC also inversely correlates with platelet membrane P-selectin expression; thus it has been proposed that MPC can be a marker of platelet activation. However, MPC is not stable in EDTA and will decrease within a few hours. It is considered a quick way to assess platelet concentrate quality but cannot replace P-selectin expression to assess platelet activation.

Mean platelet volume (MPV) is the average size of platelets in a whole blood sample and is directly measured by electrical impedance or a laser-based instrument. For reproducible results, it is best to analyze the samples 1–3 hours after collection. Over time, platelets will swell and the MPV will increase. The MPV is expressed in femtoliters, and the reference range in humans is 7.5 femtoliter (fL) to 111.5 fL. The reference in animals is species dependent and varies within species. The MPV gives an indication of platelet production by the bone marrow, and of platelet reactivity, as the younger the platelets are, the larger and the more reactive they become. MPV should be evaluated in relation with platelet count.

Meckel diverticulum is an uncommon incidental congenital finding of gastrointestinal tract in laboratory animals.

Median lethal concentration, or LC_{50}, is the concentration of a test article that will be lethal to 50% of the cells or animals exposed.

Median lethal dose is the dose level of a test drug or substance that will be lethal to 50% of the animals receiving the dose. See **LD_{50}** for further information.

Medulloblastoma is a primitive neuroectodermal tumor (PNET) originating in the cerebellum that is composed of a uniform population of neoplastic cells that resemble cerebellar granule cell neurons. Medulloblastomas can be locally infiltrative and metastasize within the central nervous system. Refer to **Nervous System** in Appendix 2 for further information.

Megacolon is an abnormal dilatation of the colon, either segmental or generalized, which may occur as either a congenital or acquired condition. As an acquired condition, luminal obstruction, constriction, or compression due to a variety of causes result in dilatation and ultimate loss of function, whereby peristalsis can no longer be maintained. In humans, acquired onset can result in a condition known as toxic megacolon, typically as a complication of infectious or inflammatory bowel disease, and resulting in systemic toxicity that can be life threatening. An idiopathic but presumably acquired form is relatively common in cats (and rare in dogs) arising from colonic inertia of undetermined cause. As a congenital and variably heritable condition, megacolon is a seen in humans as Hirschsprung disease (intestinal aganglionosis): a developmental disorder of the enteric nervous system, which occurs along some or all of the colon due to the failure of neural crest cell migration during development. As a result, there is an absence of ganglion cells in submucosal or myenteric plexus, and reduced cells of Cajal (considered the intestinal pacemaker cells important to smooth muscle peristalsis), collectively causing dysregulation, stricture, and massive dilatation of the colon. A similar condition occurs in overo spotted horses with lethal white foal syndrome, whereby impaired neural crest migration (including melanocytes) produces similar results, with foals homozygous for the heritable defect dying from fatal constipation. In horse and humans, mutations in the endothelin receptor B gene (EDNRB gene) have been implicated. In mice, a growing number of genes deleted in knockout models have resulted in intestinal aganglionosis, with germline mutations in RET and EDNRB most studied, highlighting the complexity of enteric nervous system development.

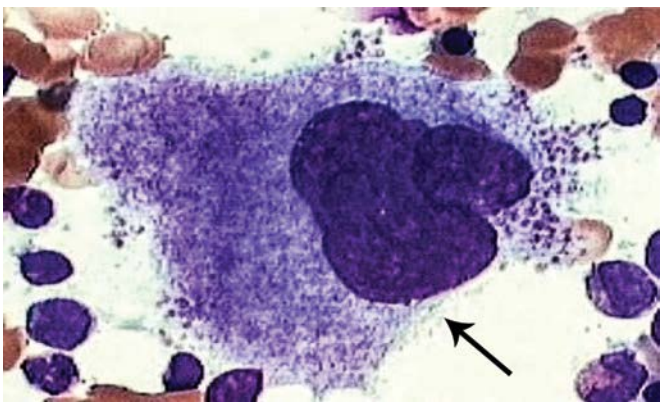
Megaesophagus is an abnormal dilatation of the esophagus, either segmental or generalized, which may occur as either a congenital or acquired condition. Some instances may be due to an obstruction within the lumen, or constriction such as with persistent right aortic arch (a vascular ring anomaly) whereby the esophagus is constricted by the surrounding vessel, resulting in upstream dilatation. Other focal lesions, for example abscesses, tumors, or chronic inflammation resulting in stricture, may also produce dilatation cranial to the blockage. It occurs congenitally, as an inherited condition in several breeds of dogs, cats, and some horses. As an acquired condition in animals, it has been associated with diseases and toxins including myasthenia gravis, systemic lupus erythematosus, polymyositis, hypoadrenocorticism, hypothyroidism, heavy metal (lead) and thallium toxicity, glycogen storage disease, neurotoxin-induced cholinesterase inhibition, dysautonomia, peripheral neuropathies of multiple causes, and as a paraneoplastic syndrome in cases of thymoma, for example. Irrespective of cause, symptoms of megaesophagus include regurgitation and an increased risk of aspiration pneumonia. In humans, megaesophagus occurs most commonly with achalasia: an idiopathic smooth muscle defect resulting in closure of the lower esophageal sphincter and upstream dilatation. It may also occur as a complication of Chagas disease in humans. Transgenic rats have been used as a model of achalasia in humans, and it has been described in some strains of mice.

Megakaryoblasts are the earliest cell type of the megakaryocytic lineage that can be identified by light

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microscopy. Megakaryocytes are responsible for the production of blood thrombocytes (platelets), which are necessary for normal blood clotting. Megakaryoblasts are large (~20–30 μm diameter) mononuclear cells that are round to slightly ovoid. They have a high nuclear-to-cytoplasmic (N:C) ratio, and dark, basophilic, granular cytoplasm. Their nucleus is round to ovoid with coarse chromatin and with usually 1–2 small nucleoli. Smaller megakaryoblasts (~15–20 μm diameter) might be difficult to differentiate from erythroblasts. Megakaryoblasts are derived from hematopoietic stem cells (HSC) which, when under the influence of thrombopoietin (TPO) and interaction with the bone marrow microenvironment (osteoblastic niche rich in collagen type I), commit to the megakaryocytic lineage. Based on cell culture, commitment to megakaryocyte lineage takes about 5 days.

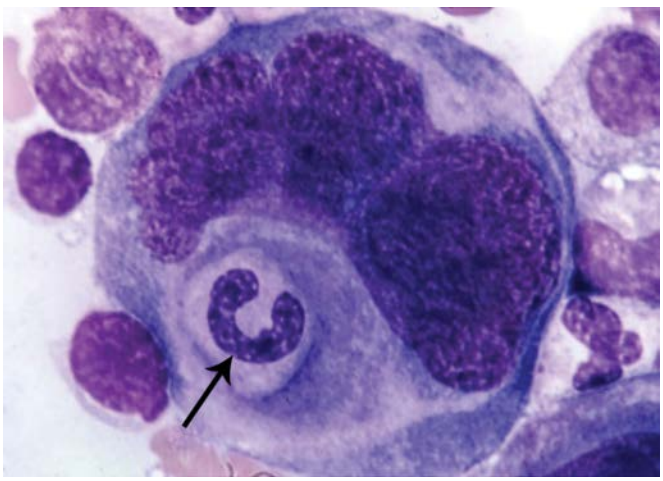
Megakaryocytes are the largest (50–100 μm in diameter) cells in the bone marrow responsible for the production of blood thrombocytes (platelets), which are necessary for normal blood clotting. They derive from megakaryoblasts and undergo endomitosis after migration into the microvascular bone marrow niche. They have a single polylobulated nucleus with a ploidy of 2n–128n. Endomitosis is followed by cytoplasmic maturation leading to a large amount of protein production, RNA synthesis, and creation of the invaginated membrane system (IMS) derived from a trans-Golgi network. The trans-Golgi network functions in the processing and sorting of glycoproteins and glycolipids at the interface of the biosynthetic and endosomal pathway. The IMS is a tubular structure present throughout the cytoplasm, contiguous with the plasma membrane, which is considered a platelet reservoir. Following cytoskeleton rearrangement, long cytoplasmic extensions are formed and proplatelets are released into bone marrow vascular sinusoids. Blood shear force helps in the release of the proplatelets. In circulation, proplatelets gain a figure-of-8 appearance which split in the middle leading to the formation of two preplatelets. Final platelet maturation occurs in the peripheral circulation or in the lung. During thrombocytopenia another mechanism of platelet formation is activated, leading to cytoplasm breakup rather than organized proplatelet formation.



Megakaryocyte (arrow), bone marrow, cynomolgus monkey.

Megakaryocytic dysplasia is the term used to describe >10% megakaryocytes with an atypical morphology when examined on a bone marrow smear. Megakaryocytic dysplasia has been described in dimorphic anemia, myelodysplastic syndrome, acute lymphocytic leukemia, blast crisis of chronic myeloid leukemia, and immune-mediated thrombocytopenia. The atypical morphology consists of micromegakaryocytes, mononuclear megakaryocytes, megakaryocytes with small nuclei, and abnormal cytoplasmic granulations or vacuolation.

Megakaryocytic emperipolesis is characterized as the active and temporary penetration of one or several cells through another cell with all cells remaining intact, differing from phagocytosis where one cell engulfs and kills another cell. The exact mechanism and physiology of emperipolesis are unknown. Megakaryocytes engulfing hematopoietic cells (erythroid and myeloid precursors, neutrophils) are seen with similar incidence and severity as part of a normal physiologic response with increased megakaryocyte production secondary to thrombocytopenia and in myelodysplastic syndrome.



Megakaryocytic emperipolesis, bone marrow, cynomolgus monkey, involving a band neutrophil (arrow).

Megakaryocytic hematopoietic dysplasia has asynchronous maturation or evidence of arrest of megakaryocytic lineages. It is observed in myelodysplastic syndrome, which affects mostly the megakaryocytic lineage and is characterized by thrombocytopenia. Giant platelets with abnormal granulations (hyper- or hypogranulation) are often observed in blood smears. Refer to **Hematopoietic System** in Appendix 2 for further information.

Megakaryocytic leukemia is a malignant tumor of the megakaryocytic lineage (i.e., large bone marrow cells responsible for the production of blood thrombocytes [platelets], that are necessary for normal blood clotting) often with a preponderance of blastic cells showing an accumulation of megakaryocytes with varying degrees of differentiation. This finding is rare in mice. Refer to **Hematopoietic System** in Appendix 2 for further information.

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Meibomian gland adenoma is a benign neoplasm of the specialized sebaceous glands of the eyelids/ lashes. Its histological characteristics are those of a sebaceous cell adenoma. Refer to **Skin** in Appendix 2 for further information.

Meibomian gland atrophy in the eyelid (responsible for the supply of meibum, an oily substance that prevents evaporation of the eye's tear film) causes irregular architecture of tubules and acini, often with flattened epithelium, which generally lacks normal vacuolated cytoplasm, and there may be increased keratinization of duct epithelium. Lumina may be decreased in size or expanded by accumulation of sebaceous secretions and cellular debris. Interstitial fibrosis and inflammatory cell infiltrates may be present in the surrounding stroma, and duct-associated lymphoid tissue (see **Mucosa-associated lymphoid tissue** for additional information) may be present around the ducts. This change occurs as an incidental finding and has been reported with chronic topical epinephrine in the rabbit. Loss of Meibomian gland function contributes to abnormal tear film production (refer to Appendix 3 for further information) and keratoconjunctivitis sicca.

Meibomian gland carcinoma is a rare, malignant or invasive neoplasm of the specialized sebaceous glands of the eyelids/ lashes. Its histological characteristics are those of a sebaceous cell carcinoma. Refer to **Skin** in Appendix 2 for further information.

Meibomian gland foreign body inflammation, see the preferred term **Meibomian gland granulomatous inflammation**.

Meibomian gland granulomatous inflammation consists of focal or diffuse accumulations of epithelioid macrophages, multinucleated giant cells, lymphocytes, and plasma cells involving alveoli and ducts. Exogenous or endogenous foreign bodies including escaped Meibomian gland secretions may or may not be identified as the inciting agent. This can be an incidental and spontaneous finding or be related to prior infections and as a senile change.

Differential diagnosis: **Meibomian gland inflammation**.

Synonym(s): **Foreign body inflammation**; **chalazion**.

Meibomian gland inflammation consists of focal or diffuse accumulations of inflammatory cells (granulocytes or heterophils [rabbit], macrophages, lymphocytes, and plasma cells) in and around the acini, ducts, and interstitial stroma accompanied by other inflammatory indicators including interstitial edema, congestion, hemorrhage, and necrosis or cellular debris. Meibomian gland atrophy, squamous metaplasia of the acini, hyperkeratinization of duct epithelium, and interstitial inflammation may occur in chronic inflammation. Inflammation is most often associated with infectious diseases, extension of cutaneous neoplasms, inflammation of the eyelid, or topical application of xenobiotics.

Differential diagnoses: **Duct-associated lymphoid tissue**; **Meibomian gland inflammatory cell infiltrate**.

Meibomian gland inflammatory cell infiltrate consists of small numbers of leukocytes associated with acini, ducts, or interstitium, in the absence of obvious inflammation. Infiltrates around ducts may be difficult to differentiate from duct-associated lymphoid tissue.

Differential diagnoses: **Duct-associated lymphoid tissue**; **Meibomian gland inflammation**.

Melanin is synthesized from tyrosine in melanosomes. In the presence of tyrosinase, tyrosine is hydroxylated to dihydroxyphenylalanine (DOPA) which is oxidized into dopaquinone. Depending upon the presence and abundance of thiols (e.g., cysteine, glutathione) and specific enzymes, dopaquinone is transformed to pheomelanin (red-yellow) or eumelanins (brown-black) pigments. The ratio of these pigments to total melanin and/or the ratio of pheomelanin to eumelanins ultimately determine skin and hair pigmentation. Genetic pathways important for melanogenesis include the melanocyte-specific melanocortin 1 receptor (MCR1) and its ligands α-melanocyte-stimulating hormone (MSH) and adrenocorticotropic hormone (ACTH), and the c-KIT/SCF and MITF pathway. Other genes important for melanogenesis include protein kinase C and the *Sox* family of genes. Melanosomes are the hallmark of melanocyte identification by ultrastructural examination. They span four different development phases, from the round, nonmelanized stage 1 to the more ovoid, heavily pigmented stage 4. Melanin, and particularly the eumelanin pigments, have antioxidant and free-radical scavenging properties that account for protection from solar ultraviolet radiation and lower skin cancer rates observed with greater amount of these pigments in the skin.

Melanocytes are cells responsible for melanin production in the skin of mammals, birds, reptiles, and fish. In mammals, they derive from the neural crest and are located in the epidermis, hair follicle, and in the dermis, though less frequently. Melanocytes are also found in other locations including the eye, cochlea, and meninges. In the epidermis, melanocytes are localized in the basal layer, and in the hair follicle where they are found in the hair bulb and in the bulge area. Epidermal melanocytes are long-lived cells, while in the hair follicle, differentiated melanocytes die with hair cycles. The commitment to the melanocyte lineage is mainly controlled by the microphthalmia-associated transcription factor (*mitf*). Other genes important in melanoblast differentiation, migration, and differentiation to melanocyte survival, proliferation, and growth include *Wnt*, *Bmp4*, *Sox10*, *Pax3*, *Sox2*, *Foxd3*, *Dct*, *Pmel*, endothelin receptor B/endothelin B, *Snail*, cadherins family of genes, *kit/kit ligand* or *stem cell factor*, *Rac1*, Fascin1, Lamellipodin, and the *Scar/WAVE complex*. Melanocytes synthesize melanin from tyrosine and package it into cytoplasmic organelles called melanosomes. Melanosomes are then transferred from melanocytes to epithelial cells in the epidermis and hair follicles. Two chemically distinct forms of melanin are found in the skin—the dark-brown

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eumelanin and the red-yellow pheomelanin. Skin pigmentation is mainly a function of the amount of melanin within melanosomes and the relative amount of eumelanin and pheomelanin as well as the amount of melanin transferred to keratinocytes.

Melanocyte-stimulating hormone(s) (MSH) are a group of hormones produced by the anterior pituitary gland, as well as a variety of other organs, from precursor proopiomelanocortin (POMP). MSH stimulates melanogenesis in various organs, including skin, and has demonstrated anti-inflammatory and antimicrobial effects in humans and in animal models.

Synonym(s): **Melanotropin**, **intermedin**.

Melanocytoma, see the preferred term **Melanoma/melanocytic tumo**r.

Melanoma/Melanocytic tumor is a benign or malignant neoplasm arising from melanocytes. Melanocytes are localized mainly within the basal keratinocytes in the epidermis or follicular epithelium, and less frequently in the dermis. The neoplastic cells in melanomas are usually arranged in sheets, nests, and/or whorls with fusiform, polygonal, and/or epithelioid cells in various proportions. Refer to **Skin** in Appendix 2 for further information.

Differential diagnoses: **Basal cell carcinoma**; Nerve sheath tumor.

Melanosis refers to focal hyperpigmentation of the skin and can result from an increased number of melanocytes, increased secretion of melanin, or a combination of both. Causes of melanosis include but are not limited to chronic inflammatory processes, endocrinopathies, and photosensitization skin reactions.

Melanostatin, see the preferred term **MSH-inhibiting hormone**.

Melanotropin, see the preferred term **Melanocyte stimulating hormone**.

Melatonin is a hormone produced by the pineal gland, regulated by the hypothalamic suprachiasmatic nuclei, and is integral to the circadian rhythm, seasonality of hair coat/color, and reproductive cycling in mammals. Serotonin is converted to melatonin by pinealocytes, which then is released into the microvasculature for distribution to target organs. Concentration of melatonin receptors is greatest at the target organs of the hypothalamus, anterior pituitary gland, and retina. Melatonin inhibits the secretions of gonadotropin-releasing hormones (GnRH) from the hypothalamus, and follicle stimulating hormone (FSH), and luteinizing hormone (LH) from the anterior pituitary gland; therefore, its release decreases reproductive receptivity. Secretion of melatonin is regulated by daylight. The effect of melatonin on sleep-wake patterns and reproductive receptivity is species specific. Exogenous melatonin is utilized as a nutritional supplement for multiple purposes, including sleep disorders, and as a dietary antioxidant.

Synonym(s): ***N*-acetyl-5-methoxy tryptamine**.

Membranoproliferative glomerulonephritis is an uncommon glomerular alteration occurring mainly in children and young adults. It is characterized by proliferation of mesangial and capillary endothelial cells, expansion of the mesangial matrix and thickening of peripheral capillary walls by immune deposits of IgG, and a splitting of glomerular basement membranes. It has been diagnosed occasionally in various strains of mice.

Membranous glomerulopathy is a diffuse glomerular lesion characterized by thickening of glomerular basement membranes, particularly the capillary basement membrane, but with little or no cellular proliferation or mesangial expansion. The basement membrane thickening represents deposition of dense aggregates and linear densities of immune complexes (containing IgG and C3) along the capillary wall, with typical "wire loop" lesions prominent after silver staining. Membranous glomerulopathy has been induced by chronic administration of low doses of mercuric chloride in the rat.

Menetrier's disease, see the preferred term **Hypertrophic gastritis**.

Meninges cover the external surfaces of the brain and spinal cord and are composed of three major layers: the pia mater on the surface of the brain that follows all the contours, the arachnoid mater which holds and forms a barrier between the cerebrospinal fluid (CSF), and external structures. Together the pia and arachnoid mater are called the leptomeninges. The third and outermost layer of the meninges is the dura mater, which forms a thick fibrous covering over the brain. Similarly, meningoencephalitis and meningomyelitis are characterized by inflammation of the meninges around the CNS. The dura mater is adhered to the internal surface of the skull, but within the vertebrae of the spinal column there is a separation called the epidural space. Nerves and blood vessels that traverse the meninges and brain do so within a cuff of dura, which in nerves becomes continuous with the external surface of the epineurium.

Meningioangiomatosis is a rare, benign, proliferative but nonneoplastic lesion considered a vascular malformation (hamartoma) that occurs within the meninges, often distributed bilaterally along the midline. The lesion may extend perivascularly along the Virchow-Robin spaces into the brain or through vascular foramina in the skull. Refer to **Nervous System** in Appendix 2 for further information.

Meningioma, benign is a clearly defined, well-demarcated, compressive but noninvasive neoplasm derived from meningeal stromal cells, forming a mass that overlies the brain,

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spinal cord, or cranial nerves. Refer to **Nervous System** in Appendix 2 for further information.

Meningioma, malignant is a poorly circumscribed neoplastic mass arising within the meninges on the surface of the brain, spinal cord, or cranial nerves. Malignant meningiomas are highly cellular, poorly demarcated, and invade tissues along vascular adventitia. Cellular features may be fibrous, spindloid, or undifferentiated. Refer to **Nervous System** in Appendix 2 for further information.

Meningitis is inflammation of the meninges covering the brain.

Meningoencephalitis is inflammation involving the meninges, brain parenchyma, and spinal cord. Polioencephalomyelitis in the human is a good example and is characterized by inflammation of the gray matter of the brain and spinal cord.

Menstrual cycle represents the recurring physiologic, histologic, and behavioral changes induced by reproductive hormones in primates. The start of menstrual cyclicity signals reproductive maturity; the cynomolgus macaque reaches sexual maturity at 2.5–4 years. The entire duration of the cycle is 28–32 days in the cynomolgus and rhesus monkey, but this differs between primate species. The nonhuman primate (NHP) menstrual cycle is divided into 3 or 4 major phases based on the hormone-mediated morphologic changes in the reproductive organs. These include the follicular, luteal, and secretory phases. Menstruation follows the secretory phase as does the regeneration phase, which is sometimes not included as a separate phase. The first day of menstrual bleeding is designated as the first day of the menstrual cycle. See also **Estrous cycle**.

Synonym(s): **Ovarian cycle**; **uterine cycle**.

Mesangial cell hyperplasia is an increase in the number of the renal glomerular mesangial cells. It is usually recognized as a component of immunologically mediated glomerular injury. Refer to **Urinary System** in Appendix 2 for further information.

Mesangial cell hyperplasia and hypertrophy is an increase in the number and size of mesangial cells in the glomerulus. It rarely occurs as a separate entity but more frequently accompanies various glomerular diseases during their progressive phases, such as in immunologically mediated glomerular injury. It is one component of the nephrotic syndrome induced by puromycin. Mesangial cell hyperplasia is not associated with tumor development. Refer to **Urinary System** in Appendix 2 for further information.

Mesangial thickening refers to an increase in thickening of the basement membranes in the mesangial capillaries of the glomerulus.

Mesangiolysis is an end-stage event where there is attenuation and degeneration of the mesangial cells of the glomerulus resulting in dilated, blood-filled capillaries, as a component of glomerular disease. The venom from a snake bite is a classical cause of mesangiolysis in an acute setting.

Mesangioproliferative glomerulonephritis is a diffuse renal glomerular lesion characterized by hyperplasia and/or hypertrophy of mesangial cells accompanied by increased mesangial matrix. Refer to **Urinary System** in Appendix 2 for further information.

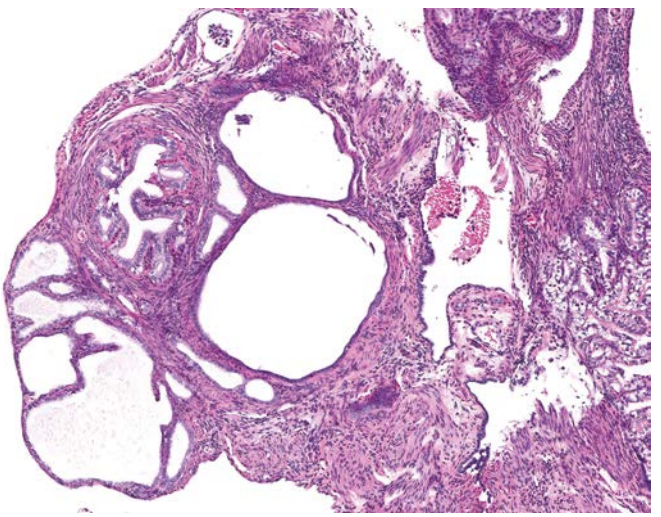
Mesenchymal bladder tumor, see the preferred term **Urinary bladder mesenchymal proliferative lesion**.

Mesenchymal cell tumor, see the preferred term **Renal mesenchymal tumor**.

Mesenchymoma, malignant is a neoplasm composed of several types of mesenchymal cells. These tumors usually comprise an undifferentiated spindle-shaped mesenchymal cell population organized in bundles or whorls and several populations of differentiated mesenchymal cells (e.g., skeletal muscle, cartilage, bone, white adipose). Refer to **Bone, Muscle, and Tooth** in Appendix 2 for further information.

Mesodermal dysgenesis, see the preferred term **Filtration angle narrowed**.

Mesonephric duct remnants are derived from the embryonic mesonephric duct system, and in females they are most frequently observed in the hilus of the ovary or in the mesovarium and mesosalpinx. The mesonephric tubules and duct give rise to efferent ducts, paradidymis (vestigial),



Cystic remnants of mesonephric duct, ovary, Wistar rat, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

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epididymis, vas deferens, and seminal vesicles in males; remnants in females are epoophoron and paraoophoron (tubular structures in the mesosalpinx and mesovarium), and Gartner ducts in the broad ligament of the uterus and wall of the vagina. These remnants may become cystic or give rise to neoplasms.

Synonym(s): **Wolffian duct remnants**.

Mesothelial hyperplasia consists of dense sheets or villous-like, nonneoplastic thickenings of the mesothelium. Mesothelial cells in these thickenings are well-differentiated, 1 or 2 layers thick, and appear as mature cuboidal cells. Cells in mesothelial hyperplasia do not exhibit mitotic figures or cellular atypia. Refer to **Bone, Muscle, and Tooth** and **Reproductive System and Mammary Gland: Male** in Appendix 2 for further information.

Mesothelioma, **malignant** is a neoplastic growth arising from the sheet of specialized cells lining serosal cavities (pleural, peritoneal, and pericardial) and the surface of organs in these cavities. This tumor usually infiltrates adjacent tissues, has high cell polymorphism, many mitotic figures, and frequently exhibits areas of necrosis. Refer to **Bone, Muscle, and Tooth** and **Reproductive System and Mammary Gland: Male** in Appendix 2 for further information.

Mesovarial leiomyoma is a benign neoplasm of smooth muscle cells located in the mesovarium, the portion of the broad ligament of the uterus that suspends the ovaries. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Mesovarial smooth muscle hyperplasia is characterized by a smooth muscle fiber proliferation within the mesovarium (the portion of the broad ligament of the uterus that suspends the ovaries), suspensory ligaments, or ovarian hilus. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Metabolic arrest change, see the preferred terms **Neuronal necrosis** and **Retinal single cell necrosis**.

Metamyelocyte is a nondividing granulocytic (neutrophil, eosinophil, or basophil) precursor cell (~10–18 μm diameter) found in the bone marrow maturation pool. During maturation, nucleoli are absent in metamyelocytes and they develop an elongated, nuclear indentation that extends greater than 25% into the nucleus. Metamyelocytes contain moderate amounts of clear pink cytoplasm and secondary cytoplasmic granules. These cells develop CD 16 expression during the metamyelocyte stage, which binds to the Fc portion of IgG antibodies to activate antibody-dependent cell-mediated toxicity. Increased numbers of metamyelocytes in the peripheral blood may be observed during inflammation associated with increased tissue demand, or in acute or chronic myelogenous leukemia.



Metamyelocyte (arrow), blood smear, monkey.

Metaphase is the phase of the cell cycle in which chromosomes are maximally condensed so they can be visualized microscopically.

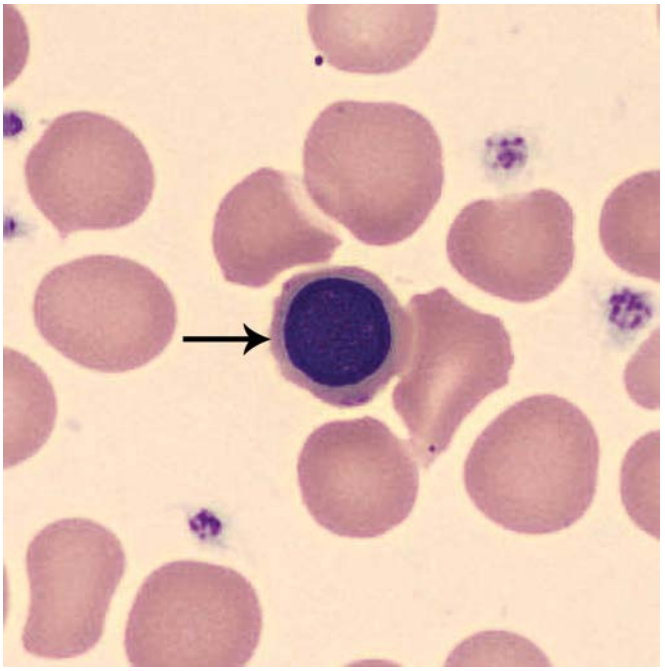
Metaplasia is the acquired, reversible change of one differentiated tissue into another differentiated type (i.e., glandular, ductal, and squamous types). Causes of metaplasia include chronic irritation and inflammation that result in epithelial injury. If the original insult or noxious stimulus is still present during attempts at tissue reconstitution, metaplasia will result in a less-specialized type of epithelium rather than the appropriate (functional) type. If the noxious stimulus has been removed, reconstitution of the original tissue type is possible. Metaplasia is not neoplasia, but it can represent a preneoplastic change. For example, Barrett's esophagus in humans is metaplastic transition of normal squamous epithelium to an intestinal epithelial phenotype; this change predisposes to adenocarcinoma of the esophagus. Chronic irritation of the cilia of the respiratory tract by smoking causes a metaplastic transition of the normal respiratory epithelium to a squamous type and is associated with an increased risk of squamous cell carcinoma. An example of metaplasia that does not transition to neoplasia is epithelial-to-mesenchymal transformation.

Metarubricyte is produced during the last stage of erythroid development before the erythrocyte extrudes its nucleus. They are the smallest of the nucleated erythroid precursors (8–12 μm in diameter). The cells are round to oval and contain a round nucleus. The nucleus is small, dense, and pyknotic, and may be central, eccentrically placed, or partially extruded. Cytoplasm ranges from slightly basophilic to pink-orange. Typically, metarubricytes are confined to the bone

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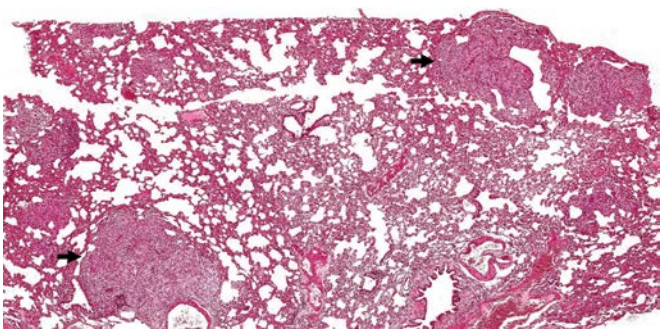
marrow, but they are the most likely stage of nucleated erythrocytes to be observed in peripheral blood in cases of regenerative or hemolytic anemia.

Synonym(s): **Orthochromatophilic normoblast**; **orthochromic erythroblast**.



Metarubricyte (orthochromatophilic normoblast), blood smear, monkey.

Metastasis is the dispersion of neoplastic cells from the original tumor to distant locations. This process is a key feature of malignancy. Neoplastic cells must be released from the primary tumor, invade lymphatics (primarily neoplasms of epithelial origin) or blood vessels (primarily neoplasms of mesenchymal origin), travel through the circulation, lodge in the microcirculation at a distant site, traverse through the vessel wall, and grow in a new location.



Metastasis of tumor cells to the lung of a rat, H&E. Multifocal hypercellular aggregates of metastatic tumor cells (as indicated by arrows) are present within the lung. Neoplastic cells expand and replace normal tissue. (Reproduced with the permission of Germann, P. and Morawietz, G. (eds). *Toxicopathology Case Collection CD-ROM. European Society of Toxicologic Pathology*. ISBN: 3-9522681-1-9. https://www.eurotoxpath.org/publications/form_cdrom.php?id=casecoll.)

Meteorism is dilatation of the stomach or intestinal lumen due to the accumulation (swallowing) of air. Meteorism in intestinal segments occurs in parasitic infestations. The stomach will be more severely affected than the intestines when meteorism occurs due to obstruction of nasal turbinates and/or nasopharynx in rodents which are obligate nose breathers.

Metestrus is the phase of the estrous cycle between estrus and diestrus. It is the period of early corpus luteum development. See **Estrous cycle** for further information.

Methemoglobin is a form of hemoglobin in which the iron in the heme moiety resides in the ferric (Fe^{3+}) or oxidized state, compared to the ferrous (Fe^{2+}) heme form found in normal hemoglobin. Heme-containing iron in the ferric state cannot bind oxygen and will cause the blood to appear dark bluish-brown in color when present in excess. See **Cyanosis** for additional information.

Methemoglobinemia refers to the oxidized form of hemoglobin where iron exists in the ferric form. Methemoglobin is brown in color and produces a characteristic peak at a wavelength of 632 nm. Mucous membranes, serum, and urine may be brown. Typically, methemoglobin forms at a rate of approximately 3% per day, but reduction occurs even more rapidly by methemoglobin reductase so that circulating methemoglobin remains less than 1%. When more than 1% methemoglobin exists in circulation it is called methemoglobinemia. Methemoglobinemia can be either congenital or acquired. Individuals with an autosomal recessive mutation for reduced levels of NADH diaphorase typically have 8–40% methemoglobin and are severely cyanotic. Acquired methemoglobinemia occurs with exposure to strong oxidants in dyes, drugs, solvents, or fertilizers.

Methylation is the metabolic addition of methyl groups to amines (*N*-methylation), alcohols (*O*-methylation), and sulfur groups (*S*-methylation).

Mexican hat cell, see the preferred term **Target cell**.

Microabscess, see the preferred term **Pustule**.

Microglia are the primary immune effector cells within the central nervous system (CNS) and are thought to derive from the monocyte-macrophage cell line. Like monocytes and macrophages in other organs, microglia secrete cytokines in response to inflammatory stimuli, serve as antigen-presenting cells, and maintain homeostasis by phagocytosing and removing cell debris from metabolism or following injury. Refer to Appendix 3 for further information.

Microglial cell nodule, see the preferred term **Neuronophagia**.

Microgliosis is an accumulation of activated microglial cells (resident phagocytes and primary immune effector cells) in response to inflammation or injury in the CNS.

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Reactive microglia can be distinguished from quiescent microglia by various features highlighted with conventional or special staining methods. Gitter cells are actively phagocytic microglia. Microgliosis is a subtype of the broader term "gliosis." Refer to **Nervous System** in Appendix 2 for further information.

Microgliosis (brain), see the preferred term **Macrophage hyperplasia**.

Micronucleus test is an assay for the induction of clastogenicity (chromosome breaks) or aneugenicity (abnormal number of individual chromosomes). Micronuclei are formed when damaged parts of the chromosome are formed, or whole chromosomes are lagging behind the other chromosome during mitosis so that they become enveloped as an extranuclear body, the micronucleus, in one of the daughter cells. Thus, an increase in micronucleus frequencies indicates an induction of structural or numerical chromosome aberrations. Assays to investigate micronucleus formation are generally performed in vitro in the preclinical phase of drug development using freshly isolated human peripheral blood lymphocytes, and in vivo either as an adjunct to repeat-dose toxicity studies in the rodent, where micronuclei in circulating erythrocytes are assessed by flow cytometry, or as a separate assay, generally looking at micronucleus formation in bone marrow cells after acute treatment of the animals.

Microphthalmia is a unilateral or bilateral developmentally small eye that correlates to one or more architectural irregularities or degenerative changes in portions of, or the entire globe. In laboratory animals, microphthalmia is most frequently identified as a sporadic spontaneous finding in certain strains of rodents (e.g., C57BL/10 mice), in genetically engineered mice with mutations in SOX2, OTX2, STRA6, BCOR, HCCS, BMP4, and SMOC1, and in teratogenic studies in rodents and rabbits.

Differential diagnosis: **Anophthalmia**.

Synonym(s): **Microphthalmos**.

Microphthalmos, see the preferred term **Microphthalmia**.

MicroRNA (miRNA) are small RNA molecules that are involved in cellular regulation of gene expression. They function by binding to complementary regions of mRNA, thereby silencing the mRNA either through destabilization and enhanced breakdown, or by decreasing the efficiency of translation. MicroRNA nomenclature uses the prefix miR followed by a hyphen and a number, which reflects the order in which the microRNAs were discovered. (e.g., miR-122). The prefix mir is used for the precursor forms of the microRNAs.

Microsomes are fragments of endoplasmic reticulum with attached ribosomes formed during tissue homogenization and subsequent centrifugation. Microsomal is a term given to macromolecules found in the microsomal fraction. Generally, tissue homogenates are centrifuged at 9000 g to produce a 9000-g supernatant (S9), a post-mitochondrial fraction which contains microsomal and cytoplasmic components. S9 is often used as a metabolic activating system for in vitro assays. Further centrifugation of the S9 at 100,000 g separates the microsomal membranes, which are found in the pellet, from the cytoplasmic proteins, which are found in the supernatant. Microsomal suspensions contain cytochromes P450 and may be used to examine oxidative reactions.

Microvesicular vacuolation, see **Lipid accumulation** for further information.

Middle ear bone atrophy is characterized by scalloping of the bone margins, with or without osteoclasts, and thinning of the bone of the small ossicles or tympanic bulla. This loss of bone may be the consequence of middle ear inflammation or instillation of irritants. New bone formation may also be present.

Synonym(s): **Middle ear bone decreased**.

Middle ear bone decreased, see the preferred term **Middle ear bone atrophy**.

Middle ear bone necrosis is characterized by empty osteocyte lacunae due to loss of nuclei in the bones of the tympanic bulla or ossicles. Bone necrosis occurs secondary to severe middle ear bacterial or fungal inflammation, high-dose radiation, and administration of severe irritants into the middle ear.

Synonym(s): **Middle ear osteonecrosis**.

Middle ear catarrhal inflammation is characterized by accumulation of a frequently acellular serous exudate in the tympanic cavity that may progress to eosinophilic material (fluid and mucus) filling the bulla space. Lining epithelial cell hyperplasia or squamous cell metaplasia with abundant goblet cells is usually also present. Persistence of serous effusions in the tympanic cavity may be followed by bacterial infections and result in more severe middle ear inflammation. Middle ear catarrhal inflammation can be induced by experimental or spontaneous inflammatory or neoplastic occlusion of the Eustachian tube.

Differential diagnoses: **Tympanic bulla edema**; **Middle ear inflammation**.

Synonym(s): **Otitis media**; **middle ear mucous hyperplasia**.

Middle ear cholesteatoma is an expansive, nonneoplastic mass that may be pedunculated or polypoid that develops from the squamous epithelium on the medial side of the tympanic membrane. A squamous cyst is generally present that progressively enlarges due to accumulation of desquamated keratin, nucleated or anuclear cells. Progressive growth may cause destruction of the adjacent tissues, especially bone. Additional findings include cholesterol clefts from degenerating cell membranes, hemorrhage, pigment deposition, granulomatous inflammation, and fibrosis. The lesion most often results from trauma or chronic inflammation, either spontaneously or after administration of irritants to the external or middle ear. Spontaneous cholesteatomas are described in many species,

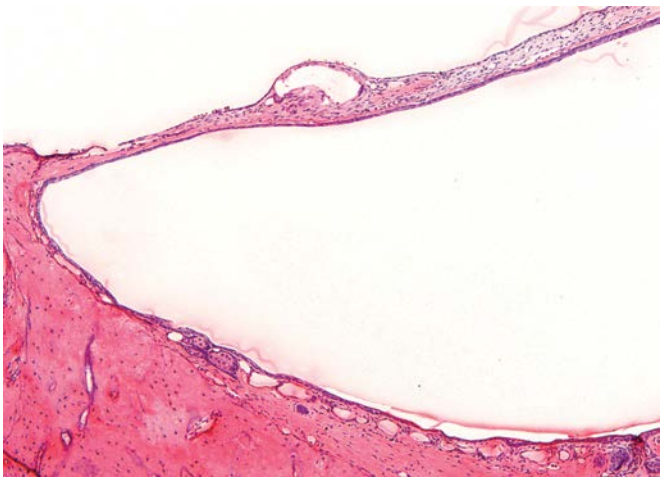
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including dogs. In addition, various animal models exist for studying the pathogenesis of cholesteatomas using Mongolian gerbils, chinchillas, Guinea pigs, pigs, or rats. Methods include ligation of the external ear canal or blocking of the Eustachian tube, chemical or biologic material injections into the middle ear, or using autologous dermal implants.

Differential diagnoses: **Tympanic membrane cyst**; **Middle ear granulomatous inflammation**.

Middle ear granulomatous inflammation is characterized by infiltration of epithelioid macrophages, multinucleated giant cells, lymphocytes, and occasionally necrotic debris and neutrophils into limited or expansive areas of the tympanic bulla. Granulomatous inflammation occurs as a reaction to direct xenobiotic administration into the middle ear by foreign material entering via a perforated tympanic membrane, or indwelling cannulas to treat middle ear inflammation. Inert material may induce the accumulation of foamy macrophages.

Differential diagnoses: **Middle ear inflammation**; **Middle ear cholesteatoma**.



Middle ear granulomatous inflammation with multinucleated giant cells due to a foreign body (glue), Guinea pig, H&E. (Image courtesy of Schafer, K. *Vet Path Services*. Mason, Ohio.)

Middle ear hyperostosis, see the preferred term **Tympanic bulla new bone formation**.

Middle ear inflammation, mostly of the mucosal lining of the tympanic bulla, but also the ossicles, round window and Eustachian tube (Refer to Appendix 3 for further information), consists of infiltration of neutrophils or heterophils, lymphocytes, macrophages, and/or other inflammatory cells. The cells may also undergo hypertrophy or metaplasia (squamous cell or tall cuboidal to columnar cell metaplasia). An increase in mucosal thickness may also indicate edema and vascular congestion. Additional findings may include hemorrhage, cholesterol clefts, fibrin deposition, granulation tissue, fibrosis, membranous pseudoglands, inflammatory cells free in the tympanic bulla lumen, necrosis of the mucosal lining, and bone alterations (tympanic membrane necrosis, atrophy, and new bone formation). Inflammation reaches the middle ear from extension of an infection in the external ear canal through the tympanic membrane, retrograde movement of microorganisms from the nasopharynx into the Eustachian tube, or rarely by spread of infections by the hematogenous route. Middle ear inflammation occurs spontaneously in laboratory and domestic animals and is more frequent in immunocompromised animals. Various infectious agents have been associated with tympanic bulla inflammation, including *Mycoplasma* spp. and *Streptococcus* spp. (rodents and large animals), *Bordetella* spp., *Pseudomonas* spp. and *Pasteurella* spp. (rabbits and Guinea pig), *Actinobaccillus* spp. (Guinea pig), *Malassezia* spp. (rabbits), *Pseudomonas* (dog), and hemolytic streptococci (pigs). Experimental models in mice and chinchilla are being used to define the immune response and role of biofilms in the pathogenesis of middle ear inflammation. Administration of irritants into the middle ear also causes inflammation. Severe middle ear inflammation may spread to the Eustachian tube (see **Eustachian tube inflammation** for further information), the inner ear (see **Inner ear inflammation** for further information), and the brain.

Synonym(s): **Otitis media**.

Middle ear inflammatory cell aggregate, see the preferred term **Middle ear inflammatory cell infiltrate**.

Middle ear inflammatory cell infiltrate mostly involves the tympanic bulla and is further characterized by the predominant cell type that frequently consists of small foci of neutrophils or heterophils, macrophages, foamy macrophages, and mononuclear or mixed cells in the absence of tissue damage or evidence of an inflammatory process. A few foamy macrophages in the tympanic bulla may be observed as a spontaneous background finding, and administration of test articles into the middle ear may increase this finding. In the Eustachian tube, lymphocyte foci associated with the epithelium are likely mucosa-associated lymphoid tissue.

Differential diagnoses: **Middle ear inflammation**; **Mucosa-associated lymphoid tissue**.

Synonym(s): **Middle ear inflammatory cell aggregate**.

Middle ear mucous hyperplasia, see the preferred term **Middle ear catarrhal inflammation**.

Middle ear osteonecrosis, see the preferred term **Middle ear bone necrosis**.

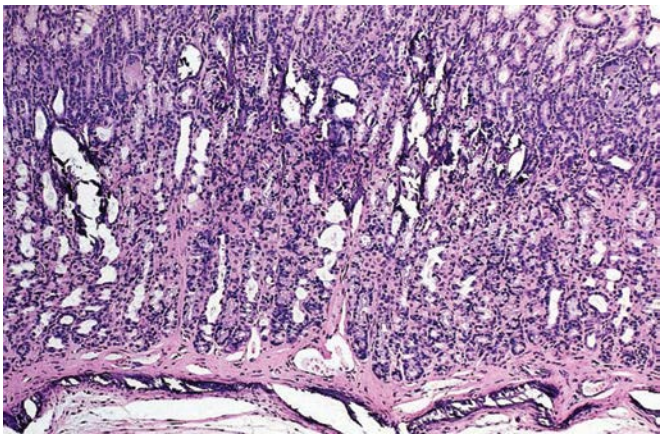
Middle ear osteosclerosis, see the preferred term **Tympanic bulla new bone formation**.

Midzonal necrosis, see the preferred term **Hepatocellular zonal necrosis**.

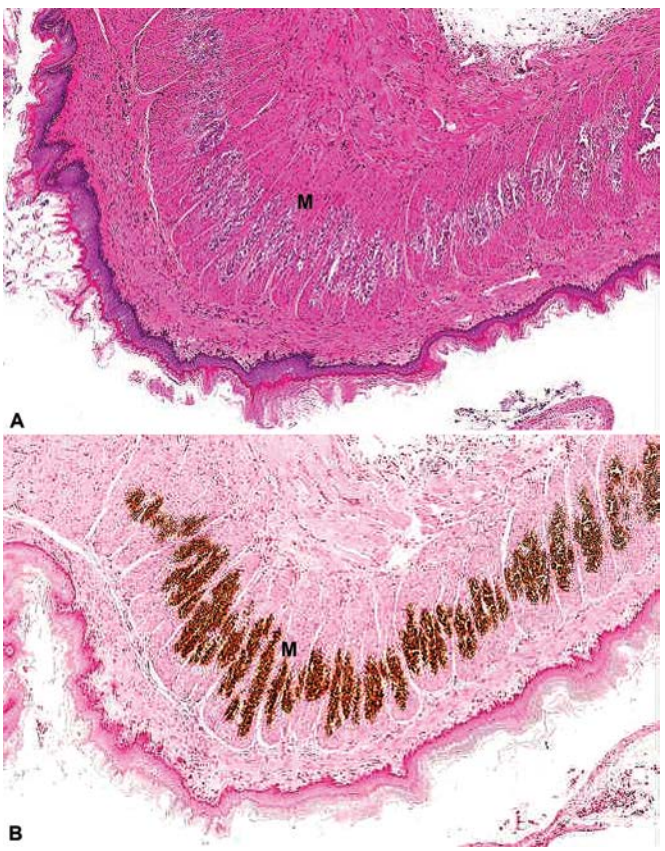
Mineralization, see the preferred term **Calcification**.

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Mineralization of glandular and nonglandular stomach is deposition of acellular basophilic-staining mineral material in the muscle layers, blood vessels, basement membranes, and/or in the interstitium of mucosa and submucosa secondary to necrosis (dystrophic mineralization) or hypercalcemia (metastatic mineralization). Mineralization of interstitium of mucosa occurs predominantly in a band paralleling the parietal cell–rich region of the corpus mucosa. Diffuse mineralization of the corpus mucosa may be accompanied by degenerative changes, mucous cell hyperplasia, or cystic dilatation of neighboring glands. Multifocal or diffuse mineralization occurs secondary to chronic progressive renal disease, altered calcium-phosphorus metabolism, and hyperparathyroidism. Mineralization secondary to necrosis (dystrophic mineralization) can be observed in combination with inflammation and neoplasia. Mucosal mineralization limited to small focal deposits is often noted as background lesion in laboratory animals. Presence of mineral can be confirmed with van Kossa or Alizarin red stains, but these are rarely needed to determine this change.



Glandular stomach, rat. H&E. Mineralization of mucosa (M) and submucosa (SM). (Image reproduced with permission of the Japanese Society of Toxicologic Pathology from Nolte, T. et al. 2016. *Toxicol. Pathol.* 29(1 Suppl):1S–124S.)



Nonglandular stomach, rat. Mineralization (M) of muscular wall. A = H&E. B = Von Kossa (calcium) stain.

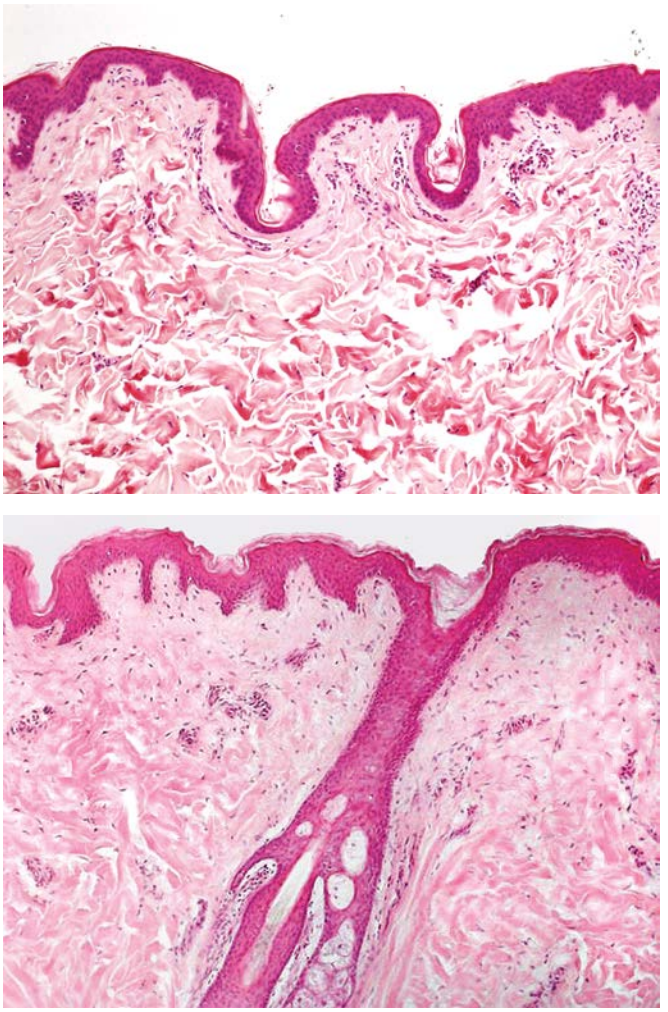
Differential diagnoses: Hematoxylin stain precipitate artifact; Bacterial colonies (*Helicobacter*); **Osseous metaplasia**.

Synonym(s): **Calcification**.

Mineralocorticoid is a steroid hormone (corticosteroid) produced by the adrenal cortex, particularly the zona glomerulosa. The primary mineralocorticoid is aldosterone, which serves to modulate sodium, potassium, and chloride levels, maintain fluid and blood pressure homeostasis, and is central to the rennin-aldosterone-angiotensin system (RAAS). Adrenal cortical dysfunction resulting in reduction of aldosterone leads to dysregulation of body fluid and affects cardiac output. When severe, aldosterone reduction may lead to hyponatremic shock and death. Conversely, hypersecretion of aldosterone leads to fluid and sodium overload, cardiac stress, inflammation, and fibrosis. In addition, as part of the RAAS, alterations in aldosterone directly affect levels of angiotensin and rennin, with subsequent renal, cardiac, and vascular smooth muscle modulation.

Minipigs in dermal studies have become an important animal model when evaluating potential skin toxicity. There are several breeds of laboratory minipig, but one of the most commonly utilized for regulatory toxicology is the Göttingen, based on its small size (about 45 kg as an adult). Similar to humans, the minipig has a papillary dermis with epidermal rete ridges. The cellular composition of the dermis and subcutis are also similar. Both humans and pigs have a relatively thick dermis with a large elastic fiber component. The dermis tightly adheres to the underlying subcutis and musculature, and the dermal and subcutaneous vasculature and lymphatics are rich and similarly distributed. Also similar to humans, minipig skin thickens with age and has increased permeability with reduced effectiveness at wound healing. Enzymatic properties and drug metabolism in the epidermis and some adnexa also are comparable, as are lipid composition of the epidermis and sebum. Skin pH is slightly higher in the minipig (pH 6–7) compared to human (pH 5).

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Normal skin from a minipig (top), and human (bottom), H&E.

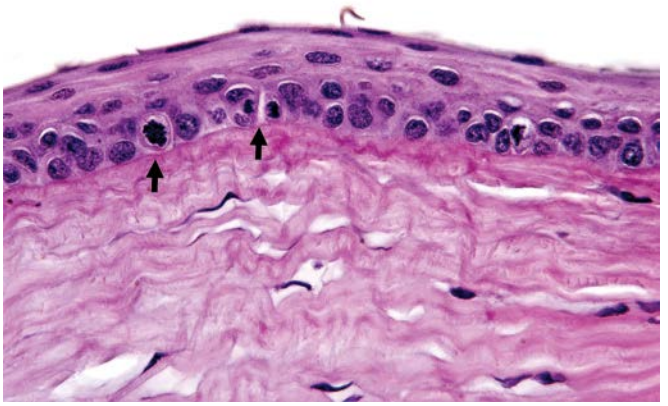
Minute volume (also referred to as respiratory minute volume) is the volume of air or gas inhaled (inhaled minute volume) or exhaled (exhaled minute volume) per minute. Typical values for preclinical toxicity species and humans are shown in the table below.

Minute Volume Values in Various Species

Species	Body Weight (kg)	Minute Volume (L/min)
Mouse	0.025	1.08
Rat	0.25	0.68
Dog	10	3.28
Monkey	4.5	1.73
Human	70	15.6

Mitogens are compounds or agents that induce mitosis (cell division), thereby stimulating cell proliferation.

Mitotic figure is the microscopic appearance of the nuclear material of a cell undergoing division (mitosis). Prior to complete cell division, nuclear material is duplicated and sister chromatids are separated by the mitotic spindle, which may be visible by light microscopy. In metaphase and anaphase of mitosis, mitotic figures have characteristic morphologies of a single basophilic line at the equatorial plane, or a mirror image basophilic pair of separated sister chromosomes, respectively. During these stages of mitosis, the nuclear membrane has disassembled and is usually not visible microscopically. Mitotic figures are hallmarks of actively replicating or regenerating tissues that are present during normal healing and growth processes, or abnormal processes such as hyperplasia and neoplasia.



Mitotic figures (as indicated by arrows) in the epithelial cells of the cornea of a rat, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

Mitotic interference involves agents or processes that interfere (normally inhibit) mitosis. This can be through various mechanisms. It is used in tumor therapy to target tumor cells, which are generally characterized by a very active mitosis.

Mitotic recombination is a process to recombine genetic material between sister chromatids in somatic cells and not during maturation of germ cells (meiosis). Mitotic recombination can be increased by genotoxic, normally clastogenic, agents.

Mixed function oxidase, see the preferred term **Cytochrome P450**. See also **Monooxygenases**.

Mixed mesodermal tumor, see the preferred term **Renal mesenchymal tumor**.

Mixed sarcoma is a rare tumor composed of two or more differentiated mesenchymal tissue types such as fat, muscle, bone, or cartilage in addition to undifferentiated or fibrosarcomatous elements that consist of two or more cellular elements, excluding fibrous tissue.

Synonym(s): **Mixed cell sarcoma**; **malignant mesenchymoma**.

Molecular cloning involves the isolation of individual genes to study their function, or to transfer a function to other cells or organisms.

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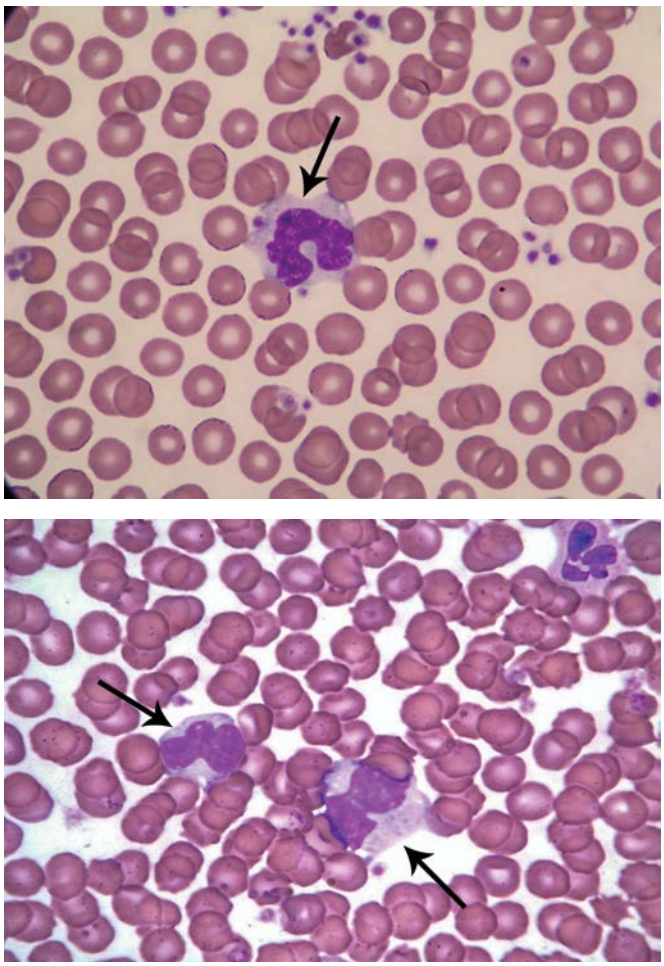
Molecular dosimetry is a term originally used in the field of radiation biology, but now used in wider context. It describes biomarkers to assess exposure, specifically for genetic toxicology, of DNA damaging agents. Biomarkers can be products of direct DNA interaction, such as DNA adducts, but also more indirect parameters such as gene expression changes.

Monoamine oxidases (EC 1.4.3.4) are mitochondrial flavoproteins which catalyze the oxidative deamination of monoamines (e.g., serotonin, norepinephrine, dopamine). There are two types: monoamine oxidase A and monoamine oxidase B, which differ in their tissue distribution and have different, but in part, overlapping substrate specificities. Although mainly involved in the metabolism of endogenous biogenic amines, they may also catalyze the oxidative deamination of amine containing drugs.

Monoblast forms from colony forming units-granulocyte macrophage (CFU-GM) cells (~15 μm in diameter) in the bone marrow. They have large, round to oval nuclei with a prominent nucleolus, deep-blue cytoplasm, and are typically indistinguishable from myeloblasts by light microscopy. Monoblasts express CD13, CD33, CD34, CD117, and HLA-DR and demonstrate diffuse acid phosphatase and nonspecific esterase activity. The monocyte lineage production is stimulated by stem cell factor (SCF), macrophage colony-stimulating factor (M-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-1, and IL-6.

Monoclonal antibody (mAb, Mab, MAb, mAB, or moAb) are target-specific immunoproteins ("antibodies") produced under laboratory conditions that are all clones of the same parent cell and, unless modified to be bi-specific, bind to the same epitope or unique binding region of the antigen. This is in contrast to polyclonal antibodies that bind to multiple epitopes and are typically derived from multiple cell line lineages. Monoclonal antibodies represent important diagnostic and therapeutic approaches in medicine, especially in cancer detection and treatment, as well as in disorders of the immune system and other disease targets.

Monocyte is a type of mononuclear leukocyte produced in the bone marrow that represents ~3–9% of the leukocyte population. They are larger cells (~15–20 μm in diameter) with abundant light blue cytoplasm that may contain faint pink granules and/or vacuoles and a kidney-shaped, band-shaped, or convoluted nucleus. Monocytes are $CD14^{+}CD16^{+}$ precursor cells with a lifespan of 0.5–3 days in the peripheral blood that then enter tissues to differentiate into macrophages or dendritic cells, which can survive for 2 weeks to 3 months. They are part of the innate immune system, and their major functions include phagocytosis, antigen presentation, and immunomodulation through the production of cytokines such as IL-1, IL-6, and TNF-α. Monocyte production is stimulated by stem cell factor (SCF), GM-CSF, M-CSF, IL-1, IL-3, and IL-6 and they stain positive with myeloperoxidase (MPO), nonspecific esterase (NSE), and Sudan Black B (SBB).



Monocyte (arrows), blood smear, monkey (top) and rat (bottom).

Monocytopenia is an uncommon condition characterized by decreased numbers of circulating monocytes. It often occurs with aplastic anemia.

Monocytosis refers to increased numbers of monocytes in the peripheral blood. This can occur with chronic inflammation, immune-mediated disease, granulomatous disease, stress, and hyperadrenocorticism.

Mononuclear cell leukemia, see the preferred term **Large granular lymphocyte (LGL) leukemia**.

Monooxygenases (mixed function oxidases) is a name given to enzymes (e.g., cytochromes P450) that are capable of reducing oxygen such that one atom of molecular oxygen is introduced into the substrate and the other is reduced to water, as opposed to dioxygenases, which incorporate both atoms of molecular oxygen into the substrate. See **Cytochrome P450** for further information.

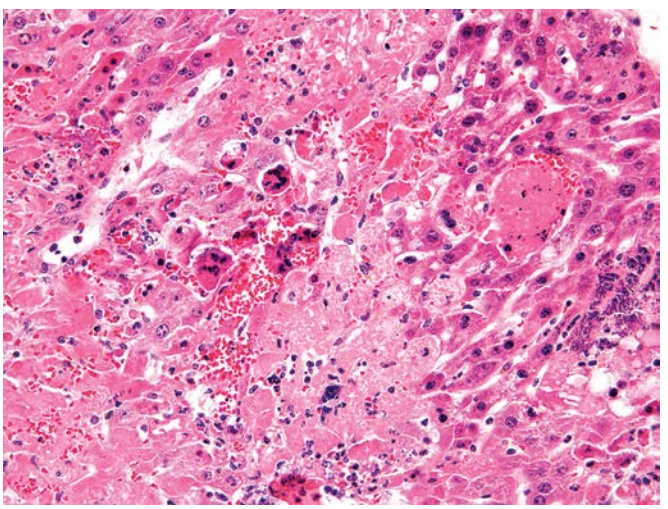
Morbidity is the incidence or prevalence of a disease condition or state, typically combined with a statistical analysis.

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Morgagnian globule, see the preferred term **Lens fiber degeneration**.

Mortality is normally characterized as a percentage of animals that have died at a given dose level in a toxicology study.

Mouse hepatitis virus (MHV) is a polytropic coronavirus of the family *Coronaviridae*, genus *Betacoronavirus*, and causes infection of the liver and other tissues (lungs, spleen, intestines, brain, lymph nodes, and bone marrow). The microscopic findings are more common in infant mice, susceptible mouse strains (e.g., BALB/c), and in immunodeficient mice. The pathognomonic lesion in the liver is multiple foci of necrosis with multinucleated syncytial cells. The necrotic foci may contain inflammatory cells. In immunodeficient mice, infection persists, and bouts of necrosis and regeneration may eventually lead to a nodular, fibrotic liver (cirrhosis). Infections with polytropic strains results in similar necrotic foci with syncytia in multiple organs, and often presents as a vascular complex due to an abundance of virus-infected endothelial cells. Enterotropic strains are often limited to disease in the distal small intestine and large intestine. Mouse hepatitis virus is highly contagious and is transmitted primarily via aerosol, direct contact, transplacentally, via fomites, and experimentally via transplantable tumors. Adult infection generally causes no overt clinical signs but can cause profound changes in the immune system, affecting the interpretation of a wide variety of experimental results in immunocompetent mice.



Mouse hepatitis virus, necrosis and multinucleated cells, mouse liver, H&E. (Reproduced with permission of the Society of Toxicologic Pathology from Thoolen, B. et al. 2010. *Toxicol. Pathol.* 38(7 Suppl):5S–81S.)

Mouse lymphoma test is an assay for the induction of gene mutations. In this test, a mouse lymphoma cell line (L5178Y) is used. After treatment of the cell culture with a potential mutagen, mutants are selected with a base analog that kills nonmutants, so that only mutants can grow. The mutant frequency is determined by calculating the number of mutants compared to the number of total cells treated. This test is sensitive to the induction of point mutations as well as chromosome mutations. There is an attempt to distinguish the two endpoints by the size of the mutant colonies formed, but this method is not reliable enough to clarify the mechanism. See **Eukaryotic mutagenicity tests** for further information.

Mouse mammary tumor virus (MMTV) is a mouse specific, type B retrovirus transmitted by milk, and infects some strains of mice (A, CH3, DBA/2, and GR) with a high incidence. Activation of mouse DNA by integration of MMTV is the primary mutagenic event leading to the formation of mammary tumors. Most of these tumors have activation of wnt, fibroblast growth factor (FGF), and/or notch. Strains positive for MMTV have high lifetime incidences of mammary neoplasia with limited tumor phenotypes, and the presence of MMTV increases the susceptibility to the development of treatment-related mammary tumors. Because the virus is mouse specific, the activation or suppression of DNA by MMTV itself is not applicable to human tumorigenesis.

Mouse spot test is an assay for mutations in developing mouse embryos. Mouse embryos are exposed in utero and after birth for skin spots; thus, the target cells are skin melanoblasts. The test is sensitive to a variety of genetic events, including point mutations and intragenic recombination. An OECD (Organization for Economic Co-operation and Development) guidance existed but has been retired, which reflects the infrequency with which the assay is performed today and its replacement by less elaborate assays with more defined endpoints such as the pig-a assay.

MSH-IH, see the preferred term **MSH-inhibiting hormone**.

MSH-inhibiting (MIF-1) hormone is produced in the anterior pituitary gland by cleavage of oxytocin. MIF-1 inhibits the release of melanocyte-stimulating hormone (MSH) from the pituitary gland, but also has varied functions in the central nervous system (CNS) through modulation of opioid receptors.

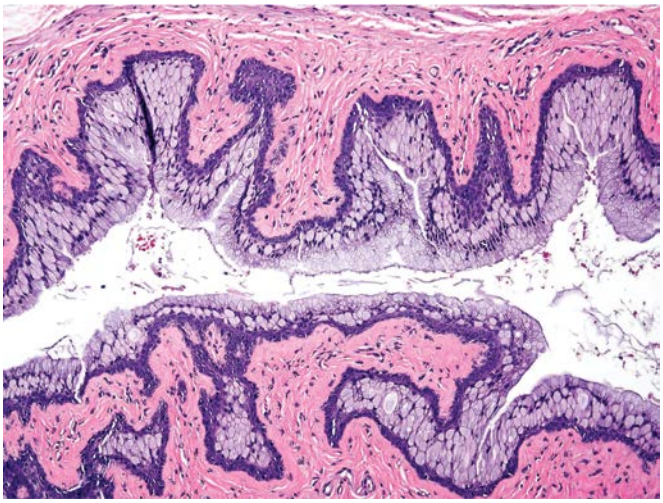
Synonym(s): **Melanostatin**; **MSH release–inhibiting hormone**; **MSH-IH, MIF-1**; **melanocyte-stimulating hormone release-inhibiting factor**.

MSH release–inhibiting hormone, see the preferred term **MSH-inhibiting hormone**.

MTD is the abbreviation for maximum tolerated dose. See **Maximum tolerated dose** for further information.

Mucification is the generation of epithelial cells in the female reproductive tract (e.g., vagina, cervix) containing large amounts of mucin. This material appears as clear to pale basophilic vacuoles in the cytoplasm in routine hematoxylin and eosin (H&E)-stained sections. Mucification is a normal/physiological process in the estrous cycle, occurring in the rodent when under the influence of progesterone (late diestrus, early proestrus) and during pregnancy and pseudopregnancy. Inappropriate or excessive mucification can be observed in the rodent with hormonal abnormalities.

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Mucification in the vagina of a rat, H&E. The superficial epithelium is distended with a large amount of clear to pale blue staining mucin. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

Mucin refers to any of a group of glycoproteins found in mucous secretions, including mucopolysaccharides. Mucin includes a broad list of glycoconjugated forms including mucoproteins, glycoproteins, glycosaminoglycans, and glycolipids. Mucins are membrane protectants and can bind pathogens, but overexpression has been associated with certain cancers and disease states.

Mucinous hyperplasia is characterized by increased numbers of epithelial cells that produce mucin, a glycoprotein constituent of mucus. Refer to **Gastrointestinal Tract** in Appendix 2 for further information.

Mucocele is a mucus-containing cystic lesion occurring most commonly in association with a minor salivary gland in humans. In dogs, they occur most frequently in association with the sublingual salivary gland. They are caused by trauma or irritation, such as a foreign body or sialolith, which occlude or damage the excretory duct resulting in leakage of saliva into the surrounding tissue. Leakage results in the formation of nonepithelialized, cystic-like spaces which encourage a local granulomatous inflammation. Although the beagle dog is not known to have a breed-related predilection, they have occasionally been seen as a necropsy finding in laboratory beagles. In one case, a ruptured sublingual interlobar duct was observed near the cyst. Leaked material is positive with Alcian blue and periodic acid-Schiff (PAS) staining as is mucin in the sublingual gland.

Synonym(s): **Ranula**.

Mucocutaneous refers to the junctions of the skin with mucosal membranes such as the oral cavity, anus, nasal cavity, eyelids, urethra, vagina, and foreskin.

Mucoepidermoid carcinoma, see the preferred term **Pulmonary adenosquamous carcinoma**.

Mucoid or serous atrophy of adipose tissue is a form of adipocyte atrophy made up of a collection of loose mucoid mesenchymal tissue with a hyaline stroma. Mucoid atrophy occurs during starvation where eosinophilic glycosaminoglycan is observed in the matrix and may occur in the bone marrow.

Differential diagnosis: **Lipoma**.

Synonym(s): **Fat atrophy**; **lipoatrophy**; **adipose tissue atrophy**.

Mucometra is characterized by a uterus that is grossly filled or distended by mucus because of vaginal obstruction.

Mucopolysaccharidosis (MPS) refers to a variety of metabolic disorders that develop secondary to abnormal activity or loss of lysosomal enzymes that are required to degrade glycosaminoglycans (GAGs). This enzymatic malfunction leads to abnormal accumulation of heparin sulfate, dermatan sulfate, and/or keratin sulfate, depending upon the specific lysosomal enzyme involved. Correlates to some of the human mucopolysaccharidoses have been noted in animals, including cats and dogs, with the majority of syndromes being autosomal recessively inherited. The undegraded GAGs may be detected in the urine, which serves as a screening test. The common clinical signs include growth retardation, skeletal deformities, corneal cloudiness, facial dysmorphia, and in some cases, neurologic signs.

Mucosa-associated lymphoid tissue (MALT) consists of loosely organized clusters of leukocytes, organized aggregates of nonencapsulated lymphoid tissue with lymphoid follicles, or large discrete encapsulated tonsils associated with mucosal tissues. Mucosal lymphoid tissue and tonsils form an extensive system of secondary lymphoid tissue protecting all mucosal surfaces by interacting with antigens, secreting immunoglobulins, and communicating with the systemic immune system. Only the Peyer's patches of the small intestine, the nasopharynx nasal/nose-associated lymphoid tissue in rodents, nasopharyngeal tonsil in other mammals, and adenoid tissue in humans as well as the palatine tonsil are formed in utero or present at birth as constitutive MALT. In most mucosal tissues, MALT is induced in the postnatal period after antigenic exposure. Such inducible MALT sites include the conjunctiva, oral, pharyngeal and nasal cavities, upper (larynx and trachea) and lower (bronchus/bronchial) respiratory tract, Eustachian tube, middle ear, stomach, gallbladder, cecum, appendix, colon, rectum, and reproductive and urinary tracts. Inducible MALT is slow to develop in animals in barrier housing, and MALT is frequently minimal (constitutive) or absent (inducible) in specific pathogen–free animals. Although not in mucosal locations, duct-associated lymphoid tissue around ducts in glandular tissues, and skin-associated lymphoid tissue are functionally similar and appear to interact with the MALT system. Most MALT is identified microscopically, but large MALT may be grossly visible on the serosa of the intestinal tract, extending into the lumen of the upper respiratory tract, and as solid tonsils in the oro- and nasopharynx. Antigenic exposure drives the development of MALT toward organized

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mature follicles with germinal centers surrounded by parafollicular (interfollicular) regions. At the luminal side, MALT is covered by a subepithelial dome region overlaid by a specialized follicle-associated epithelium. In MALT, B lymphocytes exceed the number of T lymphocytes, but the proportion varies by site, species, and strain. Subsequent to antigenic exposure, a local B-cell response will release protective immunoglobulins (Ig), mostly IgA, into the mucosal secretions, and T and B lymphocytes and macrophages migrate systemically and interact with other lymphoid tissues to produce a systemic immune system. Loose or immature MALT needs to be differentiated from subepithelial inflammation. Experimental treatments may result in changes in MALT similar to those found in other lymphoid follicles.

Mucosa-associated lymphoid tissue (MALT) calcification, see the preferred term **Mucosa-associated lymphoid tissue (MALT) mineralization**.

Mucosa-associated lymphoid tissue (MALT) dystrophic calcification, see the preferred term **Mucosa-associated lymphoid tissue (MALT) mineralization**.

Mucosa-associated lymphoid tissue (MALT) follicle-associated epithelial degeneration and necrosis is characterized by degeneration (loss of cell integrity), and necrosis (loss of cells) which may target the follicle-associated epithelium and extend into the adjacent lymphoid tissue or may only involve the lymphoid compartments of mucosa-associated lymphoid tissue.

Mucosa-associated lymphoid tissue (MALT) follicle-associated epithelial (FAE) goblet cell hyperplasia is an increase in goblet cells in the follicle-associated epithelium relative to controls. Usually associated with damage and other changes to the follicle-associated epithelium or underlying lymphoid tissue. Refer to **Lymphoid System** in Appendix 2 for further information.

Mucosa-associated lymphoid tissue (MALT) follicle-associated epithelial squamous metaplasia is characterized by a change of normal follicle-associated epithelium to nonkeratinized squamous-type epithelium. This change has been reported after inhalation exposure to an industrial compound in the nasal-associated lymphoid tissue of rats.

Mucosa-associated lymphoid tissue (MALT) hyaline material consists of extracellular deposits of eosinophilic material in one or more lymphoid compartments, most often reported in Peyer's patches. This material may stain for immunoglobulins and may be a nonspecific finding or associated with chronic diseases.

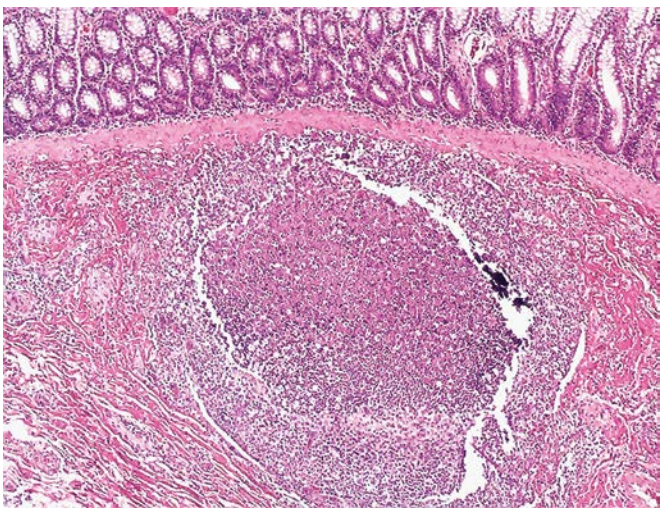
Synonym(s): **Mucosa-associated lymphoid tissue (MALT) proteinaceous material**.

Mucosa-associated lymphoid tissue lymphoma is a B-cell tumor originating from the marginal zone of mucosa-associated lymphoid tissue (MALT) that occurs at sites of MALT and in extranodal tissues. In laboratory animals MALT lymphomas are rare and mostly occur in the stomach associated with gastric bacterial colonization by *Helicobacter* spp. In laboratory animals, these tumors are of primary interest as research models of tumor promotion by bacterial microbiota. Refer to **Lymphoid System** in Appendix 2 for further information.

Mucosa-associated lymphoid tissue (MALT) mineralization is an infrequent finding consisting of usually focal mineral deposits within the lymphoid compartment of mucosa-associated lymphoid tissue, which may be associated with necrosis and inflammation.

Differential diagnosis: **Pigmented macrophage**.

Synonym(s): **Mucosa-associated lymphoid tissue calcification**; **dystrophic calcification**.



GALT necrosis with focal mineralization in the small intestine of a beagle dog.

Mucosa-associated lymphoid tissue (MALT) proteinaceous material, see the preferred term **Mucosa-associated lymphoid tissue (MALT) hyaline material**.

Mucositis is simply inflammation of the mucosa. In humans, this term most commonly refers to inflammation and ulceration of the oral cavity mucosa as a consequence of chemo and/or radiation therapy, however use of this term is not restricted to the oral cavity. Mucositis is rarely described as a specific disease entity in veterinary species, where inflammation is more broadly used as part of a morphologic diagnosis in reference to many possible underlying etiologies. Mucositis as a terminology in animal species is typically restricted to animal models of the human condition, where rats, mice, hamsters, and rabbits have all been used.

Mucus is a highly viscous, slippery secretion from glands within mucous membranes that contain mucin, leukocytes, inorganic salts, and desquamated cells suspended in an aqueous medium.

Mullerian tumor, mixed, benign is most commonly observed in the uterus or ovary and believed to arise from the pluripotent cells of the Mullerian ducts which can give rise to

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cells of both epithelial and stromal types. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Mullerian tumor, mixed, malignant is less common than its benign counterpart in the uterus or ovary and believed to arise from the pluripotent cells of the Mullerian ducts which can give rise to cells of both epithelial and stromal types. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Multifocal is a modifier attached to a diagnosis to indicate that the specific finding is present in circumscribed areas in more than one location within a tissue. It is an adjunct to severity grades in communicating the relative importance of a finding. For common test article–related findings such as degeneration, necrosis, and inflammation, the use of modifiers such as multifocal or focal often helps to communicate the distribution and pattern of spread for a specific finding. On some occasions, distribution modifiers are included in the weight of evidence to determine whether a finding is spontaneous or xenobiotic-mediated.

Multilamellar bodies are single to multiple tight whorls of membranous material within a lysosome that are observed with xenobiotic-induced phospholipidosis. Abnormalities in lysosomal enzymes, membrane proteins, and multiple metabolic pathways can result in lysosomal accumulations as part of a variety of conditions referred to as lysosomal storage diseases. See **Phospholipidosis** and **Lysosomal storage disease** for further information.

Synonym(s): **Myeloid bodies**.

Multinucleated giant cell refers to a single cell with multiple nuclei. Multinucleated giant cells originate from different cell types such as spermatocytes, lymphocytes, macrophages, and epithelial cells. In addition to their diverse origin, giant cells also have diverse pathogeneses involving cell fusion, nuclear duplication, and the formation from syncytial precursors. For example, giant cells of macrophage origin may be formed by a complex interaction of some cytokines, adhesion receptors, and protein substrates such as vitronectin while giant cells of epithelial origin (syncytial cells) may be formed by fusion proteins that are shed by certain viruses (paramyxoviruses) on the cell membrane. Lymphocytic giant cells may be formed by fusion proteins within certain retroviruses such as human immunodeficiency virus, while spermatocytic giant cells are occasionally seen during normal spermatogenesis, and in increased numbers following spermatocytic, interstitial cell, or Sertoli cell injury. When the diagnosis of multinucleated giant cells is test article–related, additional information regarding the origin and/or pathogenesis is helpful for contextual safety assessment. See **Syncytial cell** for further information.

Multinucleated hepatocytes are characterized by an increase in ploidy (DNA content), meaning the presence of 2 or more diploid or tetraploid nuclei within a single hepatocyte. This increase in hepatocellular nucleation is readily observed by light microscopy, although investigation of nuclear ploidy depends on flow cytometry of isolated hepatocytes. Multinucleation has been described as an aging change in mice and other species, but may also be present following treatment with certain chemical substances.

Multiple endocrine neoplasia (MEN) encompasses several distinct clinical syndromes featuring tumors of the endocrine glands. There are subclassifications of MEN, including MEN 1, MEN 2A, and MEN 2b; each of these subtypes is associated with specific endocrine tumors. See **Endocrine Glands** in Appendix 2 for more information.

Multiple myeloma, see the preferred term **Plasmacytic lymphoma**.

Murine local lymph node assay, see **Local lymph node assay** for further information.

Murine norovirus is represented by the prototypical MNV-1 strain and is a member of the *Caliciviridae* virus family that is closely related to the human norovirus, a cause of gastroenteritis in closed human populations. MNV is also associated with disease in immunodeficient mice including encephalitis, vasculitis, hepatitis, and pneumonia. Hepatitis is characterized by the presence of mononuclear cell infiltrates and a few neutrophils. In severe cases, periportal hepatocytic loss can occur.

Murine urologic syndrome (MUS) is a type of acute or chronic obstructive uropathy affecting male mice of various strains. Mice with the acute form are usually found dead without any prior symptoms. Firm, proteinaceous plugs may be found in the neck of the bladder and urethra at necropsy. In the chronic form, there is usually external dribbling of urine and inflammation, and ulceration of the preputial area. Proteinaceous urethral plugs may or may not be present. Lesions of septicemia-related ecchymoses or petechiae may be present. Bladder distension with cloudy urine or calculi is usually observed. The etiology is not known, but male mice caged individually appear to be resistant, so group-caging is a prerequisite, suggesting trauma as a factor.

Mutagen is a physical or chemical agent that induces mutations.

Mutagenesis is the process of inducing mutations, the term normally reserved to refer to DNA mutations.

Mycosis fungoides, see the preferred term **Lymphoma, epitheliotrophic (canine)**.

Myelin balloons/blebs, see the preferred term **Myelin bubbles**.

Myelin bubbles are focal or multifocal dilatations of the myelin sheath, where axonal degeneration is not otherwise evident. Under INHAND harmonization, this term is recommended to

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catalog artifact as a function of specimen preparation. However, as with similar terms, when the root cause is unknown, the pathologist may use it nonspecifically until the cause is established. It may also be used as a descriptor when myelin degeneration is implicated as an underlying cause. In these instances, myelin bubbles (synonymous with balloons or blebs) describe a swelling of the myelin sheath through which an intact axon traverses. Macrophages may be present within the bubble and engaged in the removal of myelin lipids, in which case myelin degeneration is implied. A variety of toxins have been shown to cause primary demyelination. For example, when tellurium is added to the diet of weanling rats, it causes myelin degeneration in the peripheral nervous system due to inhibition of squalene epoxidase activity, which prevents the cholesterol synthesis necessary for myelin formation and maintenance. Acetyl ethyl tetramethyl tetralin (AETT) causes a primary internodal peripheral nervous system (PNS) demyelination without affecting the Schwann cell body, and methyl parathion, one of the earliest generations of anticholinesterase insecticides, causes demyelination with bubble formation secondary to its effects as an acetylcholinesterase inhibitor. Myelin bubbles occur in the central nervous system (CNS) and PNS as a normal age-related finding in most species and are most often noted in the ventral spinal roots. In older rats, they are more frequent in the in the lumbosacral nerve roots compared to other areas. Age-related ballooning of the myelin sheath can be seen in microscopic and transmission electron microscopic studies of the aging macaque brain. In general, the broad variety of conditions under which myelin bubbles occur speak to a diversity of pathways leading to disruption of the myelin sheath. Given the broad usage of this term, a precise definition and pathophysiologic implication should be given wherever possible, or a more appropriate terminology selected. INHAND recommends reserving this term for artifacts of specimen preparation.

Synonym(s): **Adaxonal vacuoles**; **myelin vacuoles**; **myelin balloons or blebs**; **myelin edema**; **myelin spaces (artifact)**.

Myelin edema, see the preferred term **Intramyelinic edema**.

Myelinolysis, see the preferred term **Demyelination**.

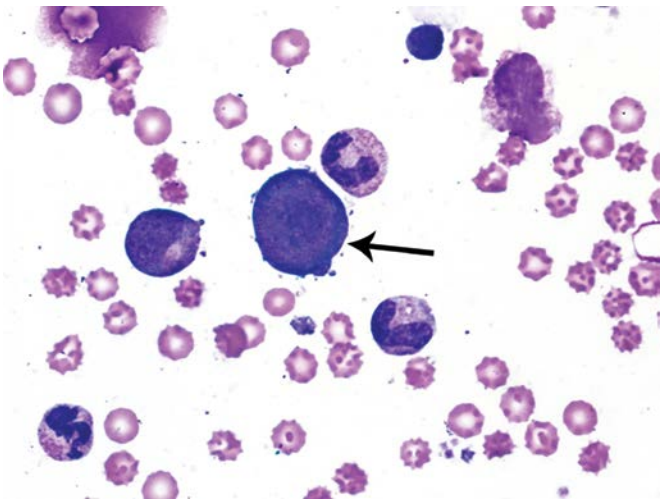
Myelinopathy, see the preferred term **Demyelination**.

Myelin spaces, see the preferred term **Myelin bubbles**.

Myelin vacuolation is a synonym for intramyelinic edema or myelin bubbles (artifact). It may be used when the pathologist is unsure whether the lesion is true edema or an artifact until further work can be done in an attempt to determine the cause. See **Intramyelinic edema** and **Myelin bubbles** for further information.

Myelitis is inflammation of the spinal cord or bone marrow.

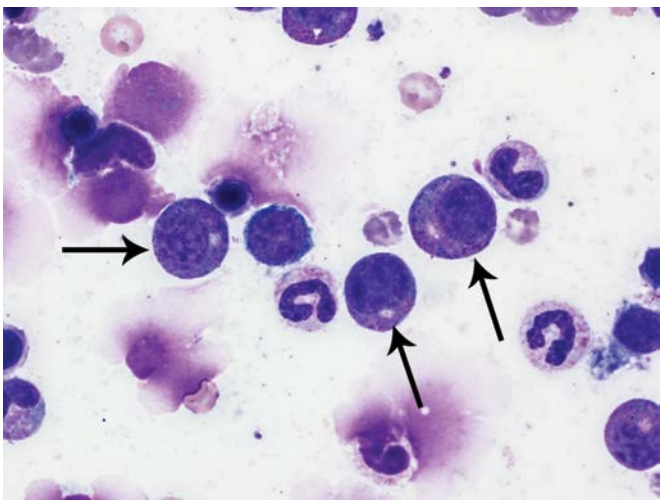
Myeloblast is a unipotent stem cell of the granulocyte lineage that is ~15–20 μm in diameter and resides in the bone marrow. Myeloblasts proliferate in response to the cytokines IL-3, GM-CSF, and G-CSF. They have a high nuclear:cytoplasm (N:C) ratio with a round nucleus containing immature chromatin, one or more nucleoli, and scant amounts of medium to dark blue cytoplasm. Type I myeloblasts lack primary granules, but small numbers of reddish purple (azurophilic) granules appear during maturation (Type II myeloblast). Myeloblasts express CD34, which is lost during maturation to the promyelocyte stage. Myeloblasts can be identified microscopically in the bone marrow but are rarely observed on blood smears except in cases of severe inflammation or leukemia.



Myeloblast (arrow), bone marrow, monkey.

Myeloblastic leukemia, see the preferred term **Myeloid leukemia**.

Myelocyte is the last mitotically active granulocyte precursor cell (~10–20 μm in diameter) that resides in the bone marrow. Their nuclei are oval to round with coarse chromatin, no nucleoli, and light blue cytoplasm containing secondary (specific) granules that allow commitment to a specific granulocyte lineage to be identified microscopically. Myelocytes



Myelocytes (arrows), bone marrow, monkey.

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gain expression of CD11b and CD11c, which help mediate mature leukocyte adhesion to endothelial cells. Myelocytes are uncommonly observed in blood smears but may be seen in the presence of inflammation or leukemia.

Myelodysplastic syndrome (MDS) is a hematologic disorder characterized by peripheral cytopenias and dysplastic changes in the bone marrow. The features of MDS include increased numbers of myeloblasts or rubriblasts, increased numbers of dysplastic cells, and megaloblastic changes in erythroid precursors. Refer to **Hematopoietic System** in Appendix 2 for further information.

Myelofibrosis, see the preferred term **Bone marrow fibrosis**.

Myeloid is a term describing cells of bone marrow origin and/or used as for example with myeloid neoplasms to describe those hematopoietic tumors that are nonlymphoid in origin. The term myeloid leukemia is generally used for tumors from the granulocytic series. Refer to **Hematopoietic System** in Appendix 2 for further information.

Myeloid bodies, see the preferred term **Multilamellar bodies**.

Myeloid depletion is partial to complete absence of myeloid cells of varying stages in the bone marrow. It may occur as part of bone marrow panhypoplasia, such as aplastic anemia in which all cell lines are depleted, or in myeloid cells only with infectious bacterial or viral conditions that cause depletion of the bone marrow storage pools of neutrophils. In leukemia and lymphoma, myeloid depletion may occur through replacement of stem cells and other progenitors by neoplastic cells. Myeloid depletion has also been reported with hypocellular myelodysplastic syndrome and hypocellular acute myeloid leukemia.

Myeloid hyperplasia represents an increase in the production of myeloid cells beyond that which is considered homeostatic and is typically associated with infection or inflammation. Refer to **Hematopoietic System** in Appendix 2 for further information.

Myeloid leukemia is a neoplasm of the myeloid cell lineage in the bone marrow or spleen. Differentiation can vary from immature and poorly differentiated blast cells to mature cells showing varying proportions of immature and segmented forms. Refer to **Hematopoietic System** in Appendix 2 for further information.

Myeloid maturation index is usually 1:4 and represents the ratio of cells in the proliferative phase compared with the cells in the maturation phase in the bone marrow. For myeloid cells, the proliferative phase includes myeloblasts, promyelocytes, and myelocytes, while the maturation phase consists of metamyelocytes and band and segmented neutrophils, eosinophils, or basophils. The ratio is determined by the output of a single committed myeloid stem cell which produces 1 myeloblast, 2 promyelocytes, 4 myelocytes, and 8 metamyelocytes that mature into 8 band and then 8 segmented neutrophils. Additional divisions at the myelocyte stage may produce 10 maturing cells for a total of 30. Deviations from the ratio can occur with infection, inflammation, and toxic effects on the bone marrow.

Myeloid-to-erythroid (M:E) ratio is the ratio of cells in the myeloid series to the cells in the erythroid series. It is determined when evaluating bone marrow smears stained with May-Grunwald Giemsa or Wright Giemsa using a 50×–100× oil objectives. The M:E ratio is obtained by counting 300–500 cells that are classified as either myeloid or erythroid precursors on an area of the smear that is representative of the overall slide or on different areas of the smears, as some areas will consist mostly of myeloid precursors, while others will contain predominantly erythroid precursors. A normal M:E ratio varies from 0.5 to 4.0, depending on the animal species. An increased M:E ratio may indicate an increase in myeloid precursor production (myeloid hyperplasia) or a decrease in erythroid precursor numbers in or (erythroid hypoplasia). A decreased M:E ratio can indicate myeloid hypoplasia or erythroid hyperplasia. To answer the meaning of a decreased or increased M:E ratio, the M:E ratio should be interpreted in conjunction with concurrent hematology data, most importantly the hemoglobin concentration and the neutrophil count. For example, if the M:E ratio is decreased and the animal has an increased neutrophil count with normal hemoglobin levels, the increased M:E ratio is due to an increased myeloid production rather than in a decrease in the erythroid precursors.

Myelophthisis is characterized by the replacement of normal bone marrow precursor cells and their stroma with abnormal cells associated with disorders such as myelogenous and lymphoid leukemias, myelodysplastic syndrome, metastatic neoplasia, and myelofibrosis. It is frequently associated with altered bone marrow microenvironment with resultant pancytopenia (decrease in red blood cells, white blood cells, and platelets). The diagnosis is typically confirmed with a bone marrow biopsy.

Myelopoiesis is the process by which granulocytes and monocytes are produced in the bone marrow from hematopoietic stem cells. Under the influence of growth factors such as G-CSF, GM-CSF, stem cell factor (SCF), and IL-3, progenitor cells become increasingly lineage-committed resulting in colony-forming unit-granulocyte/macrophage (CFU-GM). These cells develop into terminally differentiated neutrophils, eosinophils, basophils, and monocytes. The bone marrow produces as many as 10^{13} myeloid cells per day under homeostatic conditions but can by rapidly increased in the presence of infection or inflammation.

Myelosclerosis is "hardening of bone marrow." "Myelo" is a prefix meaning bone marrow or spinal cord. Sclerosis is a root word meaning hardening. Myelosclerosis occurs when bone marrow is replaced by fibrous connective tissue. Application of this term

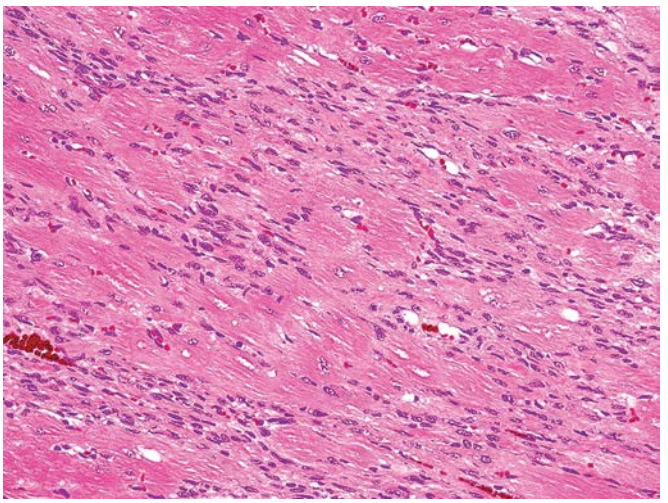
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is reserved for severe bone marrow fibrosis displacing hematopoietic elements resulting in scarring of the bone marrow cavity.

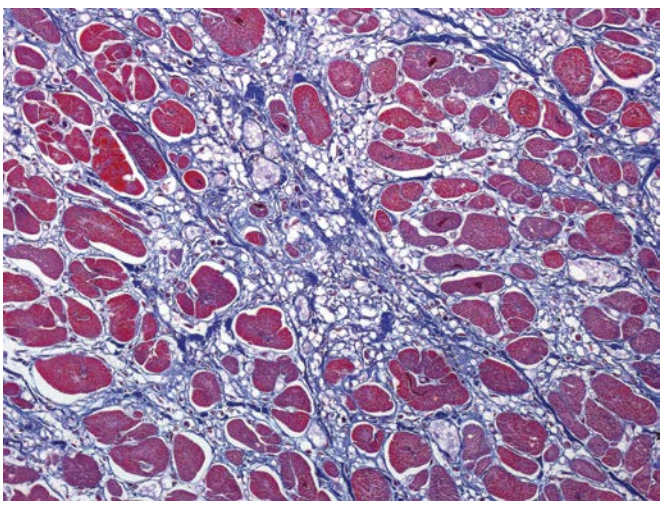
Myelostromal proliferation, see the preferred term **Bone marrow fibrosis**.

Myocardial calcification, see the preferred term **Myocardial mineralization**.

Myocardial fibrosis is the abnormal proliferation of fibroblasts and deposition of collagen within the heart musculature. Myocardial fibrosis occurs as a repair mechanism after injury to the myocardium, such as ischemic infarction, but results in stiffening of the myocardial wall, reduced function, increased risk of arrhythmia, and increased risk of heart failure. It is a hallmark of cardiomyopathy in many species, including human and nonhuman primates. In humans, cardiomyopathy involves mutations of the cardiac sarcomere that predisposes to increased profibrotic pathway activation, and collagen deposition in the heart muscle. Myocardial fibrosis is also associated with administration of some cardiotoxic drugs, including chemotherapeutic agents (e.g., alkylating agents, microtubule inhibitors) or catecholamines, and with toxic substances, such as arsenic. Cardiac fibrosis is a more generalized term for collagen deposition, inclusive of both the myocardium and other anatomic locations, including the heart valves.



Myocardial fibrosis, heart, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology.)



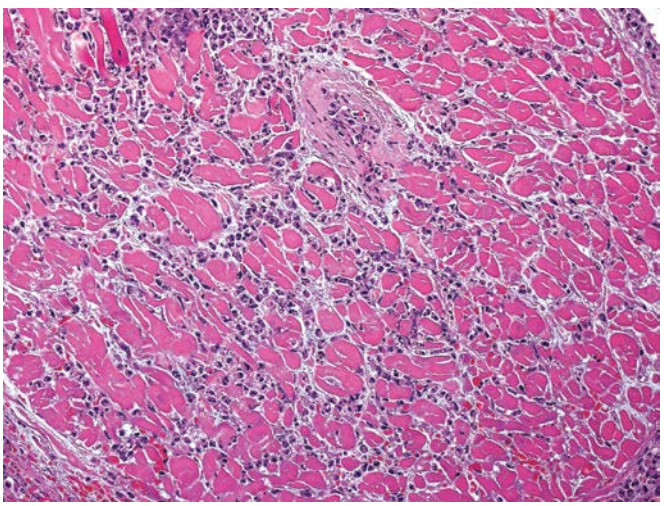
Myocardial fibrosis, heart, cynomolgus monkey. Trichrome stain reveals blue staining consistent with interstitial collagen.

Myocardial infarction is myocardial cell death due to prolonged ischemia. Inflammatory response and scar formation (fibrosis) follow the ischemic injury. Hallmarks of myocardial infarction are increases in the biomarker troponin, electrocardiographic (ECG) abnormalities, and necrosis of cardiac cells.

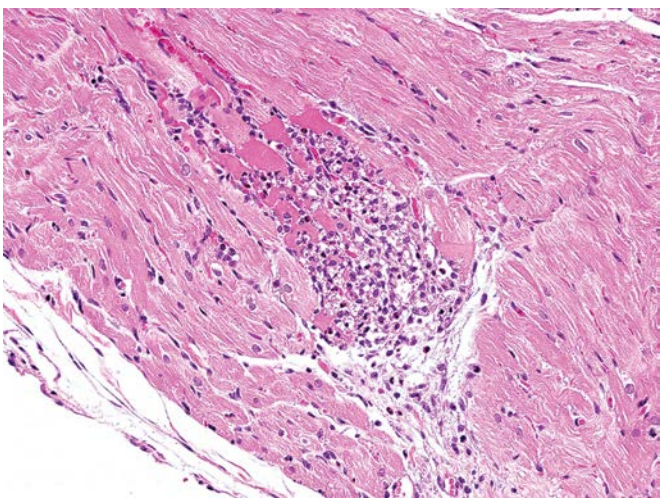
Differential diagnosis: **Cardiomyocyte necrosis** (not associated with vascular occlusion).

Synonym(s): **Myocardial necrosis**.

Myocardial inflammation is infiltration of the heart musculature by inflammatory cells. There are numerous causes of myocarditis, including bacterial, viral, fungal, and parasitic infections.



Myocardial inflammation, acute, heart, Cynomolgus monkey, H&E.



Myocardial inflammation, chronic, heart, Rat, H&E.

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Conditions such as chronic heart disease or ischemic infarction, and drugs or toxins such as doxorubicin or arsenic that result in injury to cardiomyocytes and lead to cellular necrosis and death, may induce inflammation. Immune-mediated myocarditis can be an acquired condition in which previous infection or drug administration induces antibodies against the myocardium, or can be a part of an autoimmune disease syndrome, such as systemic lupus erythematosus (SLE). Myocarditis can be acute, chronic, chronic-active, lymphocytic-plasmacytic, eosinophilic, or granulomatous, based on the nature and duration of the cellular infiltrates and inciting condition.

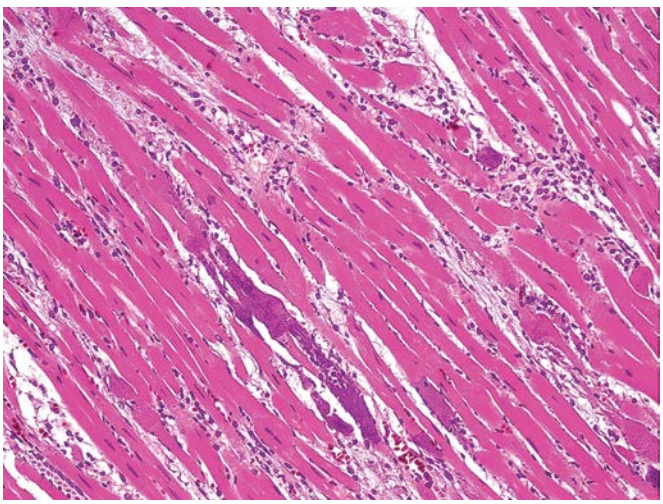
Differential diagnoses: **Cardiomyocyte degeneration**; **Cardiomyocyte necrosis**.

Synonym(s): **Myocarditis**.

Myocardial mineralization is frequently (90–100%) observed in certain inbred mice strains, guinea pigs, and rats. Generally, the lesions are insignificant, but in mice with severe calcification there may be death from congestive heart failure. Grossly, multiple small white to yellow flecks of calcification are seen in the epicardium and myocardium with mild lesions; a diffuse plaque of firm, white, gritty material is seen in the right ventricular epicardium in severe cases. Histologically and ultrastructurally, initially there is focal myocyte necrosis with subsequent calcification; older lesions may have a mild macrophagic response and accompanying fibrosis.

Differential diagnoses: **Formalin pigment**; **Osseous metaplasia**.

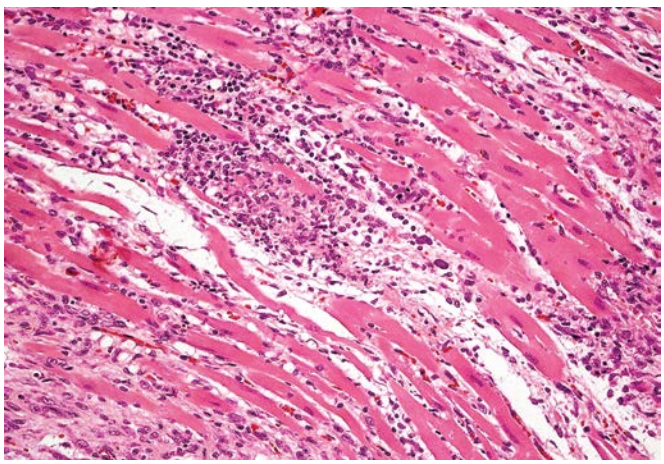
Synonym(s): **Myocardial calcification**.



Myocardial mineralization; single fiber mineralization in the heart of a rat with severe nephrotoxicity, heart, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology.)

Myocardial mononuclear cell infiltrate/fibrosis is the preferred term for rodent progressive cardiomyopathy, an age-related condition commonly seen in rats and mice on long-term studies. The syndrome is initially manifested as focal areas of degenerating cardiomyocytes that elicit a lymphohistiocytic inflammatory reaction. Vacuolation of degenerating myofibers is occasionally present. The left ventricle and apex are often affected. As the animal ages, lesions become more chronic and the inflammatory infiltration resolves. Collagen deposition and fibroblast proliferation replace damaged fibers, sometimes becoming quite extensive and forming coalescing areas. Pigmented macrophages are sometimes seen within these fibrotic areas. Lesions of varying chronicity are often seen simultaneously in older animals. Extensive severe cardiomyopathy can result in heart failure or atrial thrombosis, eventually causing the animal's death. Compounds in pharmaceutical development that are cardioactive can result in a treatment-related increase in the incidence and/or severity of this spontaneous finding in rat and mouse carcinogenicity studies.

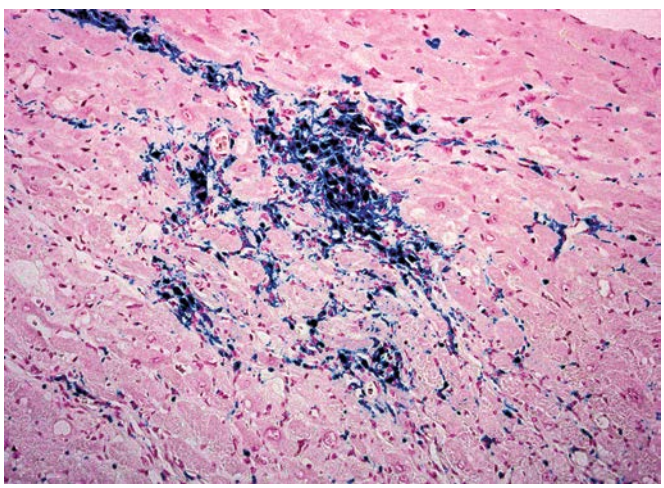
Synonym(s): **Rodent progressive cardiomyopathy**.



Myocardial mononuclear cell infiltrate/fibrosis, heart, rat, H&E.

Myocardial necrosis, see the preferred terms **Myocardial infarction** and **Cardiomyocyte necrosis**.

Myocardial pigment is the deposition of pigments lipofuscin or hemosiderin in the myocardium. Lipofuscin may occur as a consequence of advancing age or oxidative stress or cachexia. Light microscopy of affected myocytes shows perinuclear



Myocardial pigment, heart, rat. Perl's Prussian blue stain reveals iron content in deposit of hemosiderin. (Reproduced with permission of the Japanese Society of Toxicologic Pathology.)

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accumulations of residual bodies that appear as yellowish-brown granules on hematoxylin and eosin (H&E)-stained sections. The pigment granules show orange-yellow autofluorescence. Hemosiderin deposition can occur following drug-induced myocardial necrosis and hemorrhage, for example in rats treated with vasodilating antihypertensive drugs. Iron accumulation may also be associated with myocardial hemorrhage, degeneration, necrosis and fibrosis.

Differential diagnosis: **Formalin pigment**.

Myocarditis, see the preferred term **Myocardial inflammation**.

Myoepithelioma, **malignant** is a salivary gland tumor comprised of myoepithelial cells. Refer to **Gastrointestinal Tract** in Appendix 2 for further information.

Myofiber is a single skeletal muscle cell, also referred to as a myocyte. These cells contain multiple nuclei and can be very long within the muscle fascicle. Myofibers contain contractile components made up of actin and myosin myofilaments. On mammalian tissue sections, skeletal muscle myofibers are distinguished based on histochemical or immunohistochemical characteristics. Skeletal muscle fibers are classified into type I, type IIA, type IIB, and type IIX (or IID). The type IIB fibers described in earlier studies have been reclassified as type IIX and the type IIB fiber does not exist in human muscles. There is little information on existence of fiber type IIX in nonhuman primates. Hybrid fibers have also been described in various muscles (types I and IIA; types IIA and IIX; types IIX and IIB). Type I and II fibers can be distinguished using myofibrillar ATPase histochemistry by varying pH or by immunohistochemistry using antimyosin heavy chain antibodies. Type I fibers or oxidative fibers have more lipid droplets, contain more myoglobin and more mitochondria, and therefore stain more deeply with succinate dehydrogenase, NADH dehydrogenase, or cytochrome c oxidase, enzymes that are part of the respiratory chain. Phosphorylase and phosphofructokinase involved in the breakdown of glycogen stain predominantly type II fibers. Assessment of fiber types could be important in investigative toxicology as seen with lipid-lowering drugs, for example, or could help in the characterization and utilization of animal models.

Myofiber atrophy is the presence of muscle fibers of reduced size, often with basophilic cytoplasm and vesicular nuclei, indicating attempts to regenerate. Atrophy may affect either type 1 or type 2 muscle fibers. Causes include high doses of steroids, nerve damage, disuse, aging and immobilization.

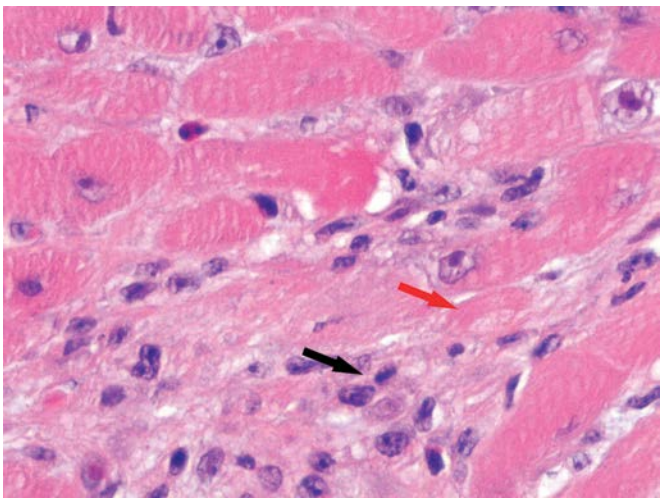
Differential diagnosis: **Myopathy**.

Synonym(s): **Skeletal muscle atrophy**; **age-related atrophy**; **disuse atrophy**; **nutritional atrophy**; **denervation atrophy**.

Myofiber cytopathic changes, see the preferred terms **Myofiber degeneration** and **Myofiber vacuolation**.

Myofiber degeneration is the reversible cell damage (degeneration) of myocytes that display cell swelling which is related to swelling of the endoplasmic reticulum and mitochondria within the cytoplasm. Various agents can induce skeletal muscle degeneration including statins and peroxisome proliferator-activated receptor agonists with preferential sensitivity of type II and type I fibers, respectively.

Synonym(s): **Myopathy**; **cytopathic changes**; **myopathic changes**.



Myofiber degeneration and necrosis of skeletal muscle in a mouse, H&E. Fibroblasts and collagen (black arrow) are evident with occasional degenerate and necrotic muscle fibers (red arrow).

Myofiber necrosis is characterized by the presence of coagulative necrosis of myocytes (i.e., the loss of nuclei, loss of striations, fragmentation, greater cytoplasmic eosinophilia, and the influx of leukocytes). Various agents can induce skeletal muscle necrosis including statins and peroxisome proliferator–activated receptor agonists with preferential sensitivity of type II and type I fibers, respectively. In addition, irritant xenobiotics administered by intramuscular injection may cause myofiber necrosis.

Differential diagnosis: **Myopathy**.

Myofiber vacuolation is the presence of small, clear spaces within the cytoplasm of the myocyte. Myofiber vacuolation may be observed following phospholipidosis or chloroquine treatment.

Synonym(s): **Myopathy**; **cytopathic changes**; **myopathic changes**.

Myoglobinuria is the presence of the muscle protein myoglobin in the urine. Myoglobinuria is typically linked with hyaline droplets in the proximal convoluted tubule (PCT), and often with pigmented hyaline tubular casts.

Myometrial artery hyalinization is commonly observed as a spontaneous change in the postpartum uterus of macaques. Arteries and veins show perivascular accumulation of pale eosinophilic extracellular matrix in multiparous animals and are evidence of previous pregnancy.

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Myometrial hyperplasia is a focal or diffuse lesion within the myometrium consisting of hyperplastic, well-differentiated smooth muscle cells with an increased nucleus/cell ratio but without nuclear atypia. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Myometrial inflammation is characterized by leukocytic cellular infiltrates (e.g., mononuclear, neutrophils, histiocytes, or mixed inflammatory cells) in the epithelium that extend significantly to the myometrium, with accompanying other inflammatory changes (e.g., hemorrhage, swelling, edema, tissue degeneration/necrosis). The appearance varies depending upon the severity and duration. This condition is more common in mice than in rats and can be associated with *Klebsiella* spp. or *Mycoplasma* spp. infections. It is uncommon in the nonhuman primate (NHP) and dogs, although postpartum metritis can occur in the dog and is usually associated with retained fetal membranes.

Synonym(s): **Myometritis**.

Myometrial leiomyoma, see the preferred term **Female sex organ, leiomyoma**.

Myometritis, see the preferred term **Myometrial inflammation**.

Myopathic changes, see the preferred terms **Myofiber degeneration** and **Myofiber vacuolation**.

Myopathy, see the preferred terms **Myofiber degeneration** and **Myofiber vacuolation**.

Myxomatous degeneration is the accumulation of dermatan sulphate, a glycosaminoglycan, within a connective tissue matrix and is often observed in heart valves. The lesion is characterized by loose extracellular matrix and interspersed interstitial cells.

Myxomatous valvular degeneration, see the preferred term **Valvular degeneration**.

Myxosarcoma is a malignant neoplasm of connective tissue arising from primitive fibroblasts. A characteristic feature of this tumor is the presence of copious amounts of stromal mucins. In laboratory animals, it has been reported in various locations including but not limited to long and flat bones, subcutaneous connective tissues, heart, peritoneum, and joints. Refer to **Bone, Muscle, and Tooth** in Appendix 2 for further information.

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N

***N*-acetyl-β-D-glucosaminidase (NAG)** is a lysosomal enzyme present in the proximal tubule cells of the kidney, particularly the S2 segment where lysosomes are most abundant. As the enzyme's molecular weight is high, it cannot be filtered through the glomerulus and therefore measurement of NAG in urine represents a biomarker originating from the renal tubule. Urinary NAG is used as a marker of renal tubule injury, but as NAG is a lysosomal enzyme, any stimulated activity of the lysosomal compartment is also likely to cause a variation in urinary NAG concentrations.

***N*-acetyl-5-methoxy tryptamine**, see the preferred term **Melatonin**.

***N*-acetyl transferases (EC 2.3.1.5)** are enzymes that catalyze the acetylation of aromatic amines, sulfonamides, and hydrazines. See **Acetylation** for further information.

NADPH-cytochrome P450 reductase (EC 1.6.2.4) is a microsomal flavoprotein containing both flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD), which are required to transfer electrons between nicotinamide adenine dinucleotide phosphate-oxidase (NADPH) and cytochrome P450. Despite the diversity of cytochrome P450 proteins, there is only one reductase that donates electrons to all cytochrome P450 isozymes. See **Cytochrome P450** for further information.

Narcosis a reversible state or condition of general stupor or unconsciousness typically in reference to a drug or chemical-induced central nervous system depression. Narcosis includes any state of insensibility or deep stupor arising from deep diving (nitrogen narcosis) or respiratory acidosis (carbon dioxide narcosis).

Nasal-associated lymphoid tissue (NALT) is microscopically identified as paired masses of organized lymphoid tissue dorsal to the cartilaginous soft palate in the distal base of the nasal cavity at the entrance of the pharyngeal duct in rodents and in smaller mammals that are obligate nasal breathers. NALT is present at birth and is positioned for maximal antigenic sampling in the nasal cavity, but germinal centers may not develop in the follicles. Small mammals lack other tonsils. In most large mammals, the nasopharyngeal tonsil, and in humans the adenoid, are the equivalent structures to the NALT.

Synonym(s): **Nose-associated lymphoid tissue**.

Nasal cavity adenocarcinoma is a malignant neoplasm of the epithelium lining the nasal cavity or arising within submucosal gland epithelium, or in a pre-existing adenoma. These tumors have differing cell patterns and may have a similar phenotype to the original epithelium or be anaplastic. Refer to **Respiratory System** in Appendix 2 for further information.

Nasal cavity adenoma is a benign neoplasm of the lining epithelium of the nasal cavity and also the nasopharynx or paranasal sinuses. Cells are usually no-ciliated, cuboidal to columnar, or have goblet cells arranged in sheets or forming acinar, or pseudoglandular structures. Refer to **Respiratory System** in Appendix 2 for further information.

Nasal cavity adenosquamous carcinoma is a malignant neoplasm arising from respiratory epithelium, submucosal duct epithelium, or from olfactory epithelium. Malignant glandular and squamous components are frequently poorly differentiated, and neoplastic growth can result in invasion and metastasis. Refer to **Respiratory System** in Appendix 2 for further information.

Nasal cavity amyloid represents extracellular accumulation of polypeptide fragments typically in a submucosal location. Amyloid appears as amorphous, pale, eosinophilic deposits in hematoxylin and eosin (H&E)-stained sections. The presence of amyloid can be confirmed by the use of Congo red stain to produce the characteristic "apple-green" birefringence when viewed microscopically under polarized light.

Differential diagnosis: **Nasal cavity eosinophilic globules**.

Nasal cavity basal cell hyperplasia appears as a thickening of the basal cell layer of the nasal cavity epithelia. It is commonly seen in response to irritation and may be precede metaplasia. Refer to **Respiratory System** in Appendix 2 for further information.

Nasal cavity corpora amylacea are basophilic or amphophilic concretions in hematoxylin and eosin (H&E)-stained sections that occur within olfactory or respiratory epithelium, in the underlying lamina propria, or in the lumen of nasal glands and in the absence of degeneration or necrosis of the affected tissue. Corpora amylacea may be partially mineralized.

Differential diagnosis: **Nasal cavity epithelial degeneration**.

Nasal cavity eosinophilic globules are bright eosinophilic inclusions in hematoxylin and eosin (H&E)-stained sections within the respiratory and glandular epithelium cytoplasm, and within the sustentacular cells of the olfactory epithelium. They can be seen in control animals, appear to increase in incidence with age, and can increase as a consequence of

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airway irritation. There is immunohistochemical evidence that the globules contain the chitinase protein Ym2.

Differential diagnosis: **Nasal cavity amyloid**.

Synonym(s): **Nasal cavity eosinophilic inclusions**; **nasal cavity hyaline droplets**; **nasal cavity hyaline change**.

Nasal cavity eosinophilic inclusions, see the preferred term **Nasal cavity eosinophilic globules**.

Nasal cavity epithelial atrophy is characterized by thinning of the affected mucosa resulting from either a decrease in height of cells and/or cell loss. Atrophy of the olfactory epithelium is often accompanied by loss of axon bundles from the subjacent lamina propria. Must differentiate from artifact (e.g., tangential section) and autolysis.

Differential diagnoses: **Nasal cavity epithelial metaplasia**; **Nasal cavity epithelial degeneration**; **Nasal cavity epithelial necrosis**.

Nasal cavity epithelial degeneration appears as a loss of organization of the cell layers and may be accompanied by deciliation, cytoplasmic blebbing, and increased intercellular spaces. Individual cells may be lost, although overall epithelial height is maintained. This may give the degenerated epithelium a vacuolated appearance. Epithelial degeneration may also be accompanied by dilatation of the submucosal glands and accumulation of secretory material.

Differential diagnoses: **Nasal cavity epithelial necrosis**; **Nasal cavity epithelial metaplasia**; **Nasal cavity epithelial atrophy**; **Nasal cavity corpora amylacea**.

Nasal cavity epithelial hyperplasia represents a proliferation of affected epithelium with an increased number of cell layers. It is often in response to irritation, and associated with degeneration, metaplasia, and inflammation. Hyperplasia may occur in the squamous, respiratory, transitional, or olfactory epithelia, and in the latter can involve all cell (basal, sensory, or sustentacular) types. Refer to **Respiratory System** in Appendix 2 for further information.

Nasal cavity epithelial hyperplasia with atypia represents the presence of hyperplasia with abnormal phenotypes and bi- or multinucleate cells. Refer to **Respiratory System** in Appendix 2 for further information.

Nasal cavity epithelial metaplasia occurs in two forms, either from a transitional, respiratory, or olfactory epithelium to a squamous phenotype, or metaplasia of olfactory epithelium to a respiratory phenotype. Metaplasia is generally not considered a preneoplastic change. Refer to **Respiratory System** in Appendix 2 for further information.

Nasal cavity epithelial necrosis is characterized by the typical features of cell death, including nuclear pyknosis or karyorrhexis, cytoplasmic eosinophilia, and cellular exfoliation, and may be associated with inflammation. It can be a prequel to partial or total loss of the epithelium through the basement membrane (i.e., erosion and ulceration, respectively). Necrosis of olfactory epithelium in the absence of evidence of damage to the other nasal cavity epithelia may indicate that toxicity is the result of local metabolism within the olfactory epithelium.

Differential diagnoses: **Nasal cavity epithelial degeneration**; **Nasal cavity epithelial atrophy**.

Nasal cavity epithelial regeneration indicates ongoing repair of the affected tissue, can be seen in any of the epithelia within the nasal cavity, and is characterized in affected cells by increased basophilia, increased nuclear-to-cytoplasm ratio, and by alteration of normal tissue architecture or differentiation. Regeneration may be seen in proximity to areas of degeneration or necrosis.

Differential diagnosis: **Nasal cavity epithelial hyperplasia**.

Nasal cavity hyaline change, see the preferred term **Nasal cavity eosinophilic globules**.

Nasal cavity hyaline droplets, see the preferred term **Nasal cavity eosinophilic globules**.

Nasal cavity inflammation is a common finding in response to inhaled irritants, whether they are test article–related or due to the presence of foreign bodies. The distribution of inflammation within the nasal cavity may follow the impact zones for inhaled particles on structures that disrupt airflow; hence the tips of the turbinates are often involved. The type of inflammation can be categorized in terms of likely duration, acute or chronic, defined by the primary cellular response seen. Acute inflammation is characterized by the presence of neutrophils and may be accompanied by vascular congestion, edema, and exudates in the nasal cavity. The presence of eosinophils may indicate an immunologic response. If the primary cellular response is mononuclear, with a variable cell population that may include lymphocytes, macrophages, and plasma cells, then the inflammation is defined as chronic. The type of cellular infiltrate may also indicate that the inciting cause is persistent or immunogenic. The presence of a persistent irritant invokes an inflammatory response termed chronic active that may progress to granulomatous inflammation. Chronic active inflammation is defined by the presence of significant granulocytic and mononuclear cell populations within the cellular infiltrate, indicating a continued stimulation of granulocytes against a background of chronic inflammation, or resolution of the acute phase. Granulomatous inflammation is characterized by the presence of large macrophages with abundant cytoplasm (epithelioid cells), lymphocytes, and plasma cells, and in longstanding lesions, the presence of fibrosis.

Nasal cavity inflammatory polyp is an exophytic mass consisting of proliferating submucosal connective tissue that is lined by metaplastic, hyperplastic, or normal mucosal epithelium. It has been described in mice in association with dental dysplasia.

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Nasal cavity, larynx, and airway vascular changes include congestion, edema, hemorrhage, angiectasis, and thrombosis. Congestion refers to a dilated and blood-filled appearance of the submucosal vessels, edema is observed as proteinaceous fluid in the tissue surrounding the vessels, and hemorrhage is evidenced by extravasation of blood cells into the surrounding tissue or lumen. Combinations of these changes are frequently seen in association with inflammation, and independent of inflammation, they can represent an early response to an irritant in the nasal cavity or be a consequence of trauma. Fibrinous exudates may also be seen in association with vascular changes. Angiectasis refers to the presence of an increased number of vessel profiles causing disruption of the normal tissue architecture. Thrombosis within the vasculature is characterized by an amorphous, eosinophilic, laminated mass often containing erythrocytes and leukocytes. Angiectasis and thrombi in the nasal cavity are associated with a generalized debilitated state and have been associated with mononuclear cell leukemia. These conditions should be differentiated from bleeding following retroorbital sinus blood collection, and postmortem clots.

Differential diagnosis: **Hemangioma**.

Nasal cavity neuroepithelial carcinoma is a malignant neoplasm arising from the olfactory epithelium (basal, sustentacular, or sensory cells). Rosette or pseudorosette structures are characteristic and invasion into bone or the brain is common. Refer to **Respiratory System** in Appendix 2 for further information.

Nasal cavity septal perforation represents total loss of the septal tissue, usually as a consequence of severe necrosis with concurrent loss of cartilage. It is most often seen ventrally where the tissue is thinnest and is likely to be accompanied by a severe inflammatory response. Must be differentiated from trauma or artifact.

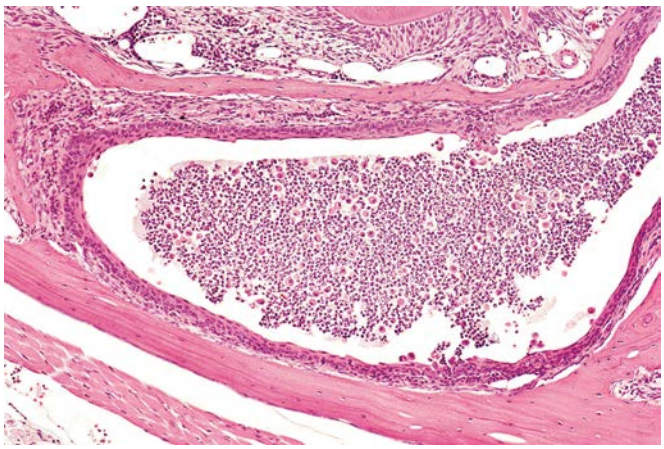
Nasal cavity squamous cell carcinoma is a malignant neoplasm located in the nasal vestibule but may also arise from metaplastic squamous epithelium in other locations. Well-differentiated or poorly differentiated cell types may be evident. Keratin immunohistochemistry may aid in the diagnosis. Refer to **Respiratory System** in Appendix 2 for further information.

Nasal cavity squamous cell papilloma is a benign exophytic neoplasm composed of well-differentiated epithelium with a vascularized stalk. The origin is either the nasal vestibule or metaplastic squamous epithelium in other locations. Refer to **Respiratory System** in Appendix 2 for further information.

Nasal yolk sac tumor is a rare, primitive germ cell neoplasm that may arise in the nasal passages, characterized by nests, ribbons, or single cells embedded in an amorphous, eosinophilic, periodic acid-Schiff (PAS) reaction and laminin positive hyaline matrix. Refer to **Respiratory System** in Appendix 2 for further information.

Nasolacrimal duct epithelial hyperplasia consists of mural or polypoid proliferation of the duct epithelium. The involved epithelium may vary from partially or nonkeratinized stratified squamous epithelium to pseudostratified cuboidal or columnar epithelium, or transitional epithelium. Refer to **Special Senses** in Appendix 2 for further information.

Nasolacrimal duct inflammation consists of focal or diffuse accumulations of inflammatory cells (granulocytes or heterophils [rabbit], macrophages, lymphocytes, and plasma cells) in and around the ducts accompanied by other inflammatory indicators including interstitial edema, congestion, hemorrhage, and necrosis or cellular debris. Inflammation may be an extension from the nasal cavity or associated with neoplastic masses.



Nasolacrimal duct inflammation, mouse, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

Nasolacrimal duct inflammatory cell infiltrate consists of small numbers of leukocytes associated with the duct epithelium, in the absence of obvious inflammation. Infiltrates around ducts may be difficult to differentiate from duct-associated lymphoid tissue.

Differential diagnoses: **Duct-associated lymphoid tissue**; **Nasolacrimal duct inflammation**.

Nasolacrimal duct squamous cell carcinoma in rodents forms a mass of variably keratinized squamous epithelial cells with cellular and nuclear pleomorphism, atypia, and invasion through the basement membrane. Refer to **Special Senses** in Appendix 2 for further information.

Nasolacrimal duct squamous cell papilloma in rodents consists of fronds of normal-appearing squamous cells, with variable keratinization, covering a fibrovascular stalk. Hyperplasia of squamous cells lacks the cellular stalk, and carcinomas include cellular atypia and invasion with destruction of the basement membrane. Refer to **Special Senses** in Appendix 2 for further information.

Nasopharyngeal clearance is the process by which particles, aerosols, gasses, or vapors are removed and cleared from entry into the distal lower portions of the respiratory airways. This

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can be accomplished by the act of sneezing, wiping, or blowing at the level of the anterior nares, to the physical entrapment, adherence, dissolution/absorption into mucus secretions, and removal by mucus and ciliary action in the posterior nasal regions and pharynx, that terminates in swallowing and coughing. Often considered the first line of defense from toxicants entering through the inhalation route, nasopharyngeal clearance removes particles in the 1–10-micron range and is aided by a robust immunologic defense system.

Nasopharyngeal tonsil is a single mass of encapsulated mucosa-associated lymphoid tissue (MALT) located posterior to the nasal cavity in the roof of the nasopharynx above the noncartilaginous soft palate. This tonsil, found in most large mammals before or at birth, is similar in function to the nasal-associated lymphoid tissue (NALT) found in obligate mouth-breathing small mammals. The nasopharyngeal tonsil, along with the paired tubal tonsils at the opening of the Eustachian tubes, the paired palatine tonsils of the oropharynx, the lingual tonsil on the posterior tongue, and subepithelial collections of isolated lymphoid tissue throughout the pharynx, form a ring of lymphoid tissue ("Waldeyer's ring") that provides immune protection for the nasooropharyngeal region. The nasopharyngeal tonsil contains one or more lymphoid follicles with high endothelial venules, and the subepithelial dome is covered by follicle-associated epithelium and lymphoepithelium generally devoid of goblet cells. The surface of the nasopharyngeal tonsil is highly invaginated but without crypts. Postnatal antigenic stimulation increases the size of this tonsil and the number of fully formed lymphoid follicles. Inhaled particulate matter may be trapped within the folds, and infections or exposure to xenobiotics may result in lymphoid enlargement and surface ulcerations and inflammation.

Synonym(s): **Pharyngeal tonsil**; **adenoid (in humans)**.

National Toxicology Program (NTP) is part of the U.S. Department of Health and Human Services and generates and interprets toxicological information about potentially hazardous environmental substances and makes the data and the assessment available to the public.

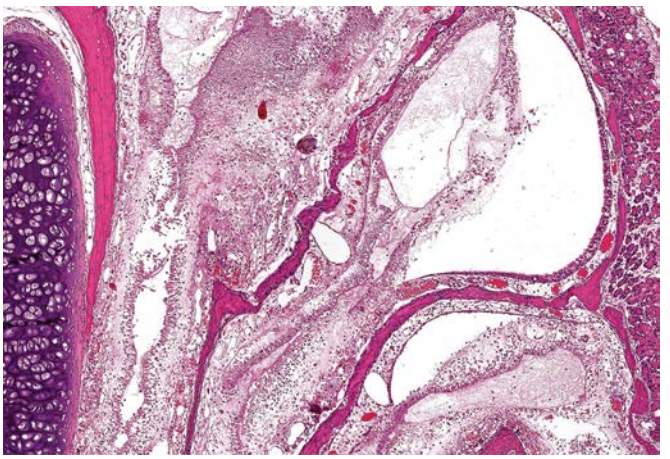
Natural cytotoxic cells or "natural killer (NK) cells" are innate lymphoid cells that contribute to rapid detection and clearance of pathogen-infected and tumor cells, and are not to be confused with cytotoxic T cells that have a similar function but scan MHC (major histocompatibility complexes) Class-I for non-self-peptide sequences, while NK cells react to cells without MHC Class-I peptide sequences.

NDA is an acronym for New Drug Application, which is official documentation demonstrating the safety and efficacy of an experimental drug against a specific disease. This documentation is submitted to a health regulatory agency to obtain permission to market a drug.

Necrolysis, see the preferred term **Toxic epidermal necrolysis**.

Necropsy is the term used for the detailed postmortem gross (macroscopic) examination of external and internal body surfaces, tissues, and organs from animals to find the cause of death and to evaluate any observations relating to injury or disease present, whereas the term "autopsy" is used for the same procedures in humans. In toxicology studies, necropsy findings are typically compared to in-life observations, clinical pathology, and histopathological findings in an attempt to correlate changes related (or unrelated) to test article administration.

Necrosis is the process whereby an irreversible series of cellular changes occurs in response to injury that leads to cell death. Types of necrosis include coagulative, liquefactive, caseous, and fibrinoid. The mechanism leading to necrosis has its fundamental basis in the opening of the mitochondrial permeability transition pore (MPTP) after a lethal insult. The mitochondria lose the ability to generate ATP. In the face of energy crisis, cellular homeostatic functions fail, metabolism ceases, and necrosis results. Necrosis is characterized microscopically by cell swelling, hypereosinophilia, and nuclear karyolysis/karyorrhexis. Ultrastructurally, there may be swelling and degeneration of mitochondria and other cytoplasmic components, loss of nuclear and cytoplasmic membrane integrity with blebbing, loss of cell junctions, and leakage of cytoplasmic materials from the cell. Expulsion of intracellular materials into the tissue environment elicits an inflammatory response. With chronicity, necrotic tissue may become partially mineralized due to dystrophic calcification. Although the terms "single cell necrosis" (i.e., "oncotic necrosis") and "apoptosis" have been used interchangeably, both reflect different pathways such that both terms should be applied separately, where possible and appropriate. Necrosis of cells in a tissue and organ can be described in different morphological patterns. It is useful to specify the zone of necrosis if the entire tissue is not involved. Tissue locators, such as centrilobular and periportal for the liver or proximal and distal tubule for the



Necrosis of the lining of the nasal cavity of a rat with gastric reflux and aspiration, H&E. There is widespread necrosis of the epithelium lining the nasal turbinates with accumulation of inflammatory cells, abundant proteinaceous fluid, and sloughed fragmented necrotic debris in the spaces between turbinates.

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kidney, often provide additional insights into the mechanisms of xenobiotic-related injury when considered with other data.

Negative control is a group designation for animals receiving treatment comparable to animals receiving the test drug or chemical, but without the same drug, chemical, or at times, only the vehicle or carrier. In common practice, negative controls can also be referred to as saline, water, or vehicle controls, or may contain drugs or chemicals that will not produce a positive response in the test system under investigation.

Nematodiasis is the presence of nematode larva or adults within tissue.

Neonatal kidney refers to the immature state of kidney morphology at the time of birth. Since the kidney has very little function during gestation, glomeruli are small, tubules are narrow, and both are not fully expanded. After birth, as blood pressure increases and the kidney begins to produce urine, these structures expand as the organ becomes functionally mature.

Neonatal period is the time of development of the individual just after birth.

Neoplasia is atypical, dysregulated growth of cells. These cells form a neoplasm or tumor which can be classified either as benign or malignant, depending on various histologic characteristics. See **Malignancy**, **tumor**, and **Tumor differentiation** for further information.

Neoplastic transformation is the transformation of immortalized cells to tumorigenic cells. The term "neoplastic" describes the ability of cells to form a tumor. See **Cell transformation** for further information.

Neovascularization is the formation of new blood vessels, primarily in response to ischemia or other tissue injury. Neovascularization occurs in various physiologic and pathologic processes, including wound healing, neoplasia, macular degeneration of the eye, and atherosclerotic plaque progression. During neovascularization, new vessels sprout off of parent blood vessels. This process includes parent vessel vasodilation, degradation of parent vessel basement membrane, migration and proliferation of endothelial cells, formation of capillary tubes, and finally blood vessel maturation and basement membrane synthesis.

Differential diagnoses: **Hemangioendothelial hyperplasia**; **Hemangioma**; **Hemangiosarcoma**.

Synonym(s): **Angiogenesis**.

Nephritis, see the preferred term **Renal parenchymal inflammation**.

Nephroblastematosis is the precursor lesion of nephroblastoma of the kidney. It is generally observed near the cortical-medullary junction and is characterized by the proliferation of a uniform population of densely basophilic cells that lack organoid differentiation. Refer to **Urinary System** in Appendix 2 for further information.

Nephroblastoma is a malignant neoplasm of the kidney composed of a population of densely basophilic blastemal cells (cells capable of growth and regeneration into organs or body parts) that can further differentiate into tubule, rosettes, or glomerular bodies, which are primitive-appearing glomeruli. The neoplasm is usually transected by dense bands of non-neoplastic fibrous tissue. Generally, nephroblastomas are spontaneous neoplasms, and can be seen in young rats but are rare in the mouse. Refer to **Urinary System** in Appendix 2 for further information.

Nephrocalcinosis is the presence of precipitated calcium salts (i.e., uroliths) in renal tubules.

Nephrogenic rest, see the preferred term **Nephroblastematosis**.

Nephron is the structural and functional unit of the kidney consisting of the glomerulus, proximal tubule, loop of Henle, and the distal tubule. The proximal tubule and distal tubules, in part, are composed of proximal and distal convoluted tubules. The proximal convoluted tubule may be further segmented into the S1, S2, or S3 segments, which have specific morphological and functional features. See Appendix 3 for more information.

Nephropathy, see the preferred term **Nephrosis**.

Nephrosis is any disease of the kidney that is not inflammatory or neoplastic in nature. It can be characterized clinically by the nephrotic syndrome. See **Nephrotic syndrome** for further information.

Synonym(s): **Nephropathy**.

Nephrotic syndrome is a constellation of signs and symptoms consisting of fluid retention with edema, proteinuria, hypoproteinemia, hypercholesterolemia, and hypertriglyceridemia. The underlying basis is glomerular damage causing loss of protein in the urine. The glomerular damage can result from diverse etiologies or as a component of other diseases.

Nephrotoxicants are any drugs or chemicals that produce kidney toxicity, by direct chemical action or indirectly through immune-mediated mechanism(s), or by alterations in renal fluid balance.

Nephrotoxicity refers to any type of toxic damage to the kidney, which can affect any individual segment of the nephron. See **Adverse effects** for further information.

Nephrotoxicity Working Group is a panel of renal experts under the Predictive Safety and Testing Consortium (PSTC), that may include pathologists and nephrologists, assembled to review a defined data set in order to determine if the test article(s) has a potential to cause renal damage. They can also

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make recommendations concerning relevance of the findings for species extrapolation to humans.

Nerve fiber degeneration, see the preferred term **Axonal degeneration**.

Nervous system, Anatomy and Histology, see Appendix 3 for further information.

Nesidioblastosis is a term for hyperinsulinemic hypoglycemia attributed to excessive function of the pancreatic beta (β) cells. There is usually an abnormal microscopic appearance of the pancreas associated with the condition. Histologically, there are areas of islet cell enlargement, islet cell dysplasia, beta cells budding from ductal epithelium, and islets in apposition to ducts. Nesidioblastosis is associated with experimentally induced chronic pancreatitis in rats but may occur as a spontaneous disease in other mammals.

Neurilemmoma, malignant, see the preferred term **Intraocular schwannoma**.

Neurinoma, malignant, see the preferred term **Intraocular schwannoma**.

Neuritis is inflammation of a peripheral nerve.

Neuroaxonal dystrophy, see the preferred term **Axonal dystrophy**.

Neurobehavioral teratology is a functional impairment of behavior resulting from an abnormal development caused by a teratogen, also referred to as **Behavioral teratology**.

Neurobehavioral toxicology is the study of effects on behavior which are caused by the toxicity of agents and developmental compounds on the nervous system. Disorders include alexia, ataxia, aphasia, and other learning disabilities. Such parameters are assessed in safety pharmacology studies during the preclinical phase of drug development.

Neuroectodermal tumor (primitive neuroectodermal tumor [PNET]) originate from small round cells of neuroectodermal origin and may be associated with teratomas or seminomas in the testis. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Neuroendocrine carcinoma, see the preferred term **Neuroendocrine tumor, malignant**.

Neuroendocrine cell tumor, benign is a neoplasm that arises from cells with both endocrine and nervous system function. Neuroendocrine cell tumors occur in many organs including the intestine, lung, and pancreas. See **Endocrine Glands** in Appendix 2 for more information.

Neuroendocrine tumor, malignant is a neoplasm that arises from cells with both endocrine and nervous system function. The cytological features of malignant neuroendocrine tumors may be similar to that of the benign neuroendocrine tumor, and only the presence of metastasis or blatant tissue invasion may separate the benign from the malignant tumor.

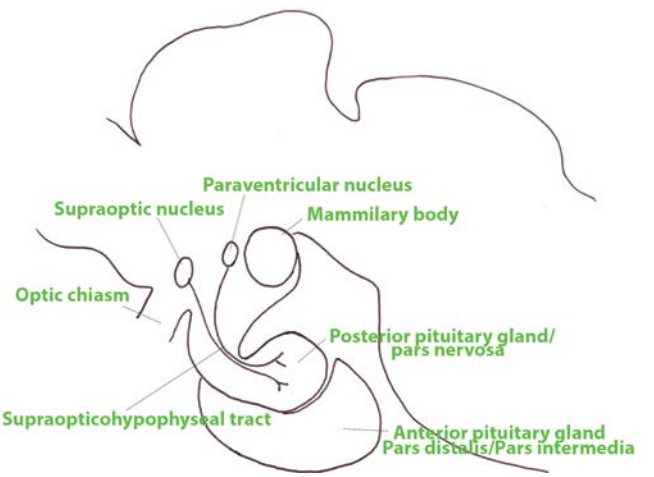
Synonym(s): **Neuroendocrine carcinoma**.

Neuroepithelial carcinoma is an uncommon tumor arising from the nasal olfactory epithelium. These tumors may infiltrate bone, the paranasal sinuses, and extend through the cribriform plate into the brain. Chemical reactive metabolites in nasal epithelial cells may be a critical determinant in neoplastic transformation of olfactory epithelium. Refer to **Nervous System** in Appendix 2 for further information.

Synonym(s): **Esthesioneuroblastoma**; **esthesioneuroepithelioma**; **olfactory neuroblastoma**; **olfactory neuroepithelioma**; **olfactory carcinoma**.

Neurofibroma, see the preferred term **Endocardial schwannoma**.

Neurohypophysis is the structural system extending from the hypothalamus to the posterior pituitary gland. Cell bodies in the hypothalamus project to the posterior pituitary gland along the supraoptico-hypophyseal tract. The neurohypophysis is responsible for production and release of the hormones vasopressin (VP) and oxytocin.



Neurohypophyseal pathway from the hypothalamus to the posterior pituitary gland.

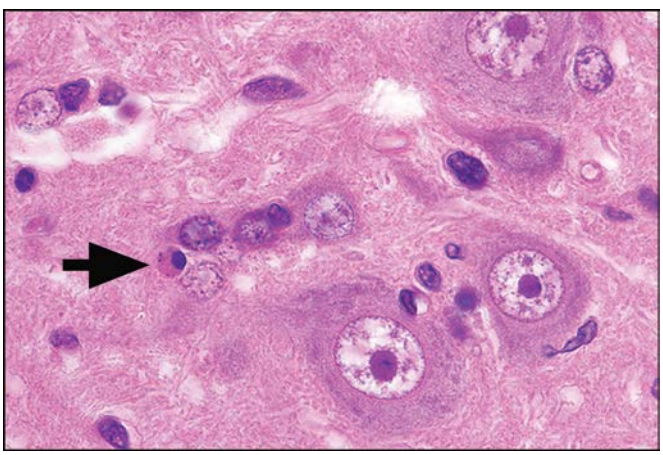
Neuroma is a nonneoplastic reactive proliferation of Schwann cells around regenerating axons in peripheral nerves. Neuromas can form after peripheral nerve transection or repetitive trauma to transected nerve endings. Refer to **Nervous System** in Appendix 2 for further information.

Neuromyoblastoma, malignant is a rare tumor derived from neuroblastic and myoblastic precursor cells, typically found in the ventral cranial cavity near the pituitary gland. Refer to **Nervous System** in Appendix 2 for further information.

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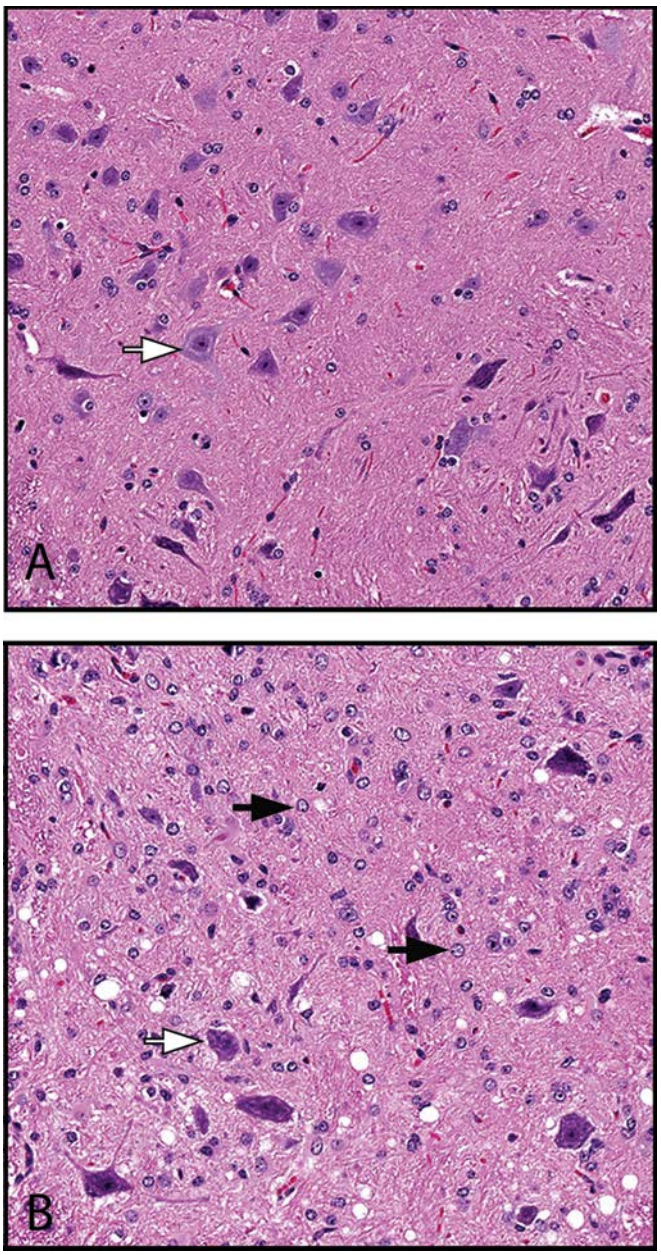
Neuron-specific enolase is a cell-specific isoenzyme of the glycolytic enzyme enolase which is expressed late in neural differentiation, and serves as a useful marker for neurons and neuroendocrine tumors. It is, for example, a reliable tumor marker for small cell lung cancer, and detection in body fluids can be useful for grading and staging various malignancies. It is also released into CSF when neural tissue is injured.

Neuronal apoptosis is programmed death of neurons. Apoptosis, sometimes referred to as "non-necrotic cell death," is a self-imposed, energy-demanding, orchestrated cascade of enzyme activation undertaken in response to a variety of "suicide-inducing" signals. Important categories of molecules that regulate apoptosis are the caspase enzymes and the Bcl2 family proteins. Apoptotic cell death is most commonly contrasted to "necrotic cell death" in which environmental changes overwhelm cellular defense mechanisms to cause lethal injuries. Neuronal apoptosis provides for an organized deletion of cells during normal nervous system development but can also be involved in some situations of pathologic neuronal death (e.g., trauma, excitotoxicity, oxidative stress, loss of neurotrophic factors). Moreover, both apoptotic and necrotic cell death mechanisms may contribute to neuronal death in some lesions. As for other cell types, morphologic features of neuronal apoptosis include chromatin condensation, nuclear fragmentation, cytoplasmic condensation and blebbing, formation of apoptotic bodies (small round fragments of condensed nuclear and/or cytoplasmic content), and absence of an inflammatory response. Importantly, however, it is often difficult to distinguish apoptosis from necrosis with certainty based on features in conventional hematoxylin and eosin (H&E)-stained histologic sections. Because both cell death mechanisms may occur concurrently, a diagnosis of neuronal apoptosis is frequently not recorded without additional confirmatory evidence such as positive immunolabeling for activated caspase 3, a positive TUNEL (terminal deoxynucleotidyl transferase dUTP nick end labeling) signal, or demonstration of ultrastructural changes characteristic of apoptosis. Verification of an apoptotic cell death mechanism is often not considered necessary for the immediate purposes of a toxicity survey study. Terminology such as "necrosis/apoptosis" or "individual cell necrosis" is often used to record the presence of scattered individual dead cells in histologic sections. The term "necrosis" is thus often used in a general sense to refer to presence of dead cells rather than to invoke a particular cell death mechanism.



Neuronal apoptosis (arrow) induced by a viral agent. Spinal cord. Mouse. H&E. (Image courtesy of Jerry Ward DVM, PhD, Diplomate ACVP. Used with permission.)

Neuronal cell loss is a demonstrable decrease in numbers of neuronal cell bodies (perikarya) that would normally be present in a brain region subsequent to neuronal death and removal of the cell remnants. When injury is recent with dead neurons still prominent in histologic sections, the diagnostic term



Neuronal loss. (A) Normal spinal cord ventral horn. (B) Similar area of spinal cord ventral horn with decreased motor neurons, increased numbers of reactive astrocytes with enlarged pale nuclei (black arrows), and mild neuropil vacuolation (round white spaces). A neuronal cell body is indicated by a white arrow in each photo. Mouse. H&E.

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"neuronal necrosis" is usually used. A few days following an episodic injury that has resulted in neuronal death, the debris will have been removed, and the diagnostic term "neuronal loss" may be appropriate when numbers of remaining neurons are demonstrably decreased and dead neurons are absent or only subtly present. Frequently, unless the degree of neuronal loss is dramatic, quantitative estimation of neuronal number using stereologic methods may be required to demonstrate and confirm the decrease in neurons. However, reactive changes in glial cells within affected regions may provide a marker of neuronal loss. When areas of decreased neurons are caused by failure of neurons to develop rather than to loss of neurons, the term **Neuronal hypoplasia** is preferred. In situations of very slow neuronal attrition such as may occur in certain degenerative genetic disorders, the term **Neuronal abiotrophy** is preferred. See **Neuronal necrosis**, **Neuronophagia**, and **Astrocytosis reactive** for further information.

Synonym(s): **Neuronal numbers, decreased**; **neuronal cellularity, decreased**.

Neuronal cellularity, decreased, see the preferred term **Neuronal cell loss**.

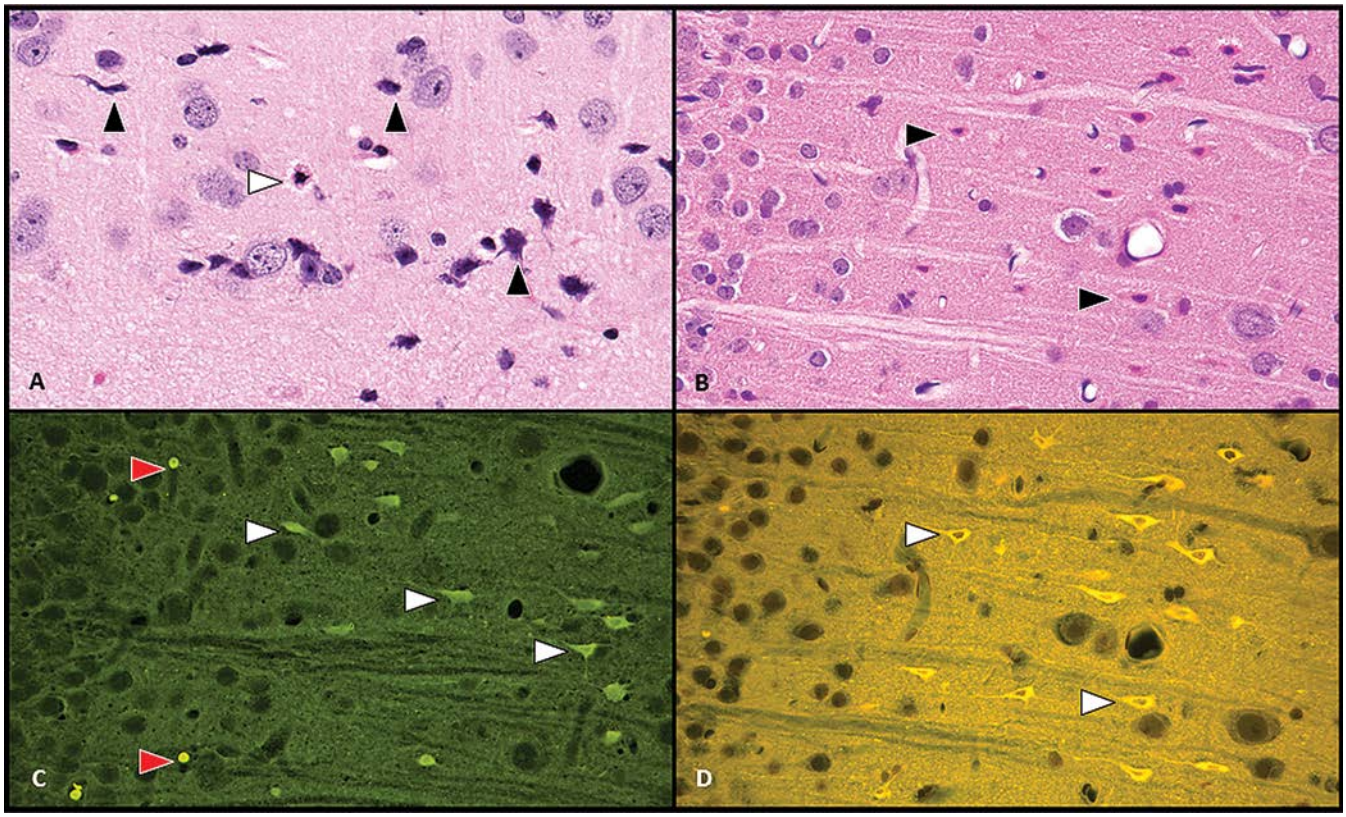
Neuronal degeneration (neurodegeneration) refers to a spectrum of regressive changes in functional capacity and vitality of neurons that may culminate in cell death. Technically, the term neurodegeneration encompasses the entire progression from degeneration through necrosis of neurons, while the term "neuronal necrosis" more specifically denotes the presence of dead neurons in histologic sections. In practice, however, the terms neurodegeneration and neuronal necrosis tend to be used interchangeably and may be combined (e.g., neuronal degeneration/necrosis) as a way to account for the full spectrum of regressive neuronal changes observed in histologic sections. Many neurodegenerative diseases (e.g., Alzheimer's disease) and their disease models are characterized by the presence of many abnormal (i.e., degenerative) neurons but actual dead neurons are infrequently encountered in any given histologic section. Neuronal death in these diseases typically involves a low-level attrition that over time involves profound neuronal loss. In conventional hematoxylin and eosin (H&E)-stained histologic sections, the most recognizable features of neuronal degeneration/necrosis focus on the nucleus and perikaryon. Depending upon the inciting cause or disease state, degenerating but still viable neurons may exhibit morphologic changes within the perikaryon such as dispersal of Nissl substance, vacuolation, or accumulation of abnormal material (e.g., neurofibrillary tangles or lysosomal phospholipid inclusions). Degenerative structural changes occurring distant from the perikaryon in neuronal processes and synapses (e.g., axonal swelling, loss of dendritic spines, loss of synapses, loss of neurotransmitter receptors) are frequently not visible in the same plane of histologic section as the perikaryon and may not be recognizable without the aid of special staining procedures or ultrastructural evaluation. See **Neuronal necrosis** and **Central chromatolysis** for further information.

Neuronal heterotopia represents neurons or groups of neurons that are abnormally positioned by virtue of errors in developmental migration. Neuronal heterotopia comprises one of several anomalies within the spectrum of developmental malformations affecting the cerebral cortex. During development, neurons and glia arise in the ventricular and subventricular zones of the brain followed by migration and differentiation, to form the laminated cortex. Defects in this migration and maturation can result in a number of anomalies, of which periventricular nodular heterotopia is best known. Here, single or multiple nodular masses of gray matter may be grossly observed, adjacent to or protruding into the walls of the lateral ventricles. Microscopically, the heterotopic gray matter forms clusters of rounded, irregular nodules separated from each other by layers of myelinated fibers. Both neurons and glial cells may be present with a pattern ranging from apparent disorganization to one with rudimentary lamination. Cerebral (and sometimes systemic) malformations associated with migrational defects have been traced to a number of genes (e.g., *FLNA*) and have been studied using knockdown/knockout and spontaneous rodent models. In rodents, prenatal exposure to a number of teratogens, such as ionizing radiation or methylazoxymethanol, may also produce heterotopic defects by damaging the proliferating neuroepithelium. Rodents have a less complicated developmental brain anatomy compared to humans, often resulting in phenotypes that do not always match well with the human condition and limiting their utility as a model. Although well known in humans, naturally occurring examples are rare in the veterinary literature. See **Periventricular nodular heterotopia** for further information.

Neuronal hyperchromatosis, see the preferred term **Dark neuron artifact**.

Neuronal necrosis is death of neurons. Dead neurons in hematoxylin and eosin (H&E)-stained histologic sections are most commonly recognized by a shrunken and variably angular cell body, homogeneous, hypereosinophilic cytoplasm and, depending upon the stage of disintegration, a nucleus exhibiting pyknosis, karyorrhexis, or karyolysis. These cytomorphologic features characterize the stereotypical endpoint often referred to as dead red neurons and less commonly, homogenizing cell change. More complete loss of nuclear remnants and cytoplasmic substance leaving a vague pale pink outline of the cell body (known as an eosinophilic ghost) may be encountered in H&E-stained histologic sections as the only recognizable vestige of the dead neuron. Following removal of dead neurons by phagocytic glial cells (neuronophagia), decreased numbers of neurons may become recognizable in affected brain regions, at which point **neuronal loss** may be the most appropriate diagnostic term. Dead neuronal cell bodies and their disintegrating processes may be autofluorescent in H&E-stained histologic sections and can be usefully highlighted by special procedures such as the Fluoro-Jade stains, and by several histochemical silver impregnation methods. Neuronal death may be incited by a variety of insults (e.g., ischemia/hypoxia, hypoglycemia,

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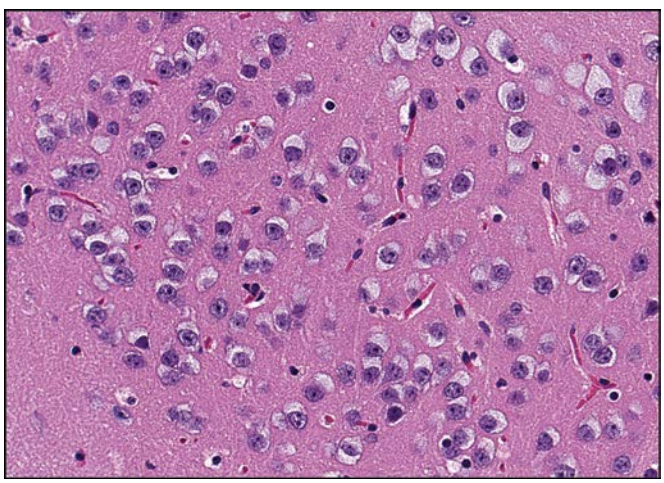
Neuronal necrosis. (A) A single necrotic neuron (white arrowhead) amid several artifactual dark neurons (black arrowheads). Cerebral cortex. Mouse. H&E. (B) Several necrotic neurons (black arrowheads). Cerebral cortex (perfused). Rat. H&E. (C) Several necrotic neurons highlighted by Fluoro Jade-B stain (white arrowheads). Autofluorescent erythrocytes within capillary lumens are indicated by red arrowheads. Serial section from the same block as B. Rat. Fluoro-Jade B. (D) Autofluorescence of necrotic neurons. Same H&E-stained slide as depicted with brightfield illumination in B. Rat. H&E.

metabolic arrest) and may initially proceed along one of several possible cell death pathways (e.g., apoptosis, oncocytic necrosis). The cytomorphologic features frequently converge toward the stereotypical endpoint of "dead red" neurons as described above so that inferences concerning specific inciting causes and cell death pathogenesis are often not possible based solely on features observed in H&E-stained histologic sections. See **Purkinje cell necrosis**, **Pyramidal necrosis**, **Laminar necrosis**, and **Neuronal cell loss** (neuronal cellularity decreased; neuronal numbers decreased) for further information (see figure above).

Synonym(s): **Homogenizing cell change**; **ischemic cell change**; **metabolic arrest change**; **oncocytic necrosis**; **red dead neurons**.

Neuronal numbers, decreased, see the preferred term **Neuronal cell loss**.

Neuronal vacuolation refers to single or multiple rounded spaces or holes within the cytoplasm of the neuronal cell body, which is commonly due to a histologic artifact, autolysis, or may represent expanded membrane-bound organelles. Non-artifactual intracytoplasmic neuronal vacuoles may reflect distention of organelles by fluid or accumulation of materials within organelles (e.g., phospholipidosis). It may be difficult to discern artifactual vacuolation from genuine cytoplasmic vacuolation. For this reason, neuronal vacuolation may be an initial call to determine the extent and distribution of this change, which may be followed up with further characterization of the vacuolar content using special stains



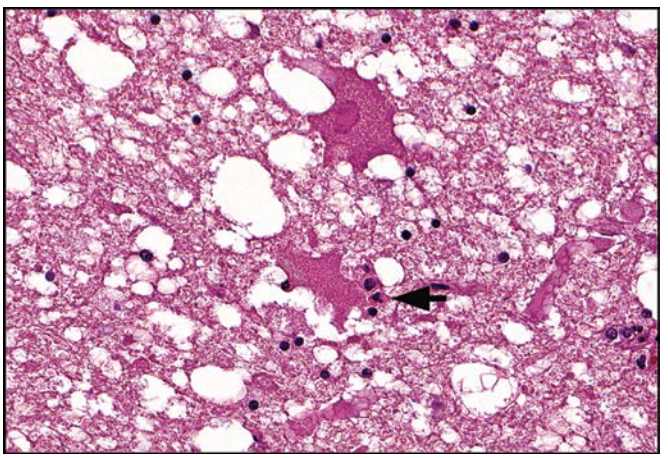
Neuronal vacuolation. The cytoplasm of the neuronal perikaryon is expanded by finely vesicular material, in this case by accumulation of material within lysosomes in an animal with an inherited storage disease. Mouse, H&E.

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or via transmission electron microscopy. Co-occurrence of other histologic features (e.g., gliosis, cellular debris, evidence of neuronal degeneration/necrosis, presence of leukocytic infiltrates) may be helpful distinguishing criteria between artifactual and genuine cytoplasmic vacuolation. Vacuolar spaces may also occur in other cell types (e.g., astrocytes) and/or appear seemingly free within the neuropil; vacuoles in these locations may also represent a histologic artifact or a genuine cellular change. Prominent large, clear cytoplasmic vacuoles within the trigeminal and/or dorsal root ganglion neurons are frequently encountered as a spontaneous background feature in rats and nonhuman primates used in toxicity studies. See **White matter vacuolation**, **Intramyelinic edema**, **Alcohol artifact,** and **Demyelination** for further information.

Neuronophagia is a microglial phagocytic response that serves to dismantle and dispose of debris from dead neurons. Neuronophagia is characterized by microglia located along the surface of the dead or dying neuronal cell body. Microglia surrounding morphologically normal neuronal perikarya are occasionally noted and should be distinguished from the nuclei of oligodendrocytes that are normal and often observed adjacent to the perikaryon of some neurons. Intracellular phagocytized material may be evident within the microglia. Activated microglial cells are typically present in the vicinity of necrotic neurons in histologic sections and, while they are involved in removal of dead cells, neuronophagia is not a prominent histologic feature in many instances of neuronal necrosis, though it surely is occurring. Neuronophagia is most frequently identified in situations wherein dying neurons display surface immune complexes or foreign antigens such as occur following viral infections and immune-mediated encephalitides.

Synonym(s): **Microglial cell nodule**.



Phagocytes (arrow) surrounding a dead neuronal cell body within a region of infarction. Dog. H&E.

Neurons are the primary effector cells of the nervous system and are responsible for processing and responding to information. Neurons have an axon that transmits information to and from the neuronal cell body, as well as allows movement of nutrients and elimination of waste necessary to maintain the health of the axon and neuron. Neurons also have dendrites that communicate with other neurons, forming an interlinked matrix. Functionally related groups of neurons reside within distinct groups that are referred to as nuclei (also called ganglia in some anatomy texts) within the brain and spinal cord, and within ganglia in the peripheral nervous system. Each neuron, nucleus, and ganglion has a specialized function or functions, and functionally related nuclei are interconnected by bundles of axons that together are referred to as tracts.

Neurons, basophilic, see the preferred terms **Dark neuron artifact** and **Neuronal necrosis**.

Neurons, red dead are true necrotic neurons histologically. The use of the descriptor "red dead neurons" distinguishes them from dark neurons that represent artifact. See **Neuronal necrosis** for further information.

Neurosarcoma, see the preferred terms **Endocardial schwannoma** and **Intramural schwannoma**.

Neurotoxicity is an adverse effect of a drug or chemical on the structure and/or function of the central or peripheral nervous system. See **Adverse effects** for further information.

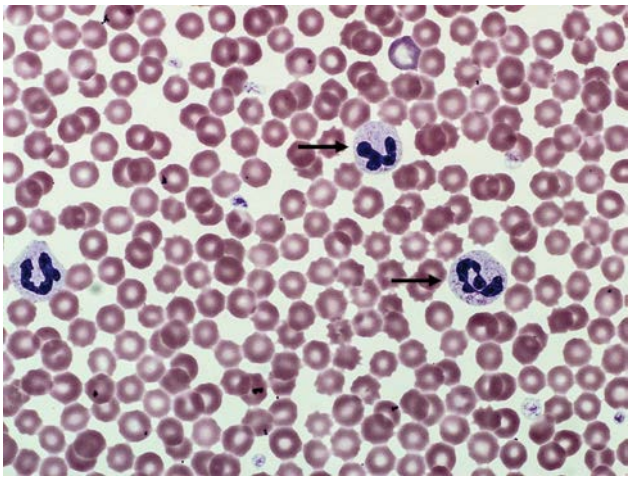
Neurotoxicity test is any evaluation intended to be diagnostic for neurotoxicity, including EEG (electroencephalogram) measurements, and behavioral, motor, and cognitive assessments (functional observational batteries). ICH guidelines require an assessment of neurotoxicity to be included in the basic tier of safety pharmacology studies included to support human trials. See **Irwin test** for further information.

Neurotoxin is an agent that produces an injury or deficit to the normal structure and function of the nervous system.

Neutrophil is a type of mature leukocyte (white blood cell) that comprises approximately 40–60% of leukocytes in the peripheral blood. They are about 10–15 μm in diameter and have up to 5 nuclear lobes separated by constrictions, with colorless to pale pink cytoplasm that contains numerous small granules that take up variable amounts of stain, depending on the species. Neutrophils are present in the circulating pool (population sampled during venipuncture), and the marginated pool adhered to vascular endothelium that each represent approximately 50% of the total neutrophil population. Neutrophils circulate in blood for 8–20 hours before migrating to tissues, where their lifespan is 1–4 days. They are part of the innate immune system and represent the primary line of defense against invading microorganisms, mainly through phagocytosis and release of preformed granular enzymes. They are activated and mobilized to the site of inflammation by bacterial products and/or cytokines such as TNF-α, IL-1β, IL-8, and IFN-γ. Neutrophils produce cytokines, chemokines, proteases, prostaglandins, and reactive oxidants that neutralize microorganisms, recruit cells to the site of inflammation, and potentially contribute to further

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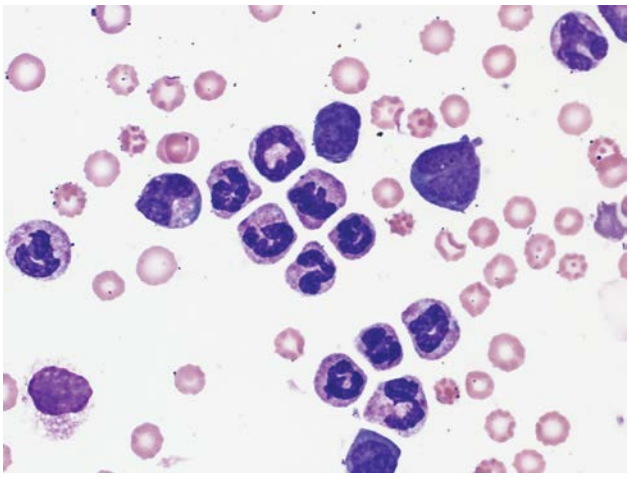
tissue damage. They are also capable of MHC Class II antigen presentation leading to T-cell activation and proliferation. Neutrophilia (i.e., an increased number of circulating neutrophils) is most commonly associated with inflammation, infection, and drug administration (e.g., glucocorticoids), but rarely myeloid neoplasia. Causes of neutropenia (decreased numbers of circulating neutrophils) include drug administration (e.g., chemotherapeutic, anti-inflammatory, antibiotics), autoimmune disease, and idiopathic and neoplastic conditions.



Segmented neutrophils (arrows), blood smear, beagle dog.

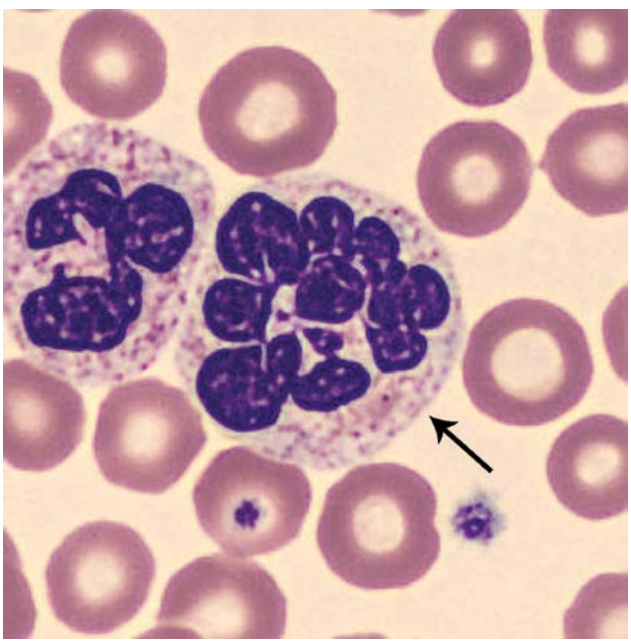
Neutrophil hypersegmentation can occur as an age-related change associated with prolonged blood transit time, or infrequently as a sign of dysplasia in dysgranulopoiesis, myelodysplastic syndrome, or chronic myeloid leukemia. Most commonly, hypersegmentation is observed as an artifactual change in smears of aged EDTA-anticoagulated blood or in neutrophils of animals treated with glucocorticoids. Nuclear hypersegmentation of neutrophils is characterized by having five or more lobes.

Neutrophilia (increased numbers of neutrophils) results from an increased release of neutrophils from the bone marrow, decreased margination of cells, and decreased migration of neutrophils from peripheral blood to tissues. The retention of neutrophils within the circulation may lead to nuclear hypersegmentation.

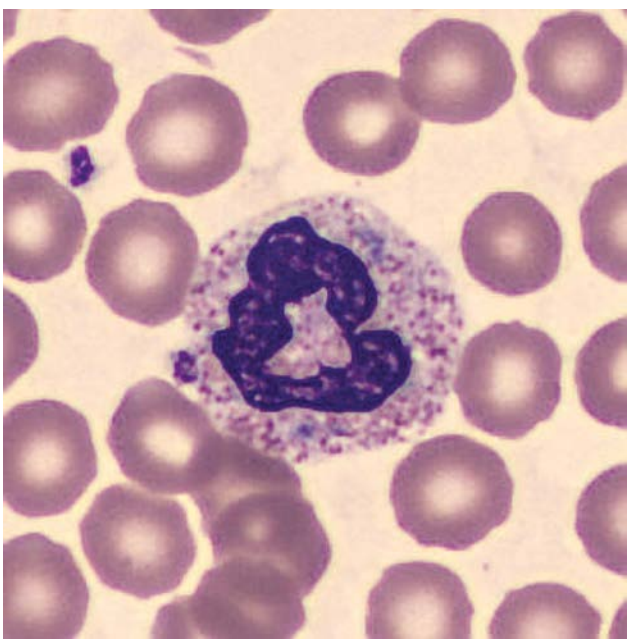


Neutrophilia, peripheral blood smear, monkey, with a bacterial infection.

Neutrophilic toxic granulation is an uncommon morphologic change in segmented neutrophils, bands, and metamyelocytes, caused by increased permeability of primary granules to Romanowsky stains. These purple to dark blue granules may be observed together with other morphologic changes including vacuolation, cytoplasmic basophilia, and Döhle bodies. Toxic granulation can be seen with severe inflammation, infection, and drug toxicity (i.e., cytotoxic drugs).



Hypersegmented neutrophil (arrow), blood smear, monkey.



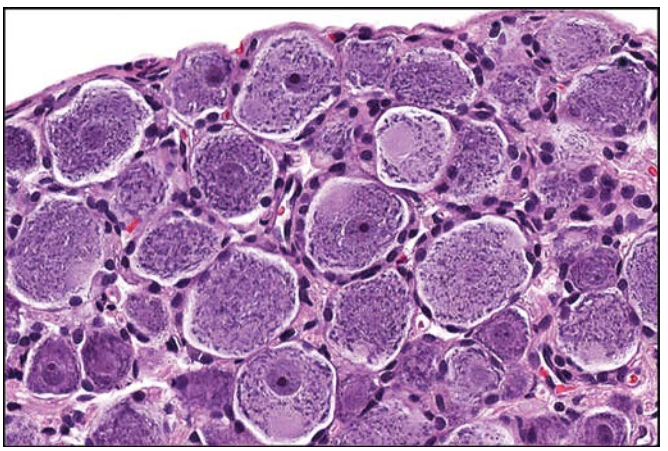
Toxic granulation and Döhle bodies, blood smear, monkey.

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Neutrophil karyolysis is a morphologic change observed in degenerate neutrophils. These cells are characterized by decreased staining intensity with a loss of affinity for basic dyes, swollen nuclear lobes, hyalinization of chromatin, and disruption of nuclear membranes that indicate progression of rapid cell death in a toxic environment outside the bone marrow.

Nevus is a term that in veterinary and medical dermatology refers to a benign, usually hyperpigmented congenital papule or plaque. In veterinary pathology, nevi correspond to hamartomatous lesions that are benign, mature, sometimes dysplastic proliferations of skin cells of the epidermal, adnexal (e.g., hair follicles, sebaceous glands) or dermal structures (e.g., collagen), and may be hyperpigmented or not. Mixed cell nevi comprising several skin structures have been reported (e.g., fibrolipomatous, fibroadnexal).

Nissl substance is the cytoplasmic material within neuronal cell bodies. It becomes dispersed with chromatolysis. See **Chromatolysis** for further information.



The basophilic granular material within the cytoplasm of the perikaryon is ribosome-rich material, the Nissl substance. Dorsal root ganglion. Rat. H&E.

NME is an abbreviation for new molecular entity, indicating a new drug molecule.

NOAEL an abbreviation for no observed adverse effect level, the dose in a toxicology study at which no adverse effects were observed. Defining whether any effects that were observed at this dose were in fact adverse requires a knowledge of the pharmacological properties of the compound and an understanding of the types of effects or pathologies observed. The NOAEL in the initial IND-enabling toxicology studies is used to define the safe starting dose for the Phase 1 clinical trial, with the addition of appropriate safety factors.

Nodular regeneration, see the preferred term **Hepatocellular hyperplasia, regenerative**.

No-effect level (NEL) is a synonym for no observed effect level (NOEL). See the preferred term **No observed effect level (NOEL)**.

NOEL is an abbreviation for no observed effect level, a dose in a toxicity study at which the animals do not differ at all from the concomitant control animals in appearance behavior, clinical pathology, gross pathology or histopathology.

Nonclinical overview is a document to discuss the nonclinical data, interpretation, clinical relevance of the findings, and quality aspects (GLP) and implications of the findings relevant to the safe use of a pharmaceutical. A nonclinical overview is submitted with a new drug application as part of the Common Technical Document (CTD).

Nonclinical safety evaluation is the overall assessment of findings resulting from in vitro and in vivo animal pharmacology, pharmacokinetic, and toxicology studies for the purpose of determining a potential impact on human safety. Nonclinical safety evaluation is usually discussed in reference to projected doses or exposures anticipated in human safety trials, or in review of a marketing permit or authorization request for a product intended for human or veterinary use. It typically includes calculation of safety margins and relevance of nonclinical findings to the safe use of the product or dosage regimen projected for the target human population.

Synonym(s): **Preclinical safety evaluation**.

Non-disjunction is an abnormal or atypical segregation of chromosomes during the metaphase-anaphase transition in mitosis that usually results in uneven distribution of chromosomes between the daughter cells.

Non-genotoxic carcinogen is a compound or agent that can lead to carcinogenesis in rodent carcinogenicity studies without obvious induction of DNA damage, and negative results when tested for genotoxicity in such assays. Examples are phenobarbital, PPAR alpha agonists, and many chlorinated hydrocarbons.

Nonglandular stomach atrophy of squamous epithelium is characterized by a focally extensive or diffuse decrease in normal thickness/cellularity of squamous mucosa of the nonglandular mucosa in rodents.

Differential diagnosis: **Nonglandular stomach erosion/ulcer**.

Nonglandular stomach benign basal cell tumor is a rare neoplasm with predominant proliferation of the basal layer of the stratified squamous epithelium belonging to the forestomach of rodents. This neoplasm may exhibit an endophytic growth pattern of closely packed, small or oval cells from the stratum germinativum forming garlands or nests surrounded by palisade-like cells. Refer to **Gastrointestinal Tract** in Appendix 2 for further information.

Differential diagnoses: Nonglandular stomach basal cell hyperplasia; **Nonglandular stomach squamous cell carcinoma**.

Nonglandular stomach epithelial cyst, see the preferred term **Nonglandular stomach squamous cyst**.

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Nonglandular stomach erosion/ulcer is focal or multifocal loss of squamous epithelium with either partial mucosal disruption (erosion) or with extension of the lesion through the mucosa and muscularis mucosa (ulcer). Inflammation, hemorrhage in submucosa, regeneration of the epithelium, hyperkeratosis, and parakeratosis with increased thickness of adjacent keratinized squamous epithelial cell layers typically accompanies ulcerations. Macroscopically, the regenerative hyperplasia of the surrounding epithelium can present a thickened rim of the mucosa around a dark red/black depressed area of the ulcerated region. Ulcers of nonglandular squamous epithelium in rodents are induced by a wide range of irritant agents, while marked protein restriction/food restriction has also been shown to produce ulcers. Reasons for incidental erosion/ulceration in control or treated animals are often unclear, although gavage accidents, advanced age, parasitism, infection, diet, feeding regimen, generalized debility, and stress are. This lesion is typically diagnosed under the single combined term of erosion/ulcer with an appropriate severity grade in most instances.

Differential diagnosis: **Nonglandular stomach squamous cell carcinoma**.



Nonglandular stomach, rat. H&E. Arrows = edges of ulcer.

Nonglandular stomach malignant basal cell tumor is a very rare malignant neoplasm showing predominant proliferation of basal layer of the stratified squamous epithelium with the absence of differentiation or keratinization. This neoplasm may exhibit endophytic growth pattern infiltrating into the lamina propria of the mucosa and submucosa. Neoplastic cells are round to oval closely packed nonspinous cells with dark nuclei and little cytoplasm with frequent mitotic figures, often forming palisade-like garlands or chains. Growth pattern suggests loss of the basement membrane integrity. Superficial layers appear almost normal, but are sometimes ulcerated. Refer to **Gastrointestinal Tract** in Appendix 2 for further information.

Differential diagnoses: **Nonglandular stomach squamous cell carcinoma**; **Nonglandular stomach basal cell hyperplasia**; **Nonglandular stomach benign basal cell tumor**.

Synonym(s): **Nonglandular stomach basal cell carcinoma**.

Nonglandular stomach squamous cell carcinoma usually appears macroscopically as a firm, white, irregular mucosal mass that is often ulcerated. This forestomach neoplasm is characterized microscopically by exophytic and/or endophytic growth of neoplastic stratified squamous epithelium with moderate to marked cellular atypia, pleomorphism, and mitotic activity. There is clear evidence of invasion into the submucosa, muscle layer, and serosa. Refer to **Gastrointestinal Tract** in Appendix 2 for further information.

Differential diagnoses: Nonglandular stomach squamous cell papilloma; **Nonglandular stomach benign basal cell tumor**; Nonglandular stomach malignant basal cell tumor; **Nonglandular stomach squamous cell hyperplasia**; Nonglandular stomach basal cell hyperplasia.

Nonglandular stomach squamous cell hyperplasia is a proliferation and thickening of the stratum spinosum (layer of cells between the stratum granulosum and stratum basale) which is often associated with hyperkeratosis or parakeratosis. Refer to **Gastrointestinal Tract** in Appendix 2 for further information.

Differential diagnoses: Nonglandular stomach squamous cell papilloma; Nonglandular stomach basal cell hyperplasia; **Nonglandular stomach squamous cell carcinoma**.

Synonym(s): **Nonglandular stomach squamous hyperplasia**.

Nonglandular stomach squamous cyst is characterized by an inward folding of stratified squamous epithelium into the wall of the nonglandular stomach. Squamous cysts are incidental, congenital lesions most commonly seen in the nonglandular stomach, and more often in the mucosa near the limiting ridge (i.e., lined by keratinized stratified squamous epithelium). The lumen frequently contains keratinized material which may be mineralized and surrounded by chronic inflammation.

Differential diagnosis: **Nonglandular stomach squamous cell carcinoma**.

Synonym(s): **Nonglandular stomach epithelial cyst**.

Nonglandular stomach squamous hyperplasia, see the preferred term **Nonglandular stomach squamous cell hyperplasia**.

Nonmyelinated axon, see the preferred term **Unmyelinated nerve fiber**.

Non-regenerative anemia can be induced by a variety of factors including inflammation, renal or hepatic disease, endocrine disease, neoplasia, severe iron deficiency, or drug or toxin exposure. Evaluation of bone marrow function can be used to classify anemia as non-regenerative if there is reduced or ineffective erythropoiesis, or regenerative anemia if erythropoiesis is active and effective. The complete blood count (CBC) in non-regenerative anemia subjects may show decreases in erythrocyte numbers alone or decreases in production of multiple lineages. Non-regenerative anemia is best

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diagnosed via bone marrow evaluation. Findings of bone marrow erythroid hypoplasia, pure red cell aplasia, myelofibrosis, leukemia, or fatty marrow with pancytopenia are consistent with non-regenerative anemia.

No observed adverse effect level (NOAEL), see **NOAEL**.

No observed effect level (NOEL) is the highest dose in a toxicology study where there are no effects that can be attributed to test article administration. This term is not to be confused with the NOAEL, which is the no observed adverse effect level (NOAEL), or the highest dose where no adverse effects related to the drug or test chemical are observed. See **Adverse effects** for further information.

Synonym(s): **No effect level (NEL)**.

Noradrenaline, see the preferred term **Catecholamine**.

Norepinephrine, see the preferred term **Catecholamine**.

Nose-associated lymphoid tissue, see the preferred term **Nasal-associated lymphoid tissue**.

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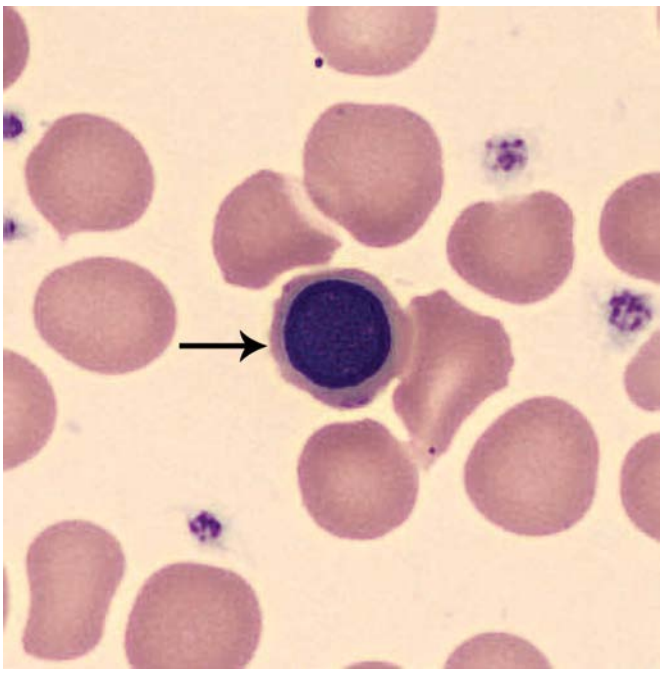
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Nuclear atypia is a descriptive term used in cytology and histopathology. It refers to a condition in which nuclei may be large (resulting in a high nuclear:cytoplasmic ratio), exhibit a coarse chromatin pattern, large nucleoli, and/or bizarre mitotic figures. While nuclear atypia may be seen in either reactive or neoplastic changes, in its most extreme form it is often associated with malignancy and may be an important consideration in prognostication. Nuclear atypia should not be confused with karyomegaly, in which the primary feature is a large nucleus, in the absence of the above-mentioned features. See **Anisokaryosis** for further information.

Differential diagnosis: **Karyomegaly**.

Nuclear pleomorphism refers to variation in the shape, size, and chromatin staining of the nucleus of cells. While some degree of pleomorphism may be present in normal tissues, it is more frequently noted in dysplastic or neoplastic tissues. Depending upon the tumor type, the degree of nuclear pleomorphism may be a critical component in tumor grading and prognosis.

Nucleated red blood cell is an erythrocyte that contains a nucleus. Under general conditions, peripheral blood is free of nucleated red blood cells in most species. An interesting exception occurs in birds and reptiles where all mature erythrocytes are nucleated. However, in most other species the nucleus is ejected before the cell is released into peripheral blood. Therefore, presence of nucleated red blood cells in peripheral blood is considered an anomaly and is more often seen in severe disease states. An increased demand for red blood cells causes the bone marrow to release erythrocytes prematurely, while they still contain their nucleus. Pathologic reasons for the presence of nucleated red blood cells in peripheral blood include severe anemia, hemolytic disease of the newborn, myelofibrosis, thalassemia, sickle cell disease, cancers involving the bone marrow, and chronic hypoxemia.



Nucleated red blood cell, blood smear, rat.

Nuclei in the nervous system are functionally related groups of neurons (also called ganglia in some anatomy texts) within the brain and spinal cord. This is different from the use of nucleus as in referring to the nucleus of an individual cell.

Nutritional effects on toxicity are commonly referenced in terms of dosing animals fasted or fed *ad libitum*, stomach contents, as well as availability of nutrients to serve as antioxidants and cofactor substrates important in the absorption, distribution, metabolism, and excretion of exogenous chemicals, and hence their toxicity. An example is the amelioration of acetaminophen-induced liver toxicity in the presence of reduced glutathione, a phenomenon that can be demonstrated indirectly by comparing the effects of acetaminophen at high doses in fed versus fasted rats. Nutritional effects on toxicity can also include the inherent toxicity of nutrients.

Nutritional toxicology is a specialty subdiscipline within toxicology that studies the effects of nutrition on toxicities, impact of toxicants on nutrition, and toxicities of nutrients alone. See **Nutritional effects on toxicity** for further information.

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Obesity-associated inflammation, see the preferred term **Lipogranulomatous inflammation**.

Obligate nose breathers are animals that, through anatomical characteristics, can only breathe naturally through their nose. An important difference between species, obligate nose breathers such as rodents, rabbits, and horses cannot inhale through the oral cavity. Such animals (particularly rodents) filter a large proportion of an inhaled dose via the nasal cavity. For dosimetry calculations in inhalation toxicology studies, test article delivery concentrations of inhalable particles reaching the lung must be reduced by the combination of efficient nasopharyngeal deposition and clearance of obligate nose breathers typically by ~90%.

Obstruction is blockage that partially or completely impinges movement or flow of a material normally meant to be in transit through an organ from place of origin to final destination. The resulting decreased passage of air (e.g., choke), blood (e.g., via thrombus or embolus), urine (e.g., via a urolith), feces (e.g., via impaction), or lymph (e.g., via compression) can result in organ dysfunction, tissue damage, or death depending on the degree of blockage, duration, and the organ system involved.

Obstructive nephropathy can be functional or structural, and is the complex renal change associated with intrarenal obstruction of the passage of urinary filtrate. It can be due to an accumulation of compounds or materials of poor solubility within the tubules, or associated with ureteral obstruction caused by, for example, congenital defects or blockage by calculi. Obstructive nephropathy is usually associated with tubule dilation and inflammation. The most commonly encountered example in preclinical studies is crystal-associated nephropathy. See **Crystal nephropathy** for further information.

Obstructive uropathy is the presence of inflammatory and proteinaceous material that blocks urine outflow (i.e., urethral obstruction) resulting in vesicoureteral reflux and secondary changes such as dilation of the bladder, ureter, and renal pelvis. The condition may also result in inflammation of the penis, urethral occlusion, or in the presence of bladder calculi. Usually the cause is related to penile trauma and bacterial infections, which often ascend up the urethra resulting in acute inflammation and ulceration.

Ocular amelanotic melanoma, see the preferred term **Uveal melanoma**.

Ocular compaction of trabecular beams, see the preferred term **Filtration angle narrowed**.

Ocular dermoid is a rare, nonneoplastic and proliferative congenital mass (choristoma) of normal but ectopic ectodermal and mesodermal tissue in the cornea and conjunctiva of dogs, rabbits, guinea pigs, and rodents. Refer to **Special Senses** in Appendix 2 for further information.

Ocular melanosis, see the preferred term **Uveal melanocyte hyperplasia**.

Ocular neurilemmoma, malignant, see the preferred term **Intraocular schwannoma**.

Ocular neurinoma, malignant, see the preferred term **Intraocular schwannoma**.

Ocular squamous cell carcinoma of the cornea or conjunctiva is a rare neoplasm in rodents and other laboratory animals. The neoplasm is composed of cords and nests of neoplastic squamous cells with variable keratinization. Refer to **Special Senses** in Appendix 2 for further information.

Ocular squamous cell hyperplasia may arise from the cells of the corneal epithelium and epithelial cells of the bulbar and palpebral conjunctiva, and epithelium of the lacrimal duct in rodents and non-rodents. Diagnostic features include an increased number of cell layers of squamous epithelium with a rete peg-like growth pattern. Refer to **Special Senses** in Appendix 2 for further information.

Ocular squamous cell papilloma of the cornea or conjunctiva is a rare neoplasm in rodents and other laboratory species. Squamous cell papilloma is characterized by exophytic growth with development of multiple branched, arborizing fronds composed of a lining of variably keratinized squamous epithelium, and a variably developed vascular connective tissue core. Refer to **Special Senses** in Appendix 2 for further information.

Ocular trabecular meshwork cell activation, see the preferred term **Ocular Trabecular meshwork proliferation**.

Ocular trabecular meshwork cell migration, see the preferred term **Ocular Trabecular meshwork proliferation**.

Ocular trabecular meshwork collapse, see the preferred term **Filtration angle narrowed**.

Ocular trabecular meshwork proliferation is a nonspecific increase in the number or layers of mononuclear trabecular

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cells in the meshwork and in the filtration angle of the eye. Refer to **Special Senses** in Appendix 2 for further information.

Odontoameloblastoma, see the preferred term **Ameloblastic odontoma**.

Odontoblast degeneration/necrosis can occur due to excess fluoride, inhibitors of mitosis, and multiple other toxicities, such as hexachlorobenzene and sonic hedgehog (smoothened) inhibitors. Degeneration results in decreased numbers, nuclear polarity, and height of odontoblasts and disorganization of this cell layer. There is reduced secretion of dentin matrix, the collagenous predentin, which becomes mineralized as it is converted to dentin. Normal odontoblasts lining the inner surface of the dentin layer have long processes that remain within straight, perpendicular tubules in the dentin. These processes and tubules may be absent, reduced, or convoluted when there is odontoblast degeneration. Rodent incisors grow and develop throughout the life of the animal, so factors affecting odontoblast and other cells active in tooth development can cause degenerative changes. Dogs and other species in which teeth develop fully prenatally or early in life are much less susceptible to such factors.

Differential diagnosis: **Autolysis**.

Odontoblasts are mesenchymal cells that develop from the dental papilla, the central part of the tooth germ. The tooth germ is derived from the ectoderm of the first pharyngeal pouch and the ectoderm and mesenchyme of the neural crest. Odontoblasts arise from the neural crest ectoderm and produce dentin, while the inner tooth pulp originates from mesenchyme. The protein "sonic hedgehog" regulates all stages of tooth development and growth. Various nutrients including calcium, phosphorus, and vitamin D are essential for normal tooth development.

Odontogenic fibroma, peripheral see the preferred term **Epulis, fibromatous of periodontal ligament origin**.

Odontogenic tumor, benign is a benign neoplasm originating from components of the tooth germ (odontogenic origin) but cannot be further specified as one of the other odontogenic tumor categories. Refer to **Bone, Muscle, and Tooth** in Appendix 2 for further information.

Odontogenic tumor, malignant is a malignant neoplasm originating from components of the tooth germ. This diagnosis is often used when the neoplasm is of odontogenic origin but cannot be specified as one of the other odontogenic tumor categories. This tumor has been described in rodents. Refer to **Bone, Muscle, and Tooth** in Appendix 2 for further information.

Odontoma, complex is a malformation (hamartoma) of dental tissues. These lesions are composed of normal mesenchymal and epithelial components such as odontoblasts, cementoblasts, pulp mesenchymal cells, dentin, cementum, and enamel. Tissues are irregularly arranged without resemblance to normal structures as compared to compound odontomas where there is more normal differentiation producing tooth-like structures. Refer to **Bone, Muscle, and Tooth** in Appendix 2 for further information.

Odontoma, compound is a malformation (hamartoma) of dental tissues. These lesions are composed of normal mesenchymal and epithelial components such as odontoblasts, cementoblasts, pulp mesenchymal cells, dentin, cementum, and enamel. Compound odontomas produce normal-appearing toothlike structures compared to complex odontomas that have irregularly arranged tissues (see **Odontoma, complex**). Odontomas occur spontaneously and following administration of nitrosourea compounds in rodents. Refer to **Bone, Muscle, and Tooth** in Appendix 2 for further information.

Olfactory pertains to the sense of smell as related to the olfactory system, nerves, or lobes of the brain.

Olfactory neuroblastoma, see the preferred term **Nasal cavity neuroepithelial carcinoma**.

Olfactory neuroepithelioma, see the preferred term **Nasal cavity neuroepithelial carcinoma**.

Oligodendrocyte satellitosis, see the preferred term **Satellitosis**.

Oligodendroglia are cells that produce myelin within the CNS and wrap around axons to insulate and speed the transmission of nerve impulses. Myelin in the CNS is composed of multiple concentric layers of oligodendroglial cell membranes.

Oligodendroglioma, malignant, high grade are well-circumscribed tumors extending over and infiltrating multiple areas of the brain or spinal cord. These tumors are highly cellular and have prominent cytologic features of malignancy (atypia, pleomorphism, high mitotic rate) as well as areas of necrosis and/or hemorrhage. Refer to **Nervous System** in Appendix 2 for further information.

Oligodendroglioma, malignant, low grade are well-circumscribed neoplasms confined to one major area of the CNS and composed of cells with typical oligodendrocyte morphology. Necrosis and hemorrhage may be present but are less extensive than in high-grade malignant oligodendrogliomas. Refer to **Nervous System** in Appendix 2 for further information.

Oncocytic adenoma, see the preferred term **Oncocytoma**.

Oncocytic hyperplasia is a proliferation of tubule oncocytes in the kidney of rats. The cells tend to be granular or slightly ground-glass and basophilic in appearance. Ultrastructurally, the granules represent enlarged, misshapened mitochondria. They are assumed to arise from the collecting tubules. Refer to **Urinary System** in Appendix 2 for further information.

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Oncocytic necrosis, see the preferred term **Neuronal necrosis**.

Oncocytoma is a glandular tumor composed of large cells with granular, eosinophilic cytoplasm due to the presence of abundant mitochondria. These neoplasms occur uncommonly in the kidney, salivary glands, and endocrine glands. Both benign and malignant forms have been documented. See **Endocrine Glands** and **Urinary System** in Appendix 2 for more information.

Oncotic necrosis is a form of energy-independent cell or tissue death following irreversible injury. Although there is discrepancy among cited pathology nomenclature, the term "oncosis" is generally applied to the microscopic features of energy-independent cell death, while "necrosis" may be applied to either the gross or microscopic features. See **Necrosis** for further information.

Oncotic necrosis ("red dead" neurons), see the preferred term **Retinal single cell necrosis**.

One-hit model is a risk assessment tool where an expected effect is seen following a single interaction with a target, resulting in a linear dose-effect relationship. Carcinogenesis resulting from the direct interaction of mutagens with DNA represents a one-hit model, requiring linear extrapolation from the animal data to determine exposure levels which would result in an acceptable risk.

Oocyte is a cell that develops into an egg or ovum; a female gametocyte.

Oocyte degeneration is characterized by a spectrum of changes limited to the oocyte including chromatin condensation, pyknosis, karyorrhexis, disorganization of corona radiata, and/or disruption and thinning of zona pellucida.

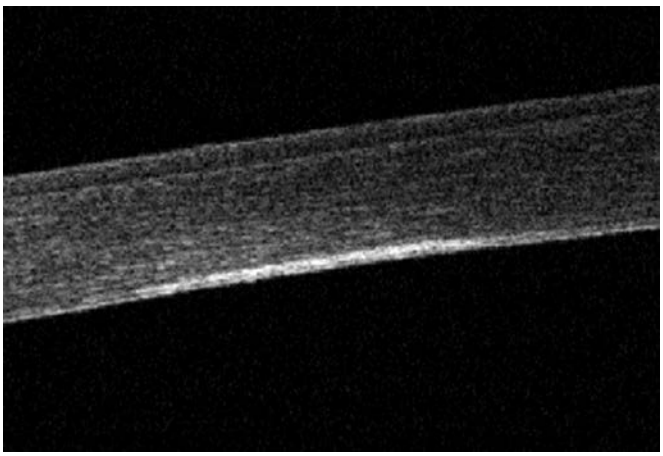
Differential diagnosis: **Oocyte follicular degeneration**.

Oocyte follicular degeneration is characterized by a spectrum of changes in the oocyte and the cellular components of the follicle (granulosa and/or thecal cells) including chromatin condensation, pyknosis, karyorrhexis, and karyolysis with the resulting loss of the oocyte and follicular atresia. Follicular degeneration normally occurs in follicles when they enter the growing stage but fail to ovulate. Follicular degeneration can be induced in multiple species by cytotoxic and genotoxic agents, and if the primordial pool is affected may lead to ovarian failure and atrophy.

Oocyte mineralization, see the preferred term **Ovarian calcified focus**.

Oogenesis is the production of ova (secondary oocyte) in the ovaries. It is the process of development of the female gamete from oogonium to ovum.

Optical coherence tomography (OCT) uses coherent light waves for noninvasive in vivo imaging of biological tissues. Due to the limitations of light penetration, OCT imaging is most applicable to thin or hollow tissues such as the eye, vasculature, skin, and intestinal tract. OCT is now an important tool in evaluation of the anterior segment (cornea, anterior chamber, and lens) and retina in toxicology studies emphasizing the eye. Two- and three-dimensional OCT high resolution digital images of the eye allow appreciation of corneal and retinal layers similar to H&E sections. OCT is a useful adjunct to confirm localization and distribution of morphological changes, for measurements, and to provide in vivo progression data to the toxicologic pathologist.



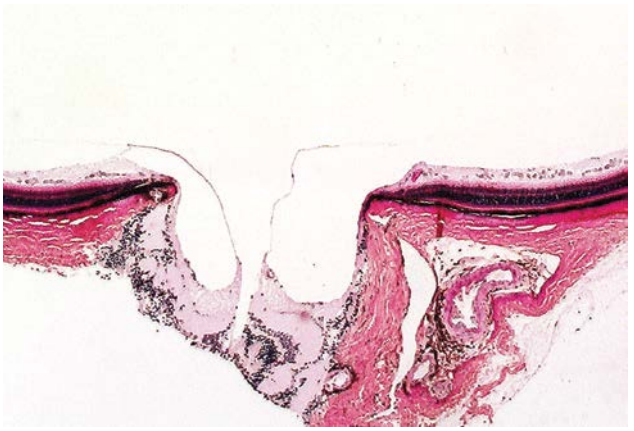
OCT image, pre-Descemet's membrane corneal opacity, New Zealand white rabbit.

Optic disc malformation, see the preferred term **Optic fissure malformation**.

Optic fissure malformation is a congenital absence of one or more ocular tissues due to failed closure of the embryologic optic fissure in the anterior and/or posterior regions of the developing globe. The main variants are uvea or iris malformation where the defect results in a "keyhole" or "cat eye" appearance to the iris and an optic disc malformation resulting in a cavitation defect of the optic disc that may extend into the optic nerve. Irregularities, folding, and failure to develop adjacent tissues and abnormal blood vessels may be apparent around the malformation. Malformations with absence of tissue can also involve the retina, lens, cornea, and eyelid. Vision may not be affected unless concurrent abnormalities are present, including microphthalmia, lens or corneal changes, and outflow tract or neural retina abnormalities. Malformations may be an incidental finding in dogs, and are found in teratogenicity studies using rodents and rabbits and should be differentiated from artifacts in tissue preparation and sectioning and shape distortion caused by inflammation. At the optic disc, large defects, neural retina atrophy, and continuation of the choroid and retinal layers over the edge of the defect assist in differentiating a malformation from other pathologies of the optic disc.

Synonym(s): **Coloboma**; **dyscoria**.

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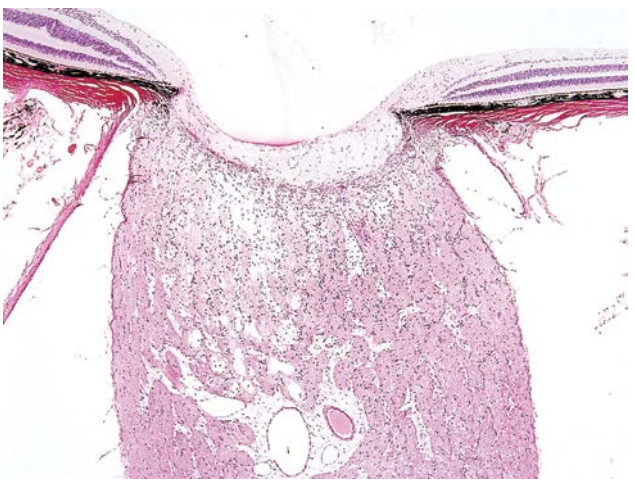


Optic fissure malformation, optic nerve head, Sprague Dawley rat, hematoxylin phloxine saffron stain.

Optic nerve cupping, see the preferred term **Optic nerve head necrosis**.

Optic nerve head necrosis results in thinning and loss of the neuropil at the optic nerve head (or cup) with collapse of the lamina cribrosa, displacement of the neuropil into the sclera, and excavation of the optic nerve head. This finding is most frequently found in association with increased intraocular pressure and glaucoma, and may be an artifact related to retrobulbar blood sampling.

Synonym(s): **Optic nerve cupping**.



Optic nerve head necrosis with collapse into the optic nerve (optic disc cupping), rhesus monkey, H&E. (Image courtesy of L. Teixeira, University of Wisconsin.)

Oral cavity erosion/ulcer is focal or multifocal disruption of the squamous epithelium continuity in the oral cavity/pharynx and tongue. This can occur incidentally (cage injury, bite, or gavage procedure), but xenobiotics may cause either partial disruption with intact basal lamina (erosion) or extension through the squamous epithelium into the muscularis (ulcer) by diverse mechanisms. Intraepithelial inflammatory cell infiltrates are frequently observed in more severe lesions. This lesion is typically diagnosed under the combined term of erosion/ulcer with an appropriate severity grade in most instances. Erosion/ulcer can be a treatment-related effect in the oral cavity but is more commonly associated with the gavage procedure and/or the presence of foreign bodies (e.g., hair shafts, food material). Gingival erosions and ulcerations are reported in polychlorinated biphenyl administered to monkeys and with administration of anticoagulants, corticosteroids, cytotoxic and cytostatic anticancer agents, drugs targeting epithelial antigens, such as tyrosine kinase inhibitors, and anti-epidermal growth factor receptor monoclonal antibodies (anti-EGFR mAbs) in other laboratory animals and in humans. Buccal ulceration is also reported as part of a generalized hypersensitivity reaction to drugs. Humans are more susceptible to direct toxicity from xenobiotics leading to ulcer/erosion of oral cavity that is lined primarily by a nonkeratinizing epithelium than the rodent oral cavity, which is lined by keratinized squamous epithelium.

Differential diagnoses: **Oral cavity squamous cell carcinoma**; **Oral cavity squamous epithelium atrophy**.

Synonym(s): **Gastrointestinal tract erosion**; **gastrointestinal tract ulcer**.

Oral cavity foreign body inflammation is a focal inflammatory cell response to the presence of foreign material, and is most often seen in the mucosa, ducts of minor salivary glands, or muscle layers of the tongue. This is comprised of a mixed inflammatory cell infiltrate (macrophage/multinucleated giant cell, lymphocyte, neutrophil) sometimes associated with imbedded hair shaft fragments or ingested foreign material (food/bedding material).

Oral cavity inflammation may occur in the mucosa or muscle layers of the oral cavity/pharynx, tongue, or esophagus consisting of an inflammatory cell infiltrate associated with other histological hallmarks of inflammation (e.g., fibroplasia or fibrosis). Inflammation may be associated with an overlying ulcer, distended/ruptured cyst, or self-induced traumatic lesion. Reactive/regenerative hyperplasia of the overlying mucosal epithelium is often observed with an inflammatory response.

Oral cavity squamous cell carcinoma is a rare spontaneous malignant neoplasm arising from epithelial squamous cells of the mucosal surface in the oral cavity that can occur in most laboratory animals.

Oral cavity squamous epithelium atrophy is characterized by focally extensive or diffuse decreases in normal thickness/cellularity of the squamous mucosa belonging to the tongue, pharynx, or esophagus.

Differential diagnosis: **Oral cavity erosion/ulcer**.

Oral dosing is the procedure relating to administration of a drug or chemical via the oral cavity. It includes oral gavage, capsule dosing, and administration of test articles in the drinking water.

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Organogenesis period is the main timeframe of organ development during gestation.

Organ toxicity is adverse effects of a drug or chemical on one or more organs or tissues, typically dictated by both the attributes of the organ and the drug or chemical. Organ toxicity may be species-specific. See **Adverse effects** for further information.

Organ weights, within the framework of repeat-dose toxicology studies, are routinely measured as one parameter for assessing potential adverse effects of an experimental compound or chemical. They should be expressed as absolute weights (by animal) and relative to the animal's body weight and brain weight at the time of necropsy. A list of organs that are typically weighed is shown below.

Recommended Organs for Weighing in Multidose General GLP Toxicology Studies[a]

Rat	Mouse	Non-Rodent
Liver	Liver	Liver
Kidneys	Kidneys	Kidneys
Heart	Heart	Heart
Adrenal glands	Adrenal glands	Adrenal glands
Brain	Brain	Brain
Testes	Testes	Testes (sexually mature)
Prostate gland		
Epididymides		
Spleen	Spleen	
Thymus	Thymus	
Thyroid/parathyroid glands		Thyroid/parathyroid glands
Pituitary gland	Pituitary gland	

Source: (In GLP general toxicology studies lasting from 7 days to 1 year) from Sellers et al. 2007. *Toxicol Pathol* 35:751–755.

[a] Excludes carcinogenicity studies.

Orthokeratotic hyperkeratosis is a type of hyperkeratosis that specifically means that the increased layers of keratinocytes (corneocytes) do not have nuclei. This is in comparison to parakeratotic hyperkeratosis, where the keratinocytes are atypical in that they have retained their nuclei. See **Epidermal hyperkeratosis** and **Parakeratotic hyperkeratosis** for further information.

Osmotic nephrosis has been observed in rats after administration of hyperosmotic carbohydrate solutions, some radiographic contrast media, and polyethylene-glycol-conjugated proteins. It presents as proximal tubule cells densely packed with small and large round, clear vacuoles, sometimes conferring a foamy appearance to the cytoplasm. The pathogenesis depends on absorption of a hygroscopic test article through pinocytosis into the proximal convoluted tubule, and then lysosomal accumulation with subsequent hydropic, phagolysosomal swelling. Despite the morphologic alterations, affected animals usually do not show evidence of functional abnormalities or an increase in cell proliferation of the tubules, and the condition is reversible. However, a dose-dependent increase in *N*-acetyl-beta-D-glucosamine has been correlated with the vacuolar histological changes in rats, probably because lysosomes are involved. Osmotic nephrosis has been suspected in humans in association with intravenous administration of immunoglobulins coupled with sugar additives as stabilizing agents, and the plasma expander hydroxyethyl starch.

Synonym(s): **Analgesic nephropathy**.

Osseous metaplasia is the transformation of one tissue type into another whereby portions of neoplasms, dense collagen (scar tissue), ischemic tissues, and areas of chronic inflammation or hemorrhage may mineralize and become organized into bone. Trabeculae of lamellar bone are often intermingled with adipose tissue containing myeloid and erythroid cells.

Differential diagnosis: **Mineralization**.

Osteoarthritis, see the preferred term **Degenerative joint disease**.

Osteoblast are large (20–30 μm) ovoid mesenchymal cells with low nuclear to cytoplasmic, round eccentric nucleus with dense chromatin pattern and 1 to 2 small round nucleoli and abundant basophilic granular cytoplasm. They are usually in seen either isolated or in small clusters, sometimes surrounded by an eosinophilic matrix. They are occasionally seen on bone marrow smear, as they can be aspirated as the same time as hematopoietic cells. Their role is to produce bone osteoid; however, they are an integral part of the bone marrow microenvironment essential for hematopoietic stem cell proliferation and differentiation.

Osteoblast hyperplasia is a proliferation of well-differentiated osteoblasts described in bones of rats administered parathyroid hormone or related peptides. This nonneoplastic finding is observed as single or multiple foci of increased osteoblast-like cells with minimal atypia. The lesion can be associated with increases in osteoid and mineralized bone locally but does not alter the existing trabeculae. Refer to **Bone, Muscle, and Tooth** in Appendix 2 for further information.

Osteoblastic surface increased is a phenomenon in which there are increased osteoblast aggregates on bone surfaces, noticeably in trabecular bone. Normal locations for high numbers of osteoblast aggregates in growing animals (particularly rodents) include the endocortical surface of the metaphysis and primary and secondary spongiosa in the metaphysis. Increased osteoblasts may be formed as a secondary response to bone marrow cytotoxicity in which mesenchymal stem cells preferentially differentiate into unaligned osteoblasts that can quickly form large amounts of woven bone. Increased osteoblasts are also present surrounding foci of necrotic bone, and in primary fracture healing, as well as with intermittent parathyroid hormone (PTH) exposure. Properly aligned osteoblasts form lamellar bone.

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Differential diagnoses: **Osteodystrophy fibrous**; **Osteoblast hyperplasia**.

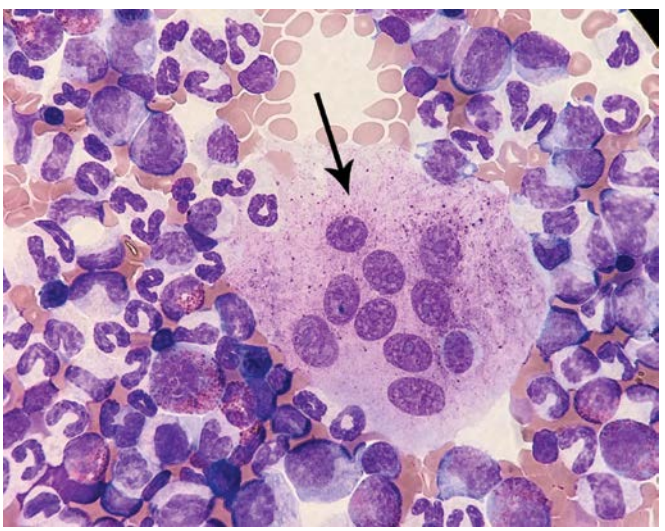
Synonym(s): **Proliferative hyperostosis (with increased bone)**.

Osteoblastoma is a benign, expansile neoplasm of bone-forming cells (osteoblasts). There is an increase in intramedullary immature bone characterized by well-differentiated osteoblasts bordering irregular trabeculae. Often, fibrovascular stroma is observed between bone trabeculae. Osteoblasts have minimal cellular atypia and the neoplasm has minimal invasion. Refer to **Bone, Muscle, and Tooth** in Appendix 2 for further information.

Osteoblasts are cells that synthesize bone. These cells line the surface of bone trabeculae where they produce matrix (osteoid), which is then mineralized to form new bone. Osteoblasts are round cells with a single nucleus and are derived from pluripotential mesenchymal cells. Osteoblasts become osteocytes once they become surrounded by bone. Osteoblasts are controlled by multiple molecules to include bone morphogenetic proteins (bone morphogenetic proteins [BMPs]), transforming growth factor-beta (TGFβ1), WNT, NOTCH, and runt-related transcription factor 2 (RUNX2). Osteoblasts also have roles in bone resorption through communication with other cells such as osteoclasts.

Osteochondroma is a benign neoplasm composed of lamellar bone and cartilage. Extending from the periosteum, the neoplasm consists of a core of mature trabecular bone with intervening marrow and overlying cartilage cap resembling a growth plate. The chondrocytes in this cap are hypertrophic and irregularly arranged. Refer to **Bone, Muscle, and Tooth** in Appendix 2 for further information.

Osteoclasts are large multinucleated cells (~100 μm in diameter) with abundant lightly basophilic cytoplasm that demineralize and resorb bone. They are derived from circulating monocytes (i.e., via cytokine-driven macrophage fusion). Osteoclasts create a depression in bone ("resorption pit," "Howship's lacunae") where they secrete acid and proteases that dissolve organic and inorganic bone components. Osteoclastogenesis is promoted by receptor activator of nuclear factor kappa-B ligand (RANKL), which is produced by osteoblasts. Osteoclast differentiation is inhibited by osteoprotegerin, also made by osteoblasts. The molecule CSF-1 (macrophage-colony stimulating factor or M-CSF) promotes their differentiation, proliferation, function, and survival.



Osteoclast, bone marrow, dog.

Osteoclasts decreased (and/or osteoclast function) occurs when the cellular signals for osteoclast recruitment or differentiation are impaired, either as an inherited condition (e.g., osteopetrosis) or as a pharmacologic target (e.g., sclerostin, RANKL, DKK-1, bisphosphonates). The effects of decreased osteoclasts are best appreciated in rapidly growing animals at the interface of a physis and primary spongiosa or at the "cut-back zone" of the cortical metaphysis. When osteoclasts are decreased, the number of primary spongiosa are increased (which in turn may lead to increased trabecular bone if osteoblast function is normal), and the cut-back zone has a clubbed appearance due to the decreased numbers of osteoclasts. TRACP5b, an osteoclast biomarker, may be reduced as it is a general indicator of osteoclast number.

Osteoclasts increased is a phenomenon in which there are increased numbers of osteoclasts present on bone surfaces, most notably in trabecular bone. Normal locations for osteoclasts in growing animals (particularly rodents) include the interface between the growth plate and primary spongiosa, the periosteal surface of metaphyseal bone ("cut-back zone"), and the distal ends of trabecular bone in the deep metaphysis. In large animals (e.g., dogs, primates, pigs, horses, cows) that remodel bone, osteoclasts are normally found within the basic multicellular unit (BMU). Increased numbers of osteoclasts are a classic response following prolonged, continuous exposure to parathyroid hormone (PTH) in which trabecula may be split by increased osteoclast activity ("tunneling resorption"), or in response to bone necrosis or the early stages of fracture healing.

Synonym(s): **Bone resorption**; **dissecting osteoclasia**.

Osteocyte is a cell surrounded by mineralized bone matrix. Osteocytes are former osteoblasts that, once embedded within bone, reside in a small space ("lacuna"). Osteocytes contact other osteocytes through cytoplasmic connections in bone channels ("canaliculi"). This communication contributes to mechanical force detection, bone turnover regulation, and control of calcium and phosphate levels.

Osteodystrophy, fibrous (FOD) is a nonneoplastic fibroproliferative lesion of bone that may impinge upon the bone marrow cavity. It has some morphological similarity to fibro-osseous lesion (FOL) in mice but is a distinct entity. Trabecular bone and proliferating spindle cells extend from the endosteal surface of cortical bone and may crowd marrow space. Osteoblasts may be visualized lining immature woven

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bone, and osteoid may be present. Proliferating spindle cells may be prominent. Cellularity of marrow may be normal or decreased. FOD is a metabolic remodeling disease of bone most often associated with secondary renal hyperparathyroidism or rarely, a functional parathyroid tumor. It may be a background change in aged rats in conjunction with chronic progressive nephropathy. It has also been reported in rats in response to administration of chemicals or anticancer drugs.

Differential diagnosis: **Fibro-osseous lesion**.

Synonym(s): **Renal osteodystrophy**.

Osteofibroma is a benign, expansile neoplasm of bone. Arising from mesenchymal stem cells and osteoblasts, these neoplasms are found predominantly in the axial skeleton, specifically from the medullary cavity of bone. The neoplasm consists of trabecular bone with intervening connective tissue stroma. Refer to **Bone, Muscle, and Tooth** in Appendix 2 for further information.

Osteofibrosis, see the preferred term **Fibro-osseous lesion**.

Osteogenic fibrosarcoma is a malignant neoplasm of fibroblasts originating in bone. Interlacing neoplastic fibroblasts are pleomorphic, produce collagen, and invade the adjacent bone. This tumor has been reported in rodents in control and treated animals in 2-year carcinogenicity studies. Refer to **Bone, Muscle, and Tooth** in Appendix 2 for further information.

Osteogenic sarcoma, see the preferred term **Osteosarcoma**.

Osteoid is bone matrix. It is initially unmineralized after being synthesized by osteoblasts, then becomes mineralized once calcium hydroxyapatite is deposited. Osteoid is composed of collagen fibrils and matrix. Undecalcified bone sections are required to identify osteoid. Modified Goldner's trichrome stain will detect osteoid in tissue sections.

Osteoid increased indicates either a rapid production of bone matrix due to increased osteoblast activity or a mineralization defect preventing maturation to normal bone. Homeostatic causes of increased osteoid include fracture healing and response to bone necrosis. Increased osteoid occurring due to a mineralization defect is generally termed "rickets" in growing animals and "osteomalacia" in adults. Vitamin D deficiency or other causes of insufficient mineral absorption are primary causes of mineralization defects. Examination of undecalcified bone and histochemical stains identifying mineral can confirm this finding.

Differential diagnosis: **Osteosarcoma**.

Synonym(s): **Hyperosteoidosis**; **osteomalacia**.

Osteoma is a benign, expansile, well-circumscribed neoplasm of bone derived from osteoblasts and osteocytes arising from cortical bone (periosteal surface). These tumors have been observed frequently in the skull but also arise from other bones. Although there are features specific to either rats or mice, osteomas typically are composed of dense mature bone trabeculae, with or without osteoid, with fewer cells in the interior of the neoplasm. Refer to **Bone, Muscle, and Tooth** in Appendix 2 for further information.

Osteomalacia, see the preferred term **Osteoid increased**.

Osteomyelitis is inflammation, usually in response to a local infection, of the bone and arises either by extension of local inflammation/infection or via septic thrombi. The inflammatory response can be exuberant and locally destructive with bone necrosis. If a focus of necrotic bone becomes detached from the surrounding bone, the necrotic structure is termed a sequestrum. New bone (periosteal origin) will form as part of the response to the sequestrum and is termed an involucrum.

Synonym(s): **Bone inflammation**; **osseous inflammation**.

Osteonecrosis, see the preferred term **Bone necrosis**.

Osteopenia, see the preferred term **Bone decreased**.

Osteopetrosis, see the preferred term **Bone increased**.

Osteophytes are part of a stabilization attempt by the animal to compensate for joint instability causing or resulting from degenerative joint disease. Osteophytes can emanate around the periphery of the affected joint ("abaxial osteophytes") or internally ("axial osteophyte") near a tendinous structure (e.g., the cruciate ligaments of the stifle joint). Osteophytes are initially cartilaginous but become bone as they mature.

Osteoporosis, see the preferred term **Bone decreased**.

Osteosarcoma is a malignant neoplasm of bone-forming cells (osteoblasts). These highly invasive tumors arise in the skeleton but can occur in other locations (e.g., skin, gastrointestinal tract). Neoplastic cells can be variable in shape and size (polygonal to spindle-shaped to multinucleated) and form tumor osteoid, an important diagnostic feature. Bone lysis and necrosis are sometimes present. Refer to **Bone, Muscle, and Tooth** in Appendix 2 for further information.

Osteosclerosis, see the preferred term **Bone increased**.

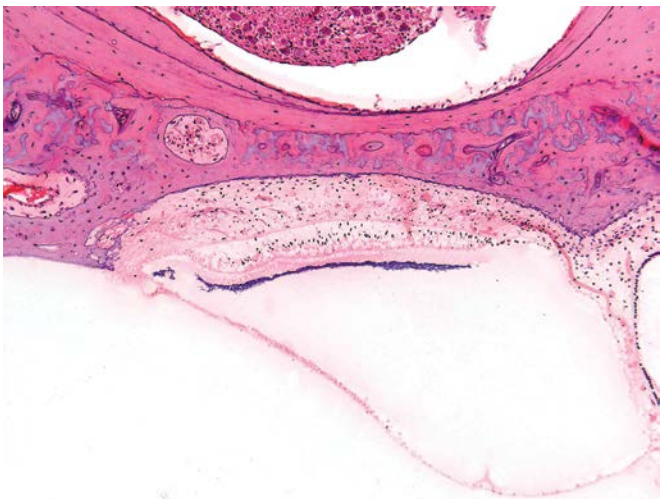
Otitis externa, see the preferred term **External ear canal inflammation**.

Otitis interna, see the preferred term **Inner ear inflammation**.

Otitis media, see the preferred terms **Middle ear inflammation** or **Middle ear catarrhal inflammation**.

Otolith loss, disorganization, and disruption of the vestibular organ in the inner ear consists of misalignment, disruption, or absence of otoliths, which are normally contained within the gel lining the surface of the vestibular organ (refer to Appendix 3 for further information). Abnormalities or damage to the otoliths likely result from damage to the otolith epithelium which maintains the gel matrix.

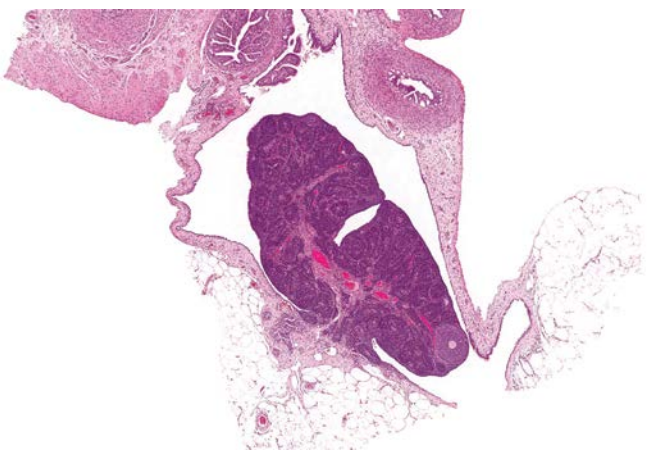
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Otolith loss, disorganization, and disruption, inner ear, chinchilla, H&E. (Image courtesy of Schafer, K. *Vet Path Services*. Mason, Ohio.)

Oval cell is a rare cell type in the liver that lines the short and narrow passage, sometimes called the "canal of Hering," which carries bile between the bile canaliculi and the bile ducts. These cells are small possess oval-shaped nuclei and indistinct cytoplasm. They express cytokeratins and thus may be considered epithelial cells. Furthermore, they are considered to represent a population of hepatic progenitor (stem) cells that, based on models of hepatic injury, may proliferate and differentiate into bile duct epithelial cells and hepatocytes. They are not usually observed in normal liver by light microscopy but are readily detected when they become hyperplastic.

Oval cell hyperplasia is a lesion characterized by increased numbers of oval cells (small cells with oval nuclei that arise in the periphery of the portal tracts that line the short and narrow passages that conduct bile between the bile canaliculi and bile ducts and can differentiate into either hepatocytes or bile duct epithelium). Refer to **Liver, Gallbladder, and Exocrine Pancreas** in Appendix 2 for further information.



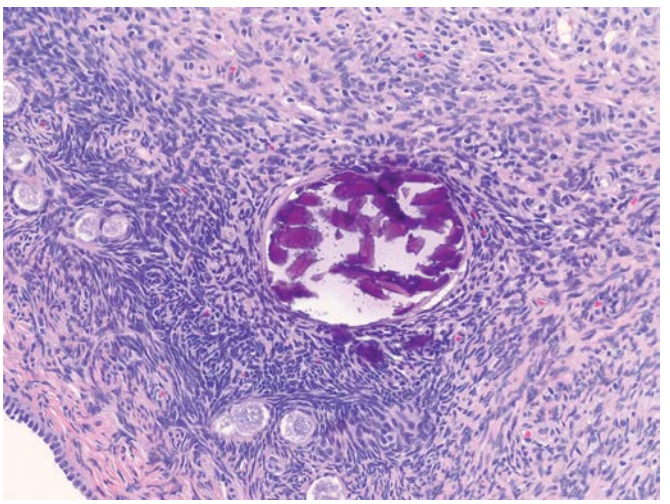
Atrophy characterized by lack of follicles and corpora lutea, ovary, rat, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

Ovarian atrophy is characterized by the decreased size of the ovary/decreased ovarian weight because of decreased/absent oocytes/follicles, cystic follicles and/or corpora lutea (CL), and/or decreased/absent CL. This condition is induced by exposure to xenobiotics or other toxicants that directly affect the ovary (i.e., oocytes, follicles, stroma) or alter the hypothalamic-pituitary-ovarian axis, resulting in decreased gonadotropin-releasing hormone, luteinizing hormone, and/or follicle-stimulating hormone and secondary ovarian atrophy. The effect on ovarian function results in cessation of the normal estrous or menstrual cycles (see **anestrus** for further information). The morphologic appearance of the ovary depends on the age of the animal at the beginning of exposure, duration of dosing or exposure, and the specific target of the toxic agent. Morphologic changes in other reproductive tract organs are reflective of the pathogenesis and may include atrophy or hypertrophy/hyperplasia. This condition may be difficult to discern from spontaneous senescence. See **Age-related ovarian atrophy** for further information.

Differential diagnosis: **Age-related ovarian atrophy**.

Ovarian calcified focus is a common incidental finding in nonhuman primates characterized by laminated foci of basophilic material (calcium salts) within ovarian follicles, usually of the primary type. The change represents dystrophic mineralization and is not generally reported in the pathology raw data collected in the context of a toxicology study. Calcified foci are also reported in rodent and minipig ovaries, most commonly in mice, and is generally dystrophic in nature (i.e., observed in areas of previous hemorrhage).

Synonym(s): **Ovarian follicular mineralization**; **oocyte mineralization**.



Mineralized primary follicle, ovary, Gottingen minipig, H&E.

Ovarian cycle, see the preferred terms **Estrous cycle** and **Menstrual cycle**.

Ovarian cystadenocarcinoma is an infiltrative, malignant neoplasm of the surface epithelium of the ovary. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

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Ovarian cystadenoma is a benign neoplasm derived from the surface epithelium of the ovary that is composed of well-differentiated cuboidal or low columnar epithelial cells. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Ovarian cystic follicle, see the preferred term **Follicular cyst**.

Ovarian epidermoid cyst, see the preferred term **Ovarian epithelial cyst**.

Ovarian epithelial cyst is derived from the superficial epithelium of the ovary and lined by a cuboidal to low columnar epithelium. These cysts are more common in aged rodents and are usually found in the ovarian cortical region.

Synonym(s): **Ovarian epidermoid cyst**.

Ovarian epithelial hyperplasia, see the preferred term **Ovarian tubulostromal hyperplasia**.

Ovarian fatty change, see the preferred term **Ovarian granulosa cell vacuolation**.

Ovarian follicle is composed of the ovum and its surrounding supporting somatic cells (i.e., granulosa and theca cells) found in the ovarian cortex. These somatic cells are required for oocyte development, physiology, and survival. The major stages of ovarian folliculogenesis are as follows: (1) formation of the primordial follicle; (2) recruitment into the growing pool to form a primary, secondary, and tertiary follicle, each with distinct morphologies and hormonal physiology; and (3) ovulation. Autocrine, paracrine, juxtracrine, and endocrine factors are essential for normal ovarian folliculogenesis. See Appendix 3 for more information.

Ovarian follicular mineralization, see the preferred term **Ovarian calcified focus**.

Ovarian granulosa cell decreased vacuolation is characterized by follicular granulosa cell cytoplasm that has a decrease in vacuolation compared to background levels. Granulosa cell cytoplasm is normally finely vacuolated. The decreased vacuolation may reflect an inhibition of steroid synthesis and/or secretory activity.

Ovarian granulosa cell hyperplasia is a proliferative change of granulosa cells in the ovary in which >70% of the cells comprising the lesion are granulosa cells. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Ovarian granulosa cell tumor, benign is a proliferative change of granulosa cells (one type of sex cord stromal cell) in the ovarian follicle consisting of a compressive, cystic or solid group of well-differentiated sex cord stromal cells in which >70% of the cells comprising the lesion are granulosa cells. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Ovarian granulosa cell tumor, malignant is a proliferative change of granulosa cells (one type of sex cord stromal cell) in the ovarian follicle consisting of a compressive, cystic or solid group of poorly differentiated sex cord stromal cells in which >70% of the cells comprising the lesion are granulosa cells. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Ovarian granulosa cell vacuolation may be increased or decreased and is observed when steroid synthesis in the granulosa cell is altered, or with accumulation of lipids or fluid in intracellular organelles. Increased vacuolation is observed when steroid synthesis is inhibited as in phospholipidosis.

Differential diagnoses: Ovarian theca cell vacuolation; Ovarian interstitial cell hypertrophy.

Synonym(s): **Ovarian fatty change**.

Ovarian inflammation is characterized by the infiltration of inflammatory cells into the ovary parenchyma with occasional extension into the oviduct or periovarian fat. Extensive leukocytic cellular infiltrates (e.g., mononuclear, neutrophils, histiocytes, or mixed inflammatory cells) into the ovarian parenchyma, with or without involvement of the adjacent soft tissue, can be accompanied by other inflammatory changes (e.g., hemorrhage, swelling, edema, tissue degeneration/necrosis/regeneration). The appearance varies depending upon the severity and duration. This lesion is often secondary to septicemia (e.g., *Mycoplasma* spp., *Streptococcus* spp., *Pasteurella* spp., *Corynebacterium* spp. in rodents) or from an ascending infection from the uterus. This condition may also be immune-mediated. It is uncommon in dogs and the nonhuman primate (NHP).

Ovarian senescence, see the preferred term **Age-related ovarian atrophy**.

Ovarian Sertoli cell tumor, benign is a neoplasm characterized by a cluster of Sertoli cells that has a size greater than that of corpus luteum (CL). Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Ovarian Sertoli cell tumor, malignant is a neoplasm characterized by a nests or sheets of Sertoli cells that are locally invasive. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Ovarian subsurface epithelial structures (SES) are dilated, fluid-containing, epithelial-lined structures of the canine ovary just below the surface epithelium. The epithelial lining of the SES is typically cuboidal. SES are more common in older females and may not be evident grossly.

Ovarian theca cell decreased vacuolation is characterized by theca cells with decreased cytoplasmic vacuolation compared to background levels. Theca cell cytoplasm is normally finely vacuolated. The decreased vacuolation may reflect an inhibition of steroid synthesis and/or secretory activity.

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Ovarian tubulostromal adenoma is a benign neoplasm of the surface epithelium of the ovary, is larger than a CL, and compresses adjacent ovarian parenchyma. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Ovarian tubulostromal carcinoma is a malignant neoplasm of the surface epithelium of the ovary, is larger than a CL, and compresses adjacent ovarian parenchyma. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Ovarian tubulostromal hyperplasia is characterized by diffuse expansion of well-differentiated, noncompressive ovarian surface epithelium. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

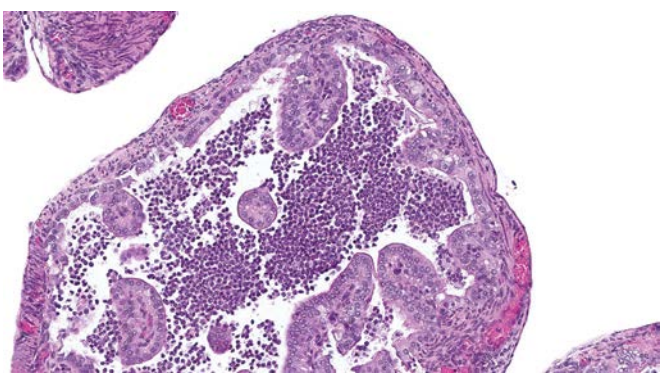
Ovary is the female gonad; it is a paired organ that contains the supply of germ cells needed to produce the next generation and is also an endocrine organ that produces steroid hormones controlling many aspects of female development and physiology. In rodents and dogs, the ovary is located near the kidneys in a bursa that isolates it from the abdominal cavity. In nonhuman primates (NHPs) the ovaries are located in the pelvis and lack a bursa. See Appendix 3 for more information.

Oviduct is a tube that transports the ova from the ovary to the uterus (in mammals) or to the exterior (in oviparous animals). The anterior portion adjacent to the ovary ends in the funnel-shaped infundibulum, which collects eggs as they are released by the ovary during ovulation.

Synonym(s): **Uterine tube**; **Fallopian tube**.

Oviduct inflammation is characterized by the infiltration of inflammatory cells in the oviduct. The ovary, mesosalpinx, and ovarian bursa and/or periovarian fat may also be involved. Extensive leukocytic cellular infiltrates (e.g., mononuclear, neutrophils, histiocytes, or mixed inflammatory cells) in the ovarian parenchyma, with or without involvement of the adjacent soft tissue, may also be observed accompanied by other inflammatory changes (hemorrhage, swelling, edema, tissue degeneration/necrosis/regeneration). The histologic appearance varies depending upon the severity and duration. This lesion often occurs secondary to septicemia (e.g., *Mycoplasma* spp., *Streptococcus* spp., *Pasteurella* spp., *Corynebacterium* spp., *Klebsiella* spp.) in rodents, or from an ascending infection from the uterus. This condition is uncommon in dogs and the nonhuman primate (NHP).

Differential diagnosis: **Oviduct inflammatory cell infiltrate**.
Synonym(s): **Salpingitis**.



Neutrophils within oviduct lumen, oviduct, B6C3F1 mouse, H&E. (Images courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

Oviduct inflammatory cell infiltrate is characterized by infiltration of granulocytes, lymphocytes, and/or macrophages in the oviduct that is not accompanied by edema, congestion, hemorrhage, necrosis, and/or fibrosis.

Ovotestis is gonadal tissue containing both ovarian and testicular tissue. An ovotestis is one expression of true hermaphroditism (see **Hermaphroditism** for further information), the other being the presence of one gonad of each sex. This condition is rare in laboratory species. In domestic animal species, true hermaphroditism is most common in swine and goats.

Differential diagnosis: **Hermaphroditism**.

Ovotoxicity is an adverse event caused by a substance (e.g., chemical, drug), a pathogen (e.g., microorganism, virus), or any other agent (e.g., radiation) that could affect the female ovaries.

Ovulatory cycle, see the preferred term **Estrous cycle**.

Ovum is the female gamete; secondary oocyte; mature female germ cell.

Oxidative dealkylation reaction is catalyzed by cytochrome P450 and results in the oxidation of the substrate with subsequent removal of *N*- or *O*-alkyl groups. See **Cytochrome P450** for further information.

Oxidative deamination is the oxidative removal of amine groups. For example, the conversion of secondary amines to ketones, a reaction catalyzed by cytochrome P450. See **Cytochrome P450** for further information.

Oxidative stress results from the excessive production of reactive oxygen species. See **Reactive oxygen species** for further information.

Oxyphilic adenocarcinoma, see the preferred term **Oncocytoma**.

Oxyphilic adenoma, see the preferred term **Oncocytoma**.

Oxytocin is a hormone primarily produced in the supraoptic and paraventricular nuclei of the hypothalamus and released by the posterior pituitary gland. Additional sources of oxytocin in some mammals, including nonhuman primates, are the ovaries (corpus luteum), testis (Leydig cells), and placenta. The target organs include the breast (lactation) and uterus (partum contraction).

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Pachytene spermatocytes are metabolically active, small spermatocytes with condensed nuclei in earlier-stage tubules, and increased cellular and nuclear volume in later-stage tubules. Pachytene spermatogenesis is a lengthy phase, lasting about 12 days in the rat. The initial effects of androgen deficiency due to xenobiotics or food restriction are sometimes recognized by degeneration of pachytene spermatocytes in stage VII/VIII tubules of rats. In general, early pachytene stages are more susceptible than late pachytene stages, which are more susceptible than mid-pachytene stages. Pachytene spermatocytes are also affected by cytotoxicants such as 2-methoxymethanol and dinitropyrroles.

Palatine tonsils are paired and encapsulated oval masses of mucosa-associated lymphoid tissue (MALT) with crypts embedded in the lateral wall of the oropharynx of mammals larger than rodents. This is one of the tonsils that form a ring of lymphoid tissue protecting the naso-oro-pharyngeal region. Particulates, food material, infections, and exposure to xenobiotics may result in tonsillar lymphoid enlargement with crypt abscesses and surface ulcerations and inflammation (tonsillitis). See **Nasopharyngeal tonsil** and Appendix 3 for further information.

Palatoschisis, see the preferred term **Cleft palate**.

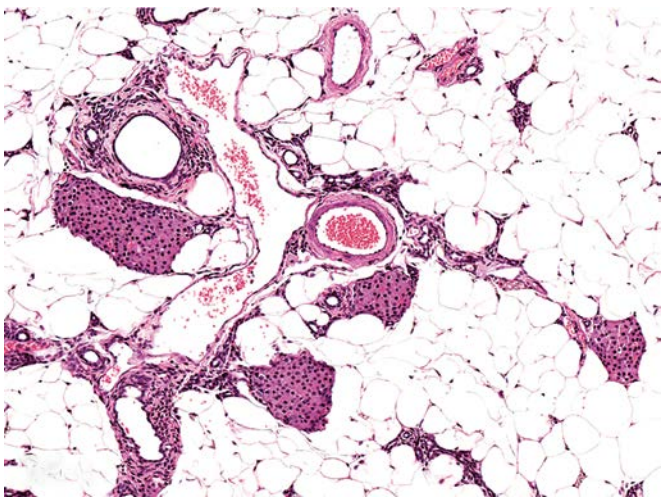
Panarteritis, see the preferred terms **Arterial inflammation** and **Polyarteritis nodosa**.

Pancreas is a glandular organ that is part of both the digestive and endocrine systems. It is located in the abdominal cavity behind the stomach and grossly appears pale yellowish white with grossly visible lobules and ducts. The pancreas is formed by fusion of the dorsal and ventral buds of the septum transversum at the junction of the embryonic fore- and midgut during embryonic development. It extends from the duodenum to the hilum of the spleen with species differences in anatomy. It is a compact gland in humans, nonhuman primates, hamsters, minipigs, and dogs. In contrast, major parts of the pancreas are dispersed within the mesentery in rats and mice, and in rabbits the pancreas is completely dispersed within the mesentery. The compact gland presents distinct anatomically defined regions. The pancreatic duct opens into the common bile duct in rats and mice, and directly into the duodenum in humans, dogs (with some variation), and rabbits. In dogs and primates, the efferent blood vessels from the islets of Langerhans supply most of the exocrine pancreas, while the blood supply to this region is direct in rats. See **Exocrine pancreas** and **Endocrine pancreas** for further information.

Pancreas adipocyte accumulation, sometimes termed pancreatic lipomatosis or fatty infiltration, is replacement of exocrine pancreatic parenchyma with adipocytes that occurs spontaneously in aged laboratory animals but can be associated with chemically induced atrophy or obesity. Histologically multifocal to coalescing adipocytes are noted within the interstitium with occasional compression of the adjacent exocrine pancreatic tissue. It is often associated with multifocal to diffuse atrophy of exocrine pancreatic acini, with the islets of Langerhans remaining unaffected.

Differential diagnosis: **Pancreatic acinar cell vacuolation**.

Synonym(s): **Pancreatic lipomatosis**; **pancreatic fatty infiltrate**.



Pancreas adipocyte accumulation, mouse pancreas, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Nolte, T. et al. 2016. *J Toxicol Pathol* 29(1 Suppl):1S–125S.)

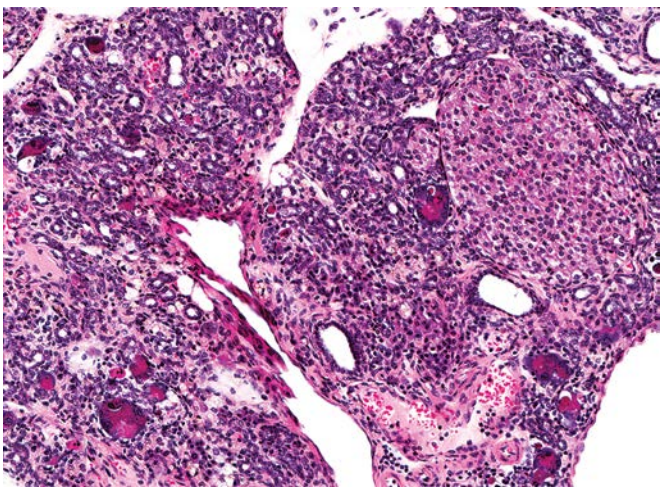
Pancreatic acinar cell adenocarcinoma is a malignant neoplasm of pancreatic acinar cells that may vary in histological appearance from well-differentiated with glandular, trabecular, or solid growth patterns to a pleomorphic or anaplastic tumor with cellular pleomorphism composed of small rounded cells or spindle cells. Loss of acinar architecture is evident in pleomorphic or anaplastic tumors with evidence of local invasion or distant metastases. These malignant tumors may show scirrhous reactions and encapsulation. Refer to **Liver, Gallbladder, and Exocrine Pancreas** in Appendix 2 for further information.

Pancreatic acinar cell adenoma is a benign neoplasm of the exocrine pancreas that is normally grossly apparent as a nodular or multinodular, sharply circumscribed

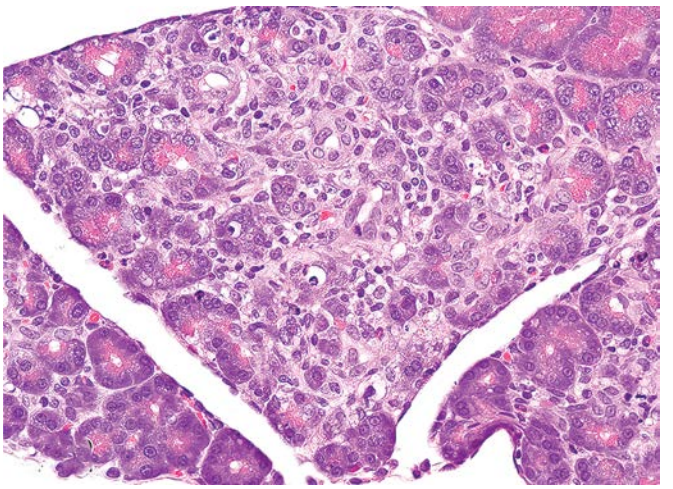
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mass. Histologically, these tumors are composed of well-differentiated pancreatic acinar cells with a variable mitotic index and nuclear polymorphism. Compression of the adjacent tissue is often present, with or without encapsulation. Refer to **Liver, Gallbladder, and Exocrine Pancreas** in Appendix 2 for further information.

Pancreatic acinar cell atrophy is a common spontaneous, age-related degenerative change in rats and mice leading to focal, lobular reduction in number and/or size of acini, with loss of acinar cell basophilia and decreased numbers of zymogen granules. It is occasionally seen in young adult rats and young beagle dogs accompanied by adipocyte accumulation. Diffuse atrophy of exocrine acini is associated with replacement by adipose tissue and dilated residual ducts, vasculature, and unaffected islets of Langerhans. Acinar atrophy frequently occurs as a consequence of chronic inflammation with mononuclear cell infiltration and fibrosis. Acinar atrophy without inflammation has also been induced by experimental pancreatic duct ligation in rats. Diffuse atrophy has been reported following hypophysectomy, prolonged fasting, starvation, treatment-related chronically reduced food consumption, induced chronic protein or essential amino acid or copper or zinc deficiency, feeding with DL-ethionine in protein-deficient diets, malonaldehyde, several cytotoxic chemicals, or high doses of glucagon. Pancreatic atrophy is accompanied by clinical insufficiency in dogs as in humans. GI181771X, a novel cholecystokinin 1 receptor agonist, causes acinar atrophy in rats and mice, but not in monkeys or humans. Gatifloxacin, a fluoroquinolone antibiotic, induces acinar cell atrophy in dogs and cynomolgus monkeys. Significant atrophy of pancreatic acinar cells, with dilated intercalated, interlobular, and intralobular ducts filled with inspissated granular material, accompanied by mild periductular inflammatory cell infiltrates, has been reported in cystic fibrosis and in transmembrane conductance regulator (CFTR)-deficient mouse.



Pancreatic acinar cell atrophy, mouse pancreas, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Nolte, T. et al. 2016. *J Toxicol Pathol* 29(1 Suppl):1S–125S.)



Pancreatic acinar cell atrophy, rat pancreas, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Nolte, T. et al. 2016. *J Toxicol Pathol* 29(1 Suppl):1S–125S.)

Differential diagnoses: Pancreatic acinar cell degranulation; **Pancreatic increased peri-insular halos**; **Chronic inflammation**.

Differential diagnoses: **Pancreatic acinar cell hyperplasia**; **Pancreatic increased peri-insular halos**.

Synonym(s): **Pancreatic acinar cell cytomegaly**.

Pancreatic acinar cell autophagy, see the preferred term **Pancreatic autophagy**.

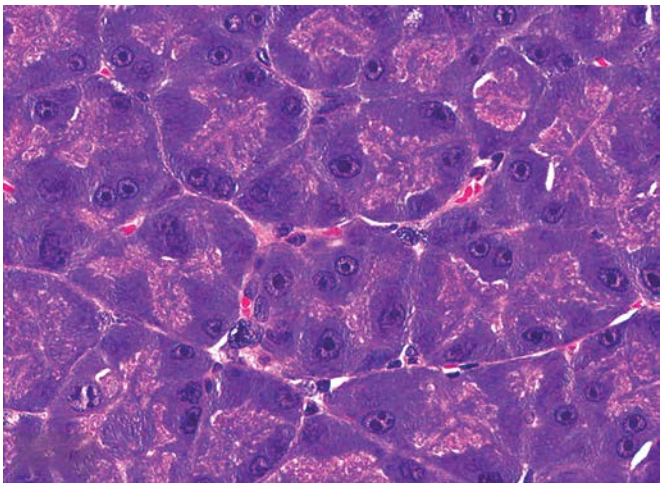
Pancreatic acinar cell cytomegaly, see the preferred term **Pancreatic acinar cell hypertrophy**.

Pancreatic acinar cell hydropic change, see the preferred term **Pancreatic acinar cell vacuolation**.

Pancreatic acinar cell hyperplasia are focal proliferations of acinar cells that are often larger than average, accompanied by increased number of cells per acinus. Refer to **Liver, Gallbladder, and Exocrine Pancreas** in Appendix 2 for further information.

Pancreatic acinar cell hypertrophy is characterized by increased size of pancreatic exocrine acinar cells that contain numerous zymogen granules due to increased dietary and trophic factors. Feeding rats with raw soy flour having trypsin inhibitors causes diffuse acinar hypertrophy, initially due to overproduction of cholecystokinin (CCK) which is trophic to pancreatic acini. Direct administration of CCK, administration of gastrin analogs such as pentagastrin, pancreozymin, and peptavlon as well as administration of isoprenaline (isoproterenol) cause pancreatic acinar cell hypertrophy. Focal hypertrophy of acini is induced by treatment with azaserine and 4-HAQO, with the affected groups of acinar cells appearing hypertrophic and more basophilic.

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Pancreatic acinar cell hypertrophy, rat pancreas, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Nolte, T. et al. 2016. *J Toxicol Pathol* 29(1 Suppl):1S–125S.)

Pancreatic acinar cells form the major portion of the exocrine pancreas (see **Exocrine pancreas** for further information). Acinar cells are arranged concentrically around a lumen. The base of the pyramidal-shaped cells is basophilic due to abundant rough endoplasmic reticulum. They also contain one or two nuclei, and the apex of these cells contains eosinophilic zymogen granules. Acinar cells produce and secrete digestive enzymes (e.g., amylase, lipase) or inactive proenzymes, and zymogens of digestive enzymes (e.g., trypsinogen, chymotrypsinogen, proelastase, prophospholipase, carboxypeptidase) that help digest dietary proteins, triglycerides, and complex carbohydrates.

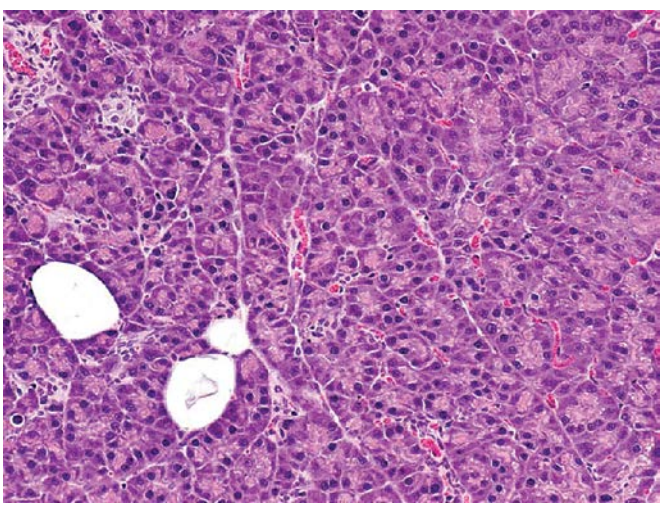
Pancreatic acinar cell secretory depletion occurs due to a partial or complete decrease in numbers of acinar cell zymogen granules leading to shrunken acinar cells with increased basophilia. The lesion may be focal, lobular, or diffuse with no evidence of fibrosis or adipocyte infiltration as well as unaffected islets of Langerhans. Pancreatic acinar cell secretory depletion occurs under several physiological conditions, such as anorexia and inanition. In moribund and/or anorexic animals with protein deficiency, zymogen granule numbers are decreased and cells are shrunken, with an apparent increase in cytoplasmic basophilia due to the relative predominance of the basally located basophilic cytoplasm.

Differential diagnoses: **Pancreatic acinar cell atrophy**; Pancreatic basophilic focus; **Pancreatic increased periinsular halos**.

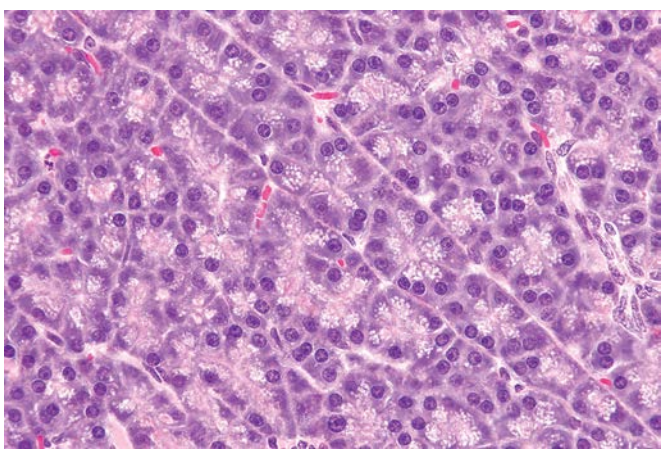
Pancreatic acinar cell vacuolation is a degenerative change leading to accumulation of fluids, lipids, phospholipids, and glycoproteins within the pyramidal acinar cells. Vacuolation can be focal, multifocal, or diffuse in distribution with moderate to complete loss of zymogen granules within the affected cells. Vacuolation can be microvesicular, macrovesicular, or foamy in nature, often resulting in nuclear displacement. The cells may be swollen with pale eosinophilic cytoplasm and contain intracytoplasmic vacuoles. Foamy vacuolation is characterized by clear vesicles with fine, eosinophilic granules. Acinar cell vacuolation is a reversible change and usually a reflection of hypoxia and metabolic insults that damage mitochondria, endoplasmic reticulum, protein machinery, and plasma membrane. Treatment-related acinar cell vacuolation is reported with cyclosporin A, caerulein, puromycin, ethyl alcohol, dioxins, dioxin-like compounds, palmitoylpentachlorophenol (PPCP), arginine, choline-deficient diet, ethionine-supplemented diet, and in zinc deficiency. Pancreatic acinar cell vacuolation is generally accompanied by other changes such as apoptosis or necrosis of acinar cells and/or edema, hemorrhage, or inflammation.

Differential diagnoses: **Phospholipidosis**; Vacuolation artifact.

Synonym(s): **Pancreatic acinar cell hydropic change**; **pancreatic epithelial vacuolation**.



Pancreatic acinar cell secretory depletion, rat pancreas H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Nolte, T. et al. 2016. *J Toxicol Pathol* 29(1 Suppl):1S–125S.)



Pancreatic acinar cell vacuolation, rat pancreas, H&E. (Reproduced with permission of CRC Press from Cattley, R. et al. 2013. In: Sahota, P. et al. (eds). *Toxicologic Pathology: Nonclinical Safety Assessment*. CRC Press, Taylor & Francis Group, Boca Raton, FL, pp. 313–366.)

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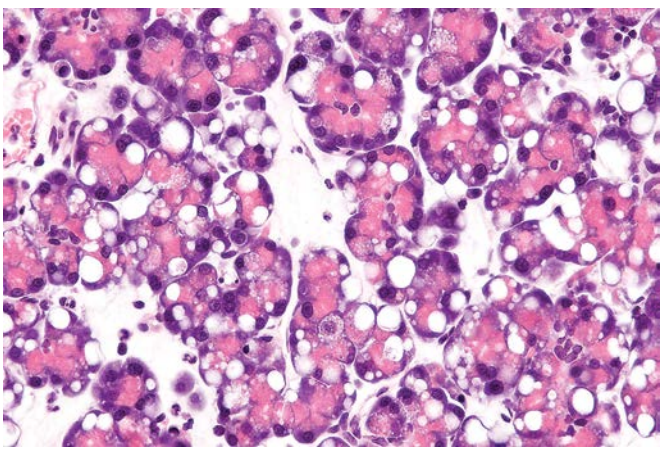
Pancreatic acinar metaplasia is characterized by normal pancreatic acini located within the liver. This finding is consistent with the definition of a choristoma (normal tissue at an abnormal location). See **Choristoma** for further information.

Pancreatic amyloidosis is an extracellular deposit of polypeptide fragments of a chemically diverse group of glycoproteins in within the interstitium and along basement membranes or within the tunica media of blood vessels. If extensive, amyloid may be associated with atrophy of acinar or ductal parenchyma. Histologically, amyloid appears as pale amorphous, homogenous eosinophilic material with hematoxylin and eosin (H&E) stain, and shows anomalous, often green birefringence under polarized light when stained with Congo red.

Pancreatic autophagy is the destruction of damaged or redundant cellular components occurring in vacuoles within pancreatic acinar cells in order to maintain cellular homeostasis. Increased numbers of autophagic vacuoles of multifocal distribution form via segregation of cytoplasmic organelles or cytoplasmic contents of sublethally injured acinar cells. Typically, the lobular architecture is maintained with formation of intracytoplasmic hypereosinophilic to basophilic globules surrounded by a thin, clear halo. Autophagy may be rapidly increased during chronic protein deficiency, hypophysectomy, energy depletion, hypoxia, endoplasmic reticulum stress, high body temperature, hormonal stimulation, or cell remodeling to combat oxidative stress. The exocrine acini are very sensitive to agents affecting autophagic flux such as vinblastine (enhances autophagic segregation), or cycloheximide (regression of the autophagic compartment). Alterations in autophagy may lead to the disruption of cellular homeostasis and can result in pancreatic inflammation and cell death.

Differential ddiagnoses: **Apoptosis**; **artifact**; **phospholipidosis**.

Synonym(s): **Pancreatic acinar cell autophagy**.



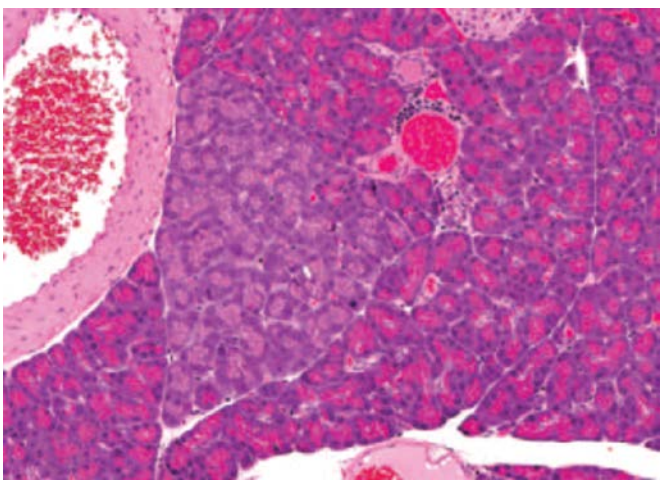
Pancreatic autophagy, mouse pancreas, H&E. (Reproduced with permission of CRC Press from Cattley, R. et al. 2013. In: Sahota, P. et al. (eds). *Toxicologic Pathology: Nonclinical Safety Assessment*. CRC Press, Taylor & Francis Group, Boca Raton, FL, pp. 313–366.)

Pancreatic basophilic-atypical acinar cell focus, see the preferred term **Pancreatic basophilic focus of cellular alteration**.

Pancreatic basophilic focus of cellular alteration is a distinct focus of morphologically atypical pancreatic exocrine acinar cells with altered staining due to decreased numbers of zymogen granules. These cells are characterized as having increased basophilia due to an abundance of rough endoplasmic reticulum (RER) in combination with slightly enlarged, basal to parabasal nuclei and prominent nucleoli, yet they manifest limited mitotic activity. Basophilic foci are variable in shape (with oval to irregular contours), and lack encapsulation. Despite the presence of a basophilic focus, the angular shape of the pancreatic lobe is retained. Cellular hypertrophy (see **Pancreatic acinar cell hypertrophy** for further information) is commonly seen with no evidence of compression or displacement of the adjacent pancreatic acini. Spontaneous basophilic foci tend to be small and few in number, with a higher incidence in aged rats, and they are observed less frequently in mice and hamsters. Increased incidence of basophilic foci has been reported in rats treated with 4-hydroxyaminoquinoline-1-oxide (4HAQO), 7,12-dimethyl-benzanthracene (DMBA), N5-(*N*-methyl-*N*-nitrosocarbamoyl)-*L*-ornithine (MNCO), raw soybean flour, plant trypsin inhibitors, and azaserine. Basophilic foci stain positively with gamma-glutamyltranspetidase (GGT).

Differential diagnoses: Pancreatic focal acinar cell hyperplasia; **Pancreatic acinar cell secretory depletion**.

Synonym(s): **Pancreatic basophilic-atypical acinar cell focus**; **pancreatic focal cellular change**; **pancreatic focal basophilic cellular change**; **pancreatic cytological alteration**.



Pancreatic basophilic focus of cellular alteration, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Nolte, T. et al. 2016. *J Toxicol Pathol* 29(1 Suppl):1S–125S.)

Pancreatic centroacinar cells are relatively clear-staining, flattened, oval-to-cuboidal cells that are part of the pancreatic ductal system that lines the luminal side of the zymogen granule-rich epithelial cells. These cells are continuous with

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the lumen of the intercalated ducts. They secrete bicarbonate ions that aid in neutralizing acidic chyme from the stomach, thus stabilizing the digestive enzymes.

Pancreatic cystic duct, see the preferred term **Pancreatic duct ectasia**.

Pancreatic cytological alteration, see the preferred term **Pancreatic basophilic focus of cellular alteration**.

Pancreatic decreased peri-insular halos are formed following degranulation of the peri-insular pancreatic acinar cells resulting from a decrease or complete loss of trophic factors, mainly ghrelin and insulin secreted by the β-cells of the islets of Langerhans. Pancreatic acini surrounding the islets show decreased numbers of zymogen granules leading to loss of size distinction between the larger peri-insular acini that are located adjacent to the islets and the smaller tele-insular acini located more distant from the islets, the latter being more distinct in mice than in rats. Markedly reduced size of peri-insular halos occurs in alloxan-induced diabetic rats compared to non-diabetic control rats. Peri-insular halos are not recorded in routine toxicity studies, but noting alterations within these halos may provide important information about chemicals that affect islet cells, such as alloxan, or about chemicals directly affecting the exocrine pancreas, such as pilocarpine.

Pancreatic ductal cell adenocarcinoma is a malignant tumor arising from neoplastic intrapancreatic duct epithelium characterized by cell atypia and invasion of duct-like structures, often accompanied by a dense fibrous stroma. Refer to **Liver, Gallbladder, and Exocrine Pancreas** in Appendix 2 for further information.

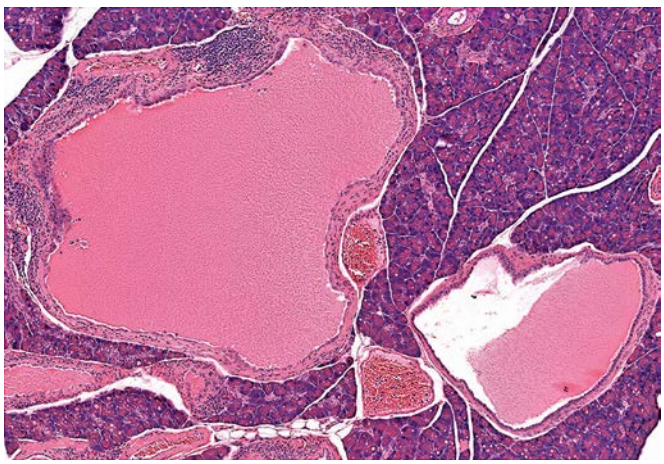
Pancreatic ductal cell adenoma is a benign neoplasm arising from intrapancreatic ducts. Histologically, this tumor is characterized as a complex of ductular structures lined by a high cuboidal epithelium resembling that of normal ductules. Pancreatic ductal adenomas may occur after administration with 7,12-dimethylbenz[a]anthracene (DMBA), infection with reo-virus 3, feeding a Western-style diet, and in transgenic mice with Kras oncogene. Refer to **Liver, Gallbladder, and Exocrine Pancreas** in Appendix 2 for further information.

Pancreatic ductal cell hyperplasia is characterized by increased numbers of intralobular and interlobular pancreatic ducts with hyperchromatic duct cells. Papillae formation and cellular pleomorphism may be present. Refer to **Liver, Gallbladder, and Exocrine Pancreas** in Appendix 2 for further information.

Pancreatic ductal cyst, see the preferred term **Pancreatic duct ectasia**.

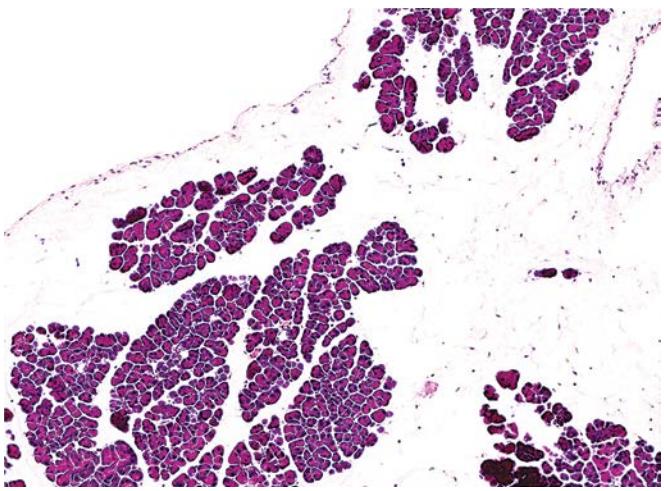
Pancreatic duct dilatation, see the preferred term **Pancreatic duct ectasia**.

Pancreatic duct ectasia is characterized by luminal dilatation due to blockage of the intralobular or interlobular ducts secondary to fibrosis, or due to calculi. Solitary or multiple enlarged irregularly tortuous ducts lined by flattened cuboidal epithelial cells are observed. Ectasia may be accompanied by mild interstitial infiltration of lymphocytes and plasma cells. Inspissated secretions may be present in the lumen. Duct ectasia is the most common age-associated ductal change in albino and gray Norway, August hooded, Fisher 344, Hap:(SD), and Crl:COBS CD (SD) rats.



Pancreatic duct ectasia, mouse pancreas, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Nolte, T. et al. 2016. *J Toxicol Pathol* 29(1 Suppl):1S–125S.)

Pancreatic edema is focally extensive or diffuse accumulation of tissue fluid leading to distension of the interstitial tissue forming clear spaces or spaces filled with lightly eosinophilic material in the exocrine pancreas. Pancreatic edema may be exudative (inflammatory edema due to capillary injury secondary to leakage of pancreatic enzymes) or transudative (hydrodynamic derangement secondary



Pancreatic edema, mouse pancreas, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Nolte, T. et al. 2016. *J Toxicol Pathol* 29(1 Suppl):1S–125S.)

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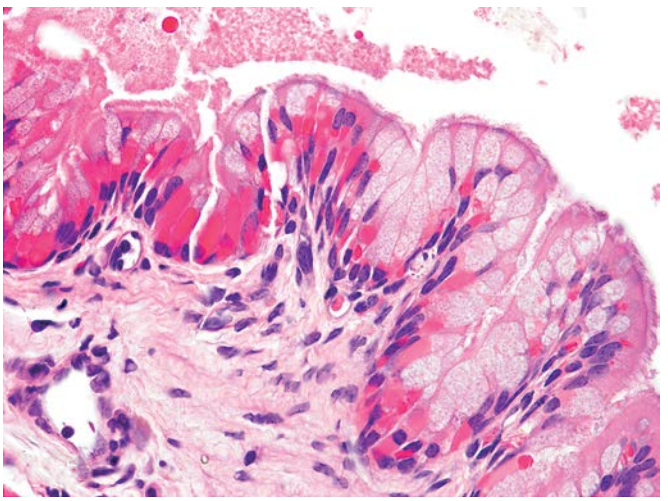
to increased hydrostatic osmotic pressure, decreased oncotic pressure, or impaired lymphatic drainage). Exudative edema is usually accompanied by inflammatory cell infiltrates and tissue injury. Xenobiotic-induced pancreatic edema has been documented in mice treated with p-nitrophenol and rats administered 4-hydroxyaminoquinoline, D & C Yellow No. 11, and PCB mixtures. Pancreatic edema occurs in the early phase of several surgical and chemical induced pancreas inflammation models in laboratory animals such as concurrent administration of ethanol, low doses of CCK and secretin, ethanol, ACE inhibitor, or caerulein-induced inflammation of the pancreas. Edema of the exocrine pancreas must be differentiated from acute inflammation.

Pancreatic eosinophilic change, see the preferred terms **Pancreatic eosinophilc globules** and **Pancreatic increased peri-insular halos**.

Pancreatic eosinophilic focus, see the preferred term **Pancreatic acinar cell hyperplasia**.

Pancreatic eosinophilic globules are focal or multifocal accumulations of intensely pink-red cytoplasmic droplets and/or crystals in usually hypertrophic pancreatic ductal cells. Crystals, if present, may be intracellular or extracellular. High incidence of eosinophilic globules in various epithelia, including glandular stomach, respiratory tract, bile duct, gall bladder, and pancreatic duct is reported in aged C57BL/6, 129, and B6-129 hybrid strains of mice. The protein isolated from the characteristic eosinophilic lesions has been identified as Ym1/Ym2, a member of the chitinase family which accumulated in pancreatic ductal cells in response to mucosal irritation.

Synonym(s): **Pancreatic hyalinosis**; **pancreatic eosinophilic change**.



Pancreatic eosinophilic globules, mouse pancreas, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Nolte, T. et al. 2016. *J Toxicol Pathol* 29(1 Suppl):1S–125S.)

Pancreatic epithelial vacuolation, see the preferred term **Pancreatic acinar cell vacuolation**.

Pancreatic exocrine acinar ductular metaplasia is a reparative process that usually occurs due to acinar cell transdifferentiation or due to pancreatic acinar cells assuming the appearance of ducts, secondary to chronic inflammation and acinar atrophy. Often focal, circumscribed ductules of variable size lined by flat cuboidal epithelial cells are surrounded by normal exocrine acini or are intermixed with pale atrophic exocrine acini. Ductal metaplasia occurs following partial pancreatectomy in rats, pancreatic duct ligation in rats, in Ela-c-myc transgenic rats and TGF-α transgenic mice, and interferon-gamma transgenic mice. Ductular metaplasia with exocrine pancreatic degeneration may be observed following administration of incretin-based therapies in normal (euglycemic) rats and rodent models of acute inflammation of pancreas and/or diabetes, including the transgenic human islet amyloid polypeptide (HIP) rats. Pancreatic acinar-to-ductal metaplasia is induced in rats by chronic ethanol, and following lipopolysaccharide exposure.

Differential diagnoses: **Pancreatic ductal cell hyperplasia**; **Pancreatic acinar cell atrophy**.

Synonym(s): **Pancreatic tubular complexes**.

Pancreatic fatty infiltrate, see the preferred term **Pancreas adipocyte accumulation**.

Pancreatic fibrosis is characterized by stellate cell proliferation and collagen deposition in response to acute or chronic inflammation, pancreatic duct ligation, pancreatic adenocarcinoma, or xenobiotic-induced toxicity. Fibrosis may be focal, lobular, or diffuse as a consequence of degeneration, atrophy, necrosis, and inflammation of the exocrine pancreas. Collagen may be identified by its birefringence under polarized light and can be stained histochemically using Masson's trichrome and van Gieson stains.

Differential diagnosis: **Pancreatic amyloidosis**.

Synonym(s): **Pancreatic interstitial fibrosis**.

Pancreatic focal basophilic cellular change, see the preferred term **Pancreatic basophilic focus of cellular alteration**.

Pancreatic focal cellular change, see the preferred term **Pancreatic basophilic focus of cellular alteration**.

Pancreatic focal eosinophilic hypertrophic cells, see the preferred term **Pancreatic increased peri-insular halos**.

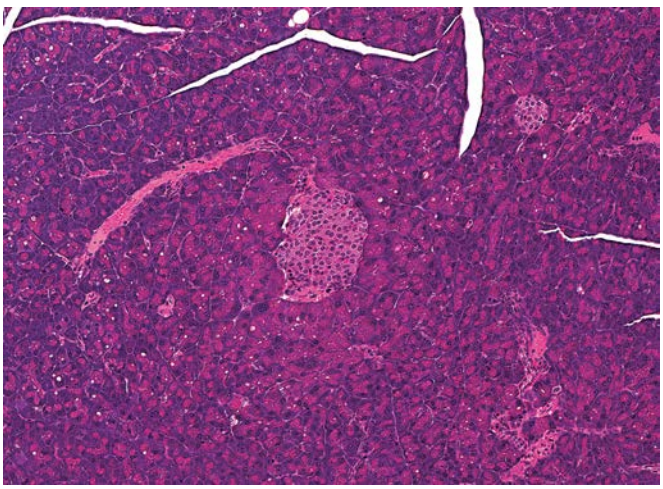
Pancreatic hyalinosis, see the preferred term **Pancreatic eosinophilic globules**.

Pancreatic increased peri-insular halos are characterized by hypertrophy of exocrine pancreatic acinar cells that are located adjacent to the islets of Langerhans, due to an increase in trophic factors, mainly ghrelin and insulin secreted by the

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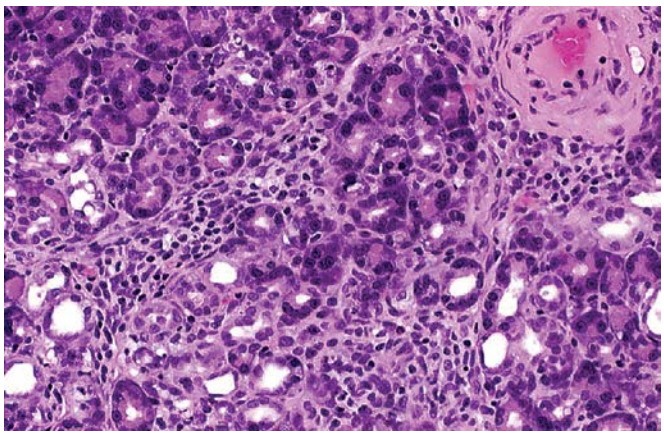
β-cells of the islets. Affected pancreatic acinar cells will have more abundant cytoplasmic volume with larger and possibly more numerous zymogen granules and larger nuclei with greater numbers of nucleoli than acinar cells that are not located adjacent to the islets. The difference in the size of peri- and tele-insular acinar cells is greater in mice than in rats, resulting in more prominent peri-insular halos in mice. Increased peri-insular halos are reported in hyperinsulinemic mice and in rats fed raw soybeans or repeatedly injected with cholecystokinin-pancreozymin (CCK-PZ). Pancreatic increased peri-insular halos must be differentiated from acinar cell hypertrophy.

Synonym(s): **Pancreatic eosinophilic change**; **pancreatic focal eosinophilic hypertrophic cells**; **pancreatic peri-insular hypertrophy**.

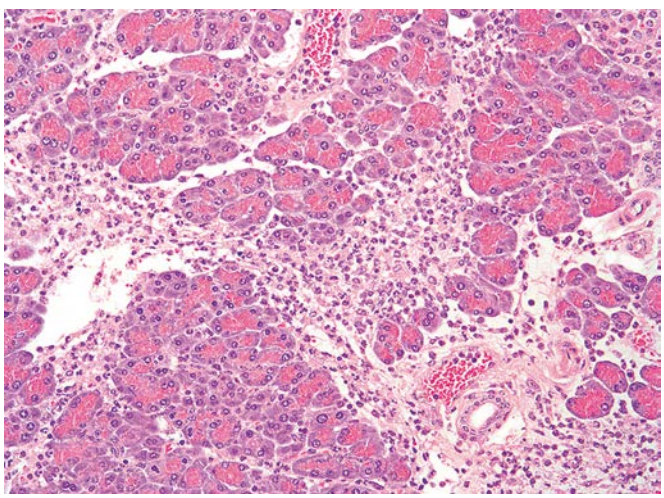


Pancreatic increased peri-insular halos, mouse pancreas, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Nolte, T. et al. 2016. *J Toxicol Pathol* 29(1 Suppl):1S–125S.)

Pancreatic inflammation is characterized infiltration with neutrophils, eosinophils, mononuclear cells, or a combination of more than one type (e.g., mixed cell infiltrates) with additional histological features of inflammation and tissue injury (e.g., hemorrhage, edema, fibroplasia) in the exocrine pancreas. It is uncommon in rats, mice, and dogs. The most common cause of inflammation in the pancreas of aging rats is spontaneous arteritis involving the pancreatoduodenal artery. Inflammation of the pancreas is induced in animal models by a variety of treatments, including dietary manipulation, surgical intervention, and administration of toxins such as choline-deficient ethionine supplements, intraperitoneal injections of arginine, intraperitoneal or intravenous administration of caerulein (a cholecystokinin analogue), administration of a muscarinic receptor agonist (carbachol), anticholinesterases (organophosphates), sodium taurocholate, vascular compromise (hypovolemic shock or occlusion of the pancreatoduodenal artery or splenic and/or gastroduodenal vein), closed duodenal loop procedure, and obstruction of the pancreatic duct or common biliopancreatic duct. Acute inflammation is observed in rodents following administration of several classes of drugs belonging to antimicrobials, antibiotics, diuretics, corticosteroids, estrogens, analgesics/anti-inflammatory agents, statins, anticholinesterases, and highly active antiretroviral therapy (HAART) drugs. Chronic inflammation occurs more commonly in diabetic (BB) Wistar rats than their non-diabetic counterparts. Chronic exposure to manganese causes chronic inflammation, fibrosis (see **Pancreatic fibrosis** for further information), and acinar atrophy (see **Pancreatic acinar atrophy** for further information) in rats. Inflammation of the pancreas has also been described after experimental infection with reo- and Coxsackieviruses. The pathogenesis of inflammation induced by xenobiotics usually involves release of inactive proenzymes from the exocrine pancreas, and activation of these digestive enzymes locally and systemically.



Pancreatic inflammation, mononuclear cells, rat pancreas, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Nolte, T. et al. 2016. *J Toxicol Pathol* 29(1 Suppl):1S–125S.)



Pancreatic inflammation, neutrophils, mouse pancreas, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Nolte, T. et al. 2016. *J Toxicol Pathol* 29(1 Suppl):1S–125S.)

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Differential diagnoses: **Granulocytic leukemia**; **Lymphoma, malignant**; **Pancreatic acinar cell atrophy**; **Pancreatic inflammatory cell infiltrate**; Postmortem autolysis.

Synonym(s): **Pancreatitis**.

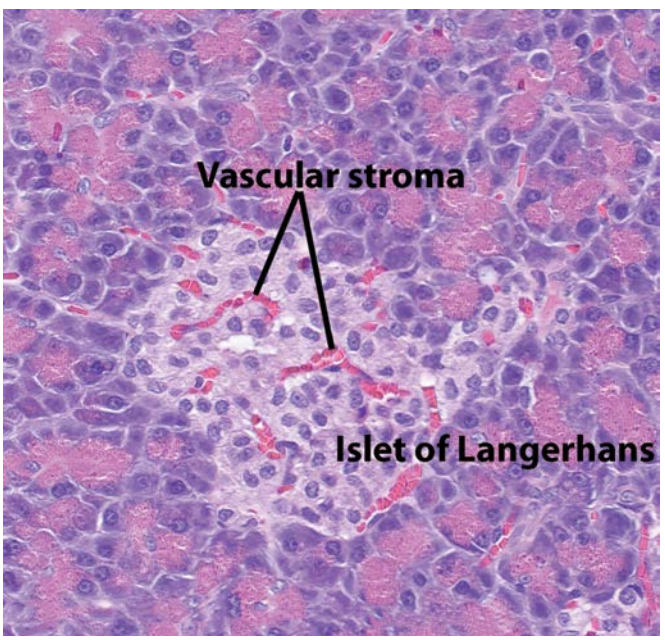
Pancreatic inflammatory cell infiltrate is characterized by presence of accumulation of neutrophils, eosinophils, mononuclear cells, or mixed inflammatory cells in the exocrine pancreas, in the absence of pancreatic tissue injury. It is uncommon in rats, mice, and dogs. Pancreatic inflammatory cell infiltrate is considered different from **pancreatic inflammation**, as the latter includes edema, congestion, or necrosis.

Differential diagnoses: **Granulocytic leukemia**; **Lymphoma, malignant**; **Pancreatic acinar cell atrophy**; Postmortem autolysis.

Pancreatic interstitial fibrosis, see the preferred term **Pancreatic fibrosis**.

Pancreatic islets represent the endocrine pancreas and are composed of small, ovoid clusters of neuroendocrine cells grouped together as islets and scattered throughout the pancreas, also called the islets of Langerhans. In adult animals, the endocrine pancreas comprises ~1–2% of the pancreatic tissue. A normal pancreas in mice will contain between 500 and 800 islets total, ~tenfold less than the human pancreas. The three major cell types in islets are α, β, and δ cells. β cells comprise the majority of the islets and contain insulin-containing secretory granules. α cells contain glucagon secretory granules and δ cells have somatostatin-containing granules within their cytoplasm. Together, these cells function to manage energy consumption, specifically through glucose regulation. See Appendix 3 for more information.

Synonym(s): **Islet of Langerhans**.



Pancreas, islets, beagle dog, H&E.

Pancreatic juxta-insular cells, see the preferred term **Pancreatic peri-insular halos**.

Pancreatic lipomatosis, see the preferred term **Pancreas adipocyte accumulation**.

Pancreatic luminal distension, see the preferred term **Pancreatic duct ectasia**.

Pancreatic oncotic cell death, see the preferred term **Pancreatic zonal necrosis**.

Pancreatic oncotic necrosis, see the preferred term **Pancreatic zonal necrosis**.

Pancreatic peri-insular halos consist of enlarged acinar cells that lie adjacent to the islets of Langerhans. They have a granular, hypereosinophilic cytoplasm due to increased numbers of zymogen granules, and enlarged nuclei. Peri-insular halos are formed when increased concentrations of insulin reach the acini adjacent to the islets of Langerhans via the insulo-acinar portal system, or by diffusion.

Synonym(s): **Pancreatic juxta-insular cells**.

Pancreatic peri-insular hypertrophy, see the preferred term **Pancreatic increased peri-insular halos**.

Pancreatic stellate cells are myofibroblast-like cells that line the basal side of the exocrine acinar cells (see **Exocrine pancreas** for further information). They can modulate between the quiescent and activated phenotypes, similar to hepatic stellate cells (see **Hepatic stellate cells** for further information). Quiescent pancreatic stellate cells produce matrix metalloproteinases, and as such they are proposed to function in matrix turnover. Pancreatic stellate cells, when activated, migrate to the site of injury, and play a major role in tissue repair. They are increasingly recognized to play an important role in pathogenesis of inflammation, fibrosis (see **Pancreatic fibrosis** for further information), and neoplastic conditions of the pancreas.

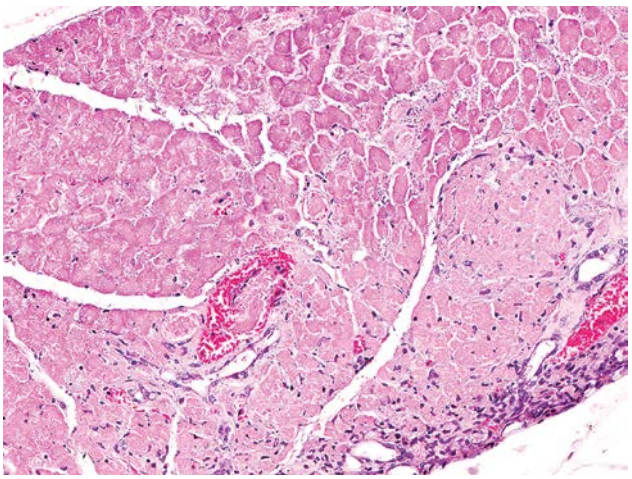
Pancreatic tubular complexes, see the preferred term **Pancreatic exocrine acinar ductular metaplasia**.

Pancreatic zonal necrosis is characterized by focally extensive, lobular or diffuse necrosis of the exocrine acinar cells. The dead cells quickly pass through the stage of coagulative necrosis to liquefaction due to a high content of hydrolytic enzymes that are activated and released by the dying cells into the surrounding interstitial tissue. Necrosis of pancreatic acini develops very rapidly, and the presence of degenerative cells is best recognized within 12–48 hours after the insult. The affected cells are swollen with pale, eosinophilic cytoplasm, loss of nuclear basophilia, pyknosis, and/or karyorrhexis. Minimal or slight inflammatory cell infiltrates, edema, and fibrin may be present as a feature of necrosis.

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Differential diagnoses: **Apoptosis**; **Acute inflammation**.

Synonym(s): **Pancreatic oncotic cell death**; **pancreatic oncotic necrosis**.

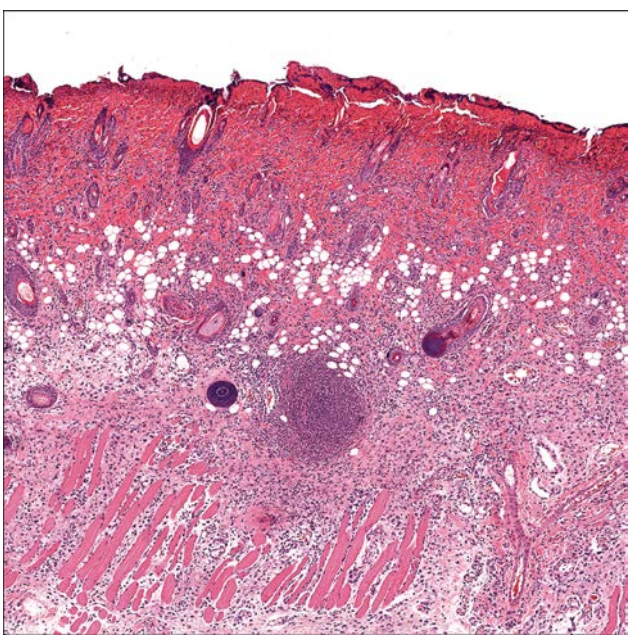


Pancreatic zonal necrosis, mouse pancreas, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Nolte, T. et al. 2016. *J Toxicol Pathol* 29(1 Suppl):1S–125S.)

Pancreatitis, see the preferred term **Pancreatic inflammation**.

Pancytopenia is a decrease below reference range for the species in red blood cell, white blood cell, and platelet counts in the peripheral circulation (i.e., anemia, leukopenia, and thrombocytopenia). It is associated with multiple etiologies ranging from hypersplenism, endocrine disorders, infections, drug administrations, and hematopoietic neoplasia.

Panniculitis is inflammation of the *panniculus adiposus*, the fat layer within the subcutis or hypodermis. (see **Subcutis** for further information). Panniculitis can be caused by infectious agents, subcutaneous injection of foreign substances including vaccines and polypeptides, by trauma, burns, vitamin E deficiency, exocrine pancreas inflammation, exocrine pancreas nodular hyperplasia, cancer, or can be associated with a dysfunctioning immune system. Panniculitis is usually referred to as factitial or artifactual when caused by foreign agents. In dog, there is a specific condition of unknown etiology called canine sterile nodular panniculitis.



Hematoxylin and eosin photomicrograph of rat skin. Panniculitis and transmural inflammation with ulceration.

Panniculus adiposis, see the preferred term **Subcutis**.

Papillary endothelial hyperplasia is a rare papillary proliferative endothelial cell lesion associated with an organizing thrombus primarily found in the subcutis of dogs. The papillary projections are lined by a single layer of plump endothelial cells that have no evidence of pleomorphism, mitotic activity, necrosis, or invasion. Refer to **Cardiovascular System** in Appendix 2 for further information.

Papillary muscles are small muscles attached to the cusps of the atrioventricular valves via the chordae tendineae, and contract to prevent inversion or prolapse of these valves on ventricular contraction.

Papillitis, see the preferred term **Renal papillary inflammation**.

Papilloma, see the preferred term **Squamous cell papilloma**.

Papule is part of the clinical veterinary and medical dermatology terminology that describes a raised, solid focal lesion of the skin with a diameter not exceeding 1 cm. Beyond 1 cm, a papule is called a plaque. The causes underlying papule or plaque formation are diverse and can be hemorrhagic, infectious, neoplastic, or immunologic in origin.

Parafollicular cell hyperplasia, see the preferred term **Thyroid C cell hyperplasia**.

Paraganglioma is a rare neuroendocrine tumor usually associated with the sympathetic nervous system (e.g., carotid and/or aortic bodies). Well-circumscribed polypoid masses are composed of nests of round to oval cells separated by fibrovascular trabeculae. Cytoplasmic neurosecretory granules within the neoplastic cells can be demonstrated with special techniques. Chemodectoma is a commonly used synonym. Refer to **Cardiovascular System** and **Nervous System** in Appendix 2 for further information.

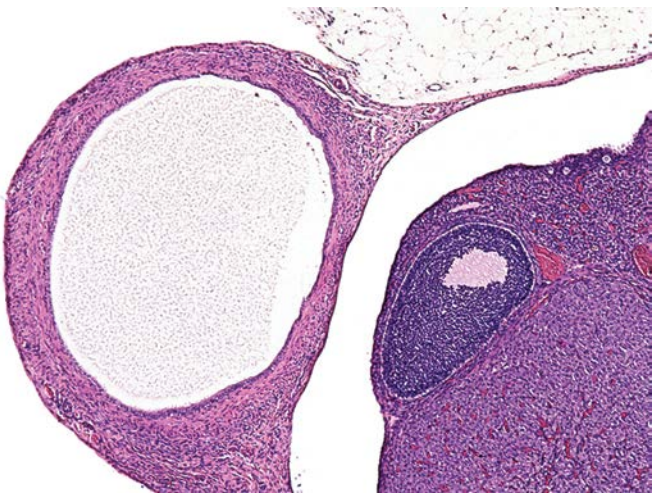
Parakeratotic hyperkeratosis is a subtype of hyperkeratosis where the increased layers of keratinocytes (corneocytes) have retained their nuclei. This is in comparison to orthokeratotic hyperkeratosis where the keratinocytes are more typical in that they are without nuclei. Parakeratosis is normal in the

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mucous membranes lining the mouth or vagina. Otherwise, parakeratosis implies abnormal or rapid turnover of keratinocytes, and is seen in many abnormal skin conditions producing scale, such as in psoriasis. It can also be associated with nutritional imbalances such as zinc deficiency. See **Epidermal hyperkeratosis** and **Orthokeratotic hyperkeratosis** for further information.

Paraovarian cyst is a fluid filled, benign epithelial structure (cyst) adjacent to but not directly connected with the ovary or rete ovarii. These cysts are typically found in the mesovarium or mesosalpinx and are thought to arise from remnants of the mesonephric or paramesonephric ducts. The cyst wall may include smooth muscle, with a cuboidal to columnar lining epithelium that may be ciliated and may become flattened secondary to pressure from a dilated cyst. Paraovarian cysts are relatively common in most species used in toxicity studies.

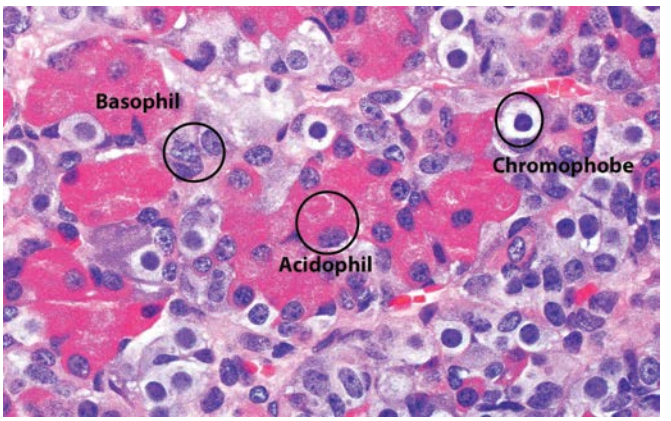
Differential diagnoses: Ovarian follicular cyst; **Luteal cyst**.



Paraovarian cyst, ovary, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Dixon, D. et al. 2014. *J Toxicol Pathol* 26(3 Suppl):1S–107S.)

Pars anterior, see the preferred term **Anterior pituitary gland**.

Pars distalis is an anatomic region of the anterior pituitary gland. The pars distalis produces multiple hormones from three cells types based on their cytoplasmic staining quality when stained with hematoxylin and eosin (H&E): acidophils, basophils, and chromophobes. Acidophils (somatotrophs and luteotrophs) have brightly colored eosinophilic cytoplasm, basophils (gonadotrophs and thyrotrophs) have basophilic cytoplasm, and chromophobes (corticotrophs) have clear cytoplasm. Each cell type produces specific trophic hormones that have target effects on peripheral organs and glands, regulating reproductive and homeostatic body functions, and respond to feedback inhibition from target organs. See Appendix 3 for further information.



Cell types of the pituitary gland pars distalis, cynomolgus monkey, H&E.

Pars distalis adenoma, benign is an adenoma of the pituitary gland pars distalis commonly identified in aging rats, and less commonly in aging dogs and cynomolgus monkeys. See **Endocrine Glands** in Appendix 2 for more information.

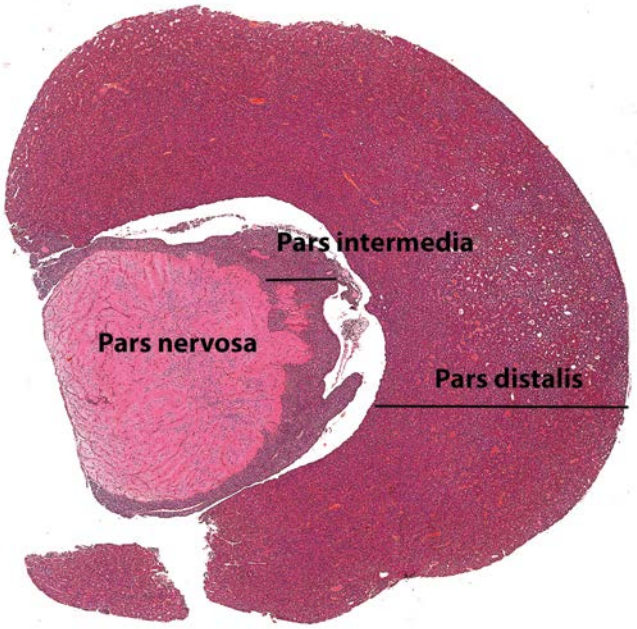
Pars distalis carcinoma, malignant is a rare tumor described in rats and dogs. These tumors have features similar to that of the benign counterpart, but with malignant characteristics, including invasion and replacement of normal architecture and metastasis. See **Endocrine Glands** in Appendix 2 for more information.

Pars distalis, pituitary hyperplasia is characterized by increased numbers of cells of normal morphology within the pars distalis. See **Endocrine Glands** in Appendix 2 for more information.

Pars distalis, pituitary hypertrophy is characterized by enlargement of cells comprising the pituitary pars distalis having cytoplasmic pallor and may be noted in conjunction with hyperplasia. See **Endocrine Glands** in Appendix 2 for more information.

Pars intermedia is an anatomic region of the anterior pituitary gland responsible for the manufacture and secretion of trophic hormones. Although not all mammals have the pars intermedia, it is present in those species commonly used in toxicological studies. In general, the pars intermedia consists of densely packed cells within lobules separated by scant fibrovascular stroma. The melanotroph is the primary cell of the pars intermedia that converts proopiomelanocortin (POMC) to melanocyte-stimulating hormone (MSH) and β-endorphin. Corticotroph cells make up a smaller cell population of the pars intermedia, and generally produce peptides, but the complete function of their products remains poorly understood. Last, glial-like cells transmit neural input from the central nervous system (CNS) to the pars intermedia, exerting influence over melanotroph secretions. See Appendix 3 for more information.

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Pars intermedia (between the pars distalis and pars nervosa), minipig, H&E.

Pars intermedia, pituitary hyperplasia is characterized by an increase in number of cells of the pars intermedia. See **Endocrine Glands** in Appendix 2 for more information.

Pars nervosa, see the preferred term **Posterior pituitary gland**.

Pars nervosa, pituitary tumor, see the preferred term **Pituicytoma**.

Pars tuberalis is the anatomic region of the anterior pituitary gland that extends from the median eminence of the brain to the pituitary gland proper. It contains an intricate vascular network extending from the hypophyseal artery that releases hormones generated by the hypothalamus to the anterior subdivisions of the pituitary gland (pars intermedia and pars distalis).

Synonym(s): **Pituitary stalk**.

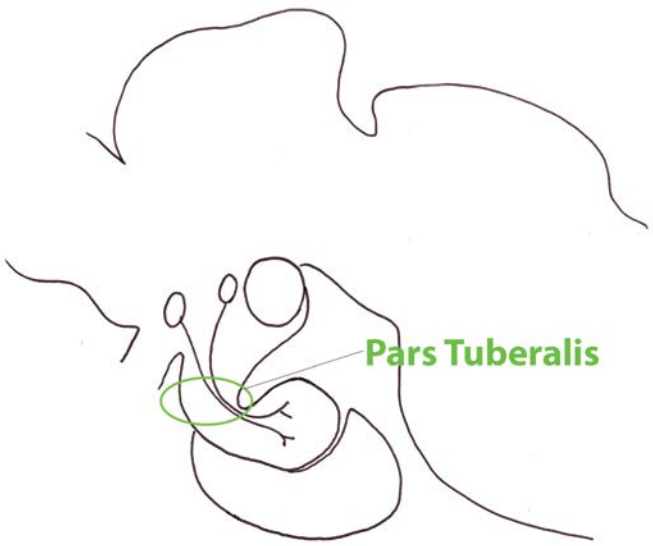
Passive avoidance is a type of conditioning where the individual or animal will experience a negative stimulus if it engages in a certain activity. If the animal does not take action (passive), the individual will avoid the negative internal or external stimuli (e.g., electric shock). In classic behavioral psychology, it is used as a method of evaluating associative learning and memory.

P53 tumor suppressor gene is the p53 gene code for a protein that regulates the cell cycle as a cell-cycle check point, thus functioning as a tumor suppressor. P53 is also known as the "guardian of the genome" due to its role in preventing genetic mutations and genetic instability. When the p53 gene is mutated, the cells grow uncontrollably and may eventually accumulate additional mutations that lead to tumor formation. A transgenic mouse which is heterozygous for a functional p53 gene (p53±) has been developed to be used as a replacement for the wild type mouse in carcinogenicity testing. As expected, this mouse model is sensitive to genotoxic carcinogens.

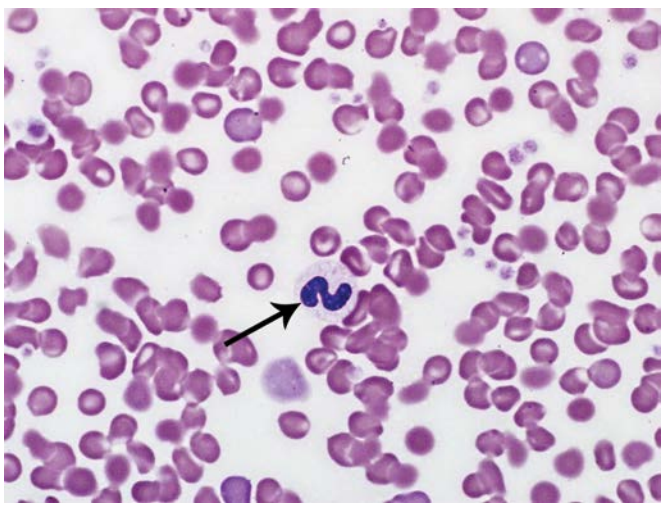
PCR is an acronym for polymerase chain reaction. See **Polymerase chain reaction** for further information.

Pectinate ligament dysplasia, see the preferred term **Filtration angle malformation**.

Pelger-Huët anomaly is an inherited condition reported in mice, rabbits, dogs, and humans caused by a mutation in the gene encoding for the lamin B receptor, and is responsible for abnormal trafficking of heterochromatin and nuclear lamins



Location of the pars tuberalis extending from the hypothalamus to the anterior pituitary gland.



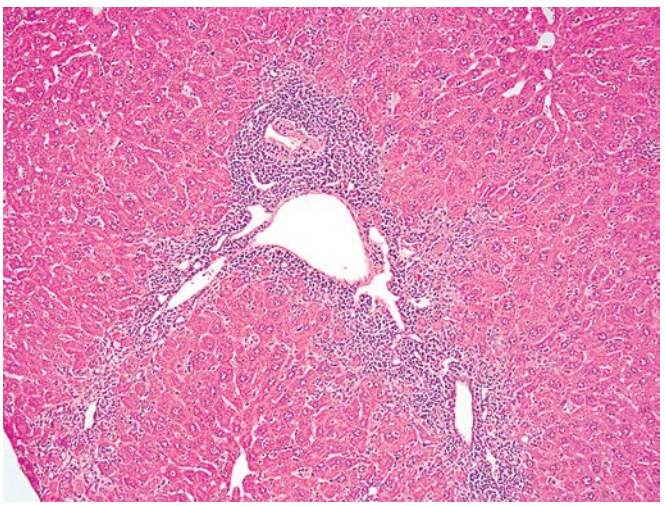
Pelger-Huët anomaly (neutrophil hyposegmentation; arrow), peripheral blood smear, dog.

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involved in shaping of the nuclear membrane. Affected animals have granulocyte hyposegmentation characterized by an immature nuclear shape (band or myelocyte) with a mature chromatin pattern. Animals with Pelger-Huët anomaly are healthy and granulocytes function normally. Identification of Pelger-Huët anomaly is important in order to differentiate this condition from a left shift associated with inflammatory disease. Pseudo-Pelger-Huët anomaly is an acquired hyposegmentation of granulocytes that is secondary to myeloid neoplasia (especially myelodysplastic syndrome), infections, or drug therapy (e.g., tacrolimus, rituximab, citalopram, lorazepam, and ibuprofen).

Peliosis hepatis, see the preferred term **Hepatic angiectasis**.

Peribiliary (intrahepatic) infiltration is characterized by the accumulation of inflammatory cells (usually lymphocytes and plasma cells) in varying numbers in the portal areas of the liver. The infiltration may be accompanied by fibrosis and/or bile duct hyperplasia in some cases. It has been observed in rats and mice and may occur as a background lesion associated with aging, but both incidence and severity may be increased by treatments. (e.g., 3,5-diethoxycarbonyl-1,4-dihydrocollidine, α-naphtylisothiocyanate).



Peribiliary (intrahepatic) infiltration, mouse liver, H&E. (Reproduced with permission of the Society of Toxicologic Pathology from Thoolen, B. et al. 2010. *Toxicol Pathol* 38(7 Suppl):5S–81S.)

Pericardial mesothelial hyperplasia describes multiple layers of mesothelial cells lining the pericardial sac, often associated with inflammation and/or effusions. The cells are typically cuboidal, have minimal supporting stroma, and exhibit no nuclear atypia or evidence of invasion. Typically, the cells do not protrude into pericardial cavity, but infrequent papillary projections can be noted.

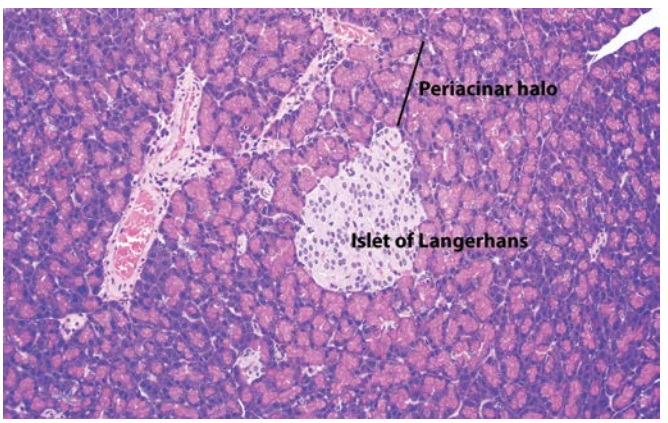
Pericardial mesothelioma is a pleomorphic neoplasm that arises from the mesothelial lining cells of the pericardial sac. Morphologically, they can be epithelioid, sarcomatoid, or biphasic, may be exophytic or plaque-like, and show evidence of increased mitotic rate and invasion. Refer to **Cardiovascular System** in Appendix 2 for further information.

Pericardium is a protective fibrous sac composed of an inner double layer of serous membrane (visceral) and outer fibrous (parietal) layer. The parietal layer is attached to the aorta and pulmonary artery dorsally, and to the sternum ventrally. The visceral layer invaginates to also form the epicardium of the heart. The space between the visceral and parietal pericardium contains a small amount of serous fluid that acts as a lubricant to allow normal heart movement.

Periductular inflammation is characterized by infiltration of single populations or mixed populations of leukocytes around and into ducts, in the presence of other indicators of inflammation such as edema, congestion, and cellular necrosis and debris. **See Duct-associated lymphoid tissue (DALT)**.

Periductular inflammatory cell infiltrate, see preferred term **Duct-associated lymphoid tissue (DALT)**.

Peri-insular halo is a region of pancreatic acinar cells immediately adjacent to the islets of Langerhans. Trophic and stimulatory insulin effects are reflected by particularly large peri-insular acinar cells packed with zymogen granules, the so-called "halo phenomenon." The cells of the peri-insular acini have larger nuclei and zymogen regions and are refractory to the secretion stimulating action of pilocarpine, in contrast to the cells of the common acini (the halo phenomenon). The halo phenomenon is lost in diabetes mellitus, and is not restored by exogenous insulin administration, probably because the physiologically high insulin concentrations in the insulo-acinar portal system, and particularly in the peri-insular region, cannot be reestablished.



Peri-acinar halo surrounding the islet of Langerhans, pancreas of the rat, H&E.

Perinatal period is the stage of development of the individual around birth.

Perineurium is composed of multiple layers of specialized fibroblasts with tight junctions and a basement membrane surrounding bundles of axons within peripheral nerves. These tight junctions are the primary constituent of the blood-nerve barrier.

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Periodontal pocket is an opening between the periodontium and tooth in which food particles and debris may accumulate. The tissue can become inflamed around this impacted material and bacteria can also be present. This lesion must be discerned from a cyst, which does not connect with the oral cavity or contain foreign material.

Differential diagnosis: Periodontal cyst.

Peripheral nervous system (PNS) is composed of the peripheral nerves and ganglia.

Periportal necrosis, see the preferred term **Hepatocellular zonal necrosis**.

Peripuberty refers to a period beginning with the initiation of hormonal and physical changes associated with sexual maturation,and continues until full reproductive potential (i.e., regular estrous cycling or sperm production) is achieved. Using peripubertal male animals can be especially challenging for the toxicologic pathologist in nonhuman primate (NHP), dog, and minipig studies. In the minipig, the large size and volume of Leydig cells (LC) in the interstitial compartment increases with age and can be quite variable in peripubertal animals (3–4 months of age) such that the more mature animals can appear to have LC "hyperplasia" when compared with the less mature animals. For NHPs and dogs, peripuberty is characterized by partial expansion of the epididymal caudal duct, few epididymal sperm in the corpus and none in the cauda, and frequent degenerate/multinucleated germ cells in the testis. In these species, the fact that maturing and peripubertal testes may be indistinguishable from testes undergoing toxicant-induced degeneration, peripuberty may mask a toxicant-induced lesion or simulate testicular toxicity.

Perisinusoidal fat-storing cell is normally present in the extrasinusoidal space of Disse in the liver. In its resting state, it is characterized by the presence of lipid vacuoles that are empty following tissue processing, due to the use of solvents in preparation for paraffin embedding. These vacuoles represent a site of storage of fat-soluble vitamin A. When activated, these cells lose their vacuoles and differentiate into collagen-producing myofibroblasts. As such, they are important participants in the process of hepatic fibrosis. In the perisinusoidal space, the deposition of collagen matrix has negative consequences for hepatocellular uptake from, and secretion into, the blood.

Synonym(s): **Ito cell**.

Perisinusoidal fat-storing cell hyperplasia, see the preferred term **Ito cell hyperplasia**.

Perisinusoidal space, see the preferred term **Space of Disse**.

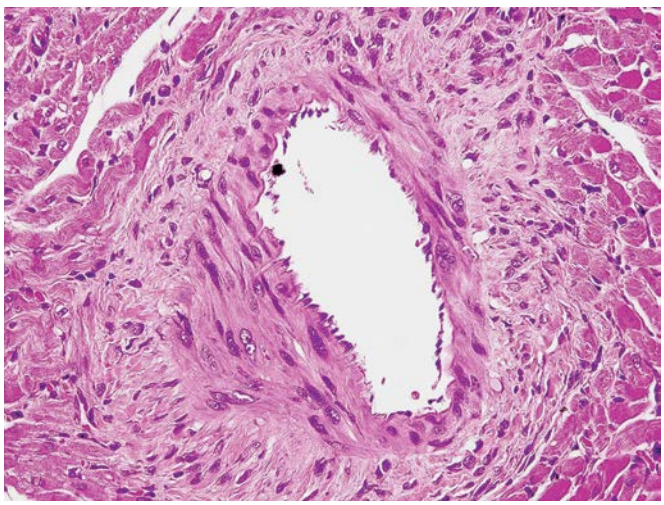
Peritoneal inflammation is an inflammatory change in the tissue that lines the inner surface of the abdominal wall and most of the abdominal organs. Peritonitis may be localized or generalized and can result from local organ infection or from a noninfectious process such as severe ulceration secondary to a tumor.

Synonym(s): **Peritonitis**.

Peritonitis, see the preferred term **Peritoneal inflammation**.

Peritubular myoid cell is a myofibroblast-like cell that surrounds the seminiferous tubules of the testis, providing structural support, producing the basement membrane, and communicating with Sertoli cells to help enable normal testicular development and eventual spermatogenic progression.

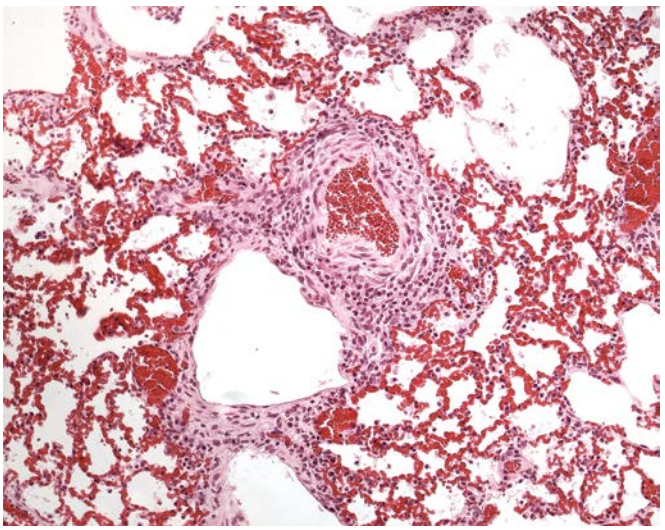
Perivascular fibrosis occurs in small to medium-sized arteries subjected to increased pressure over time. Histologically, fibroblasts proliferate around the blood vessel, creating an "onion-skin" appearance. This change can develop with continuous intravenous infusion at high pressures and is also induced by agents that produce hemodynamic stress, such as angiotensin inhibitors. Extension of inflammatory changes of the vessel wall into the adventitia can also induce fibroblast proliferation. Perivascular fibrosis can be accompanied by mural hypertrophy and hyperplasia, both of which increase the vessel's ability to withstand stress.



Perivascular fibrosis; in vessel of rat treated with angiotensin II, H&E. (Image courtesy of the National Toxicology Program; Reproduced with permission of the Japanese Society of Toxicologic Pathology.)

Perivascular inflammatory cell infiltrate is the surrounding of a vessel by inflammatory cells, which are often a mixed population. This may be part of a disease process in the vessel itself with degeneration/necrosis, or damage in the wall of the vessel. It is also seen as part of a disease process in the tissue in which it is present. In addition, with some compounds that cause drug-induced vascular injury, perivascular injury can be the first microscopic change observed in advance of eventual actual vascular involvement.

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Perivascular inflammatory cell infiltrate, lung, rat, H&E.

Permitted daily exposure (PDE) is used in pharmaceutical development to define the permitted daily intake of an impurity in the drug substance or drug product. As described in the ICH Q3 guidance, the PDE is derived from the no adverse effect level (NOAEL) in the most relevant toxicity study using the equation:

$$PDE = (NOAEL \times \text{weight adjustment})/(F1 \times F2 \times F3 \times F4 \times F5)$$

The human weight adjustment uses 50 kg as standard body weight, this low value is selected to be on the conservative side.

F1 = A factor to account for extrapolation between species
F1 = 5 for extrapolation from rats to humans
F1 = 12 for extrapolation from mice to humans
F1 = 2 for extrapolation from dogs to humans
F1 = 2.5 for extrapolation from rabbits to humans
F1 = 3 for extrapolation from monkeys to humans
F1 = 10 for extrapolation from other animals to humans
F2 = A factor of 10 to account for variability between individuals
F3 = A variable factor to account for toxicity studies of short-term exposure
F3 = 1 for studies that last at least one half-lifetime (1 year for rodents or rabbits; 7 years for cats, dogs, and monkeys)
F3 = 1 for reproductive studies in which the whole period of organogenesis is covered
F3 = 2 for a 6-month study in rodents or a 3.5-year study in non-rodents
F3 = 5 for a 3-month study in rodents or a 2-year study in non-rodents
F3 = 10 for studies of a shorter duration
F4 = A factor that may be applied in cases of severe toxicity (e.g., nongenotoxic carcinogenicity, neurotoxicity or teratogenicity)

In studies of reproductive toxicity, the following factors are used:

F4 = 1 for fetal toxicity associated with maternal toxicity
F4 = 5 for fetal toxicity without maternal toxicity
F4 = 5 for a teratogenic effect with maternal toxicity
F4 = 10 for a teratogenic effect without maternal toxicity
F5 = A variable factor that may be applied if the NOEL was not established

When only an LOEL is available, a factor of up to 10 could be used depending on the severity of the toxicity.

Peroxisome proliferation is the microscopic and/or ultrastructural observation of increased numbers of peroxisomes (organelles found in all eukaryotic cells involved in fatty acid catabolism and other oxidative processes) typically found in the hepatocytes of mice and rats treated with a broad spectrum of agents known to be peroxisome proliferators, including phthalate esters and fibrates. See **Hepatic peroxisome proliferation** for further information.

Persistence, X zone, see the preferred term **Adrenal gland X zone persistence**.

Persistent embryonic lens vasculature, see the preferred term **Vitreal persistent fetal vasculature (PFV)**.

Persistent hymen, see the preferred term **Vaginal imperforation**.

Persistent pupillary membranes, see the preferred term **Vitreal persistent fetal vasculature (PFV)**.

Persistent pupillary strands, see the preferred term **Vitreal persistent fetal vasculature (PFV)**.

Petechia is a round, flat, pinpoint red spot under the skin surface caused by intradermal hemorrhage. Slightly larger but less than 1 cm hemorrhage is called a purpura, and hemorrhage 1 cm or larger is called an ecchymosis.

Peyer's patches are mucosa-associated lymphoid tissue (MALT) within the submucosa and lamina propria of the small intestine along the antimesenteric border. Peyer's patches are constitutive MALT, present in utero, and easily form germinal centers after antigenic exposure. Peyer's patches are one form of gut-associated lymphoid tissue (GALT). See Appendix 3, **Gut-associated lymphoid tissue (GALT)**, and **Mucosa-associated lymphoid tissue (MALT)** for further information.

p-Glycoprotein (pGP) is a drug transporter (ATP-cassette binding transporter) that is responsible for the active excretion of a variety of drugs from intestinal epithelial cells and at the blood-brain barrier. See **Drug transporters** and **ATP-binding cassette transporters** for further information.

Phacoclastic uveitis is a clinical term referring to rupture of the lens and inflammation into the lens; see the preferred term **Lens inflammation**.

Pharmacodynamics (PD) is the study of drug effects on an organism. The drug effect is the result of how the drug's

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chemistry and the subject's physiology interact to yield the specific effect. This is in contrast to pharmacokinetics (PK), which focuses on the properties of absorption, distribution, metabolism, and elimination (ADME) in relation to the administration route of a chemical or experimental compound. Together these are used to determine the best approach for selecting a dose, dose frequency, and dosing scenario (e.g., with or without food, AM or PM, etc).

Pharmacogenetics is the study of the genetic differences that affect a person's response to a particular drug, often as a consequence of differences in the enzymes responsible for the metabolism of the drug; for example, individuals with a mutation in the cyp2D6 gene are unable to metabolize the drug debrisoquine and consequently are more prone to that drug toxicity. The cyp2D6 polymorphism was the first to be recognized. It is now common in the drug discovery phase to determine the enzymes responsible for the metabolism of a drug candidate to de-risk potential problems associated with metabolism by polymorphic enzymes. Genetic differences may also occur in a drug target (e.g., enzyme receptor) that can also lead to marked differences in individual responses to modulation of that drug target.

Pharmacokinetics is the study of the relationships between the movement of drugs through the body and the processes acting on them. It is a discipline that describes the time-course of the movement of a drug into, around, and out of the body.

Pharmacovigilance involves activities related to the detection, assessment, understanding, and prevention of adverse effects of drugs. It is the term used for post-marketing drug safety surveillance that relies heavily on case reports of adverse events as reported by physicians and patients, but also encompasses reviews of clinical and nonclinical literature. Guidelines and legislation require that drug market authorization holders report severe adverse events collected in this manner to the respective regulatory authorities. All case reports are also summarized and assessed on a regular basis in periodic safety updates, which are forwarded to the authorities. Pharmacovigilance reports may lead to alteration of the risk-benefit assessment for a drug, resulting in drug label changes or even withdrawal of a drug from the market.

Pharyngeal inflammation is an inflammatory change in the tissue lining the posterior portion of the oral cavity lumen that includes the opening of the esophagus and larynx.

Synonym(s): **Pharyngitis**.

Pharyngeal tonsil, see the preferred term **Nasopharyngeal tonsil**.

Pharyngitis, see the preferred term **Pharyngeal inflammation**.

Pharyngoesophageal diverticulum, see the preferred term **Esophageal diverticulum**.

Phase 1 reactions involve oxidation, reduction, or hydrolysis of a drug, and are catalyzed by enzymes such as cytochrome P450, flavine-containing monooxygenases, peroxidases, monoamine oxidases, aldehyde oxidase, xanthine oxidase, and dehydrogenases (alcohol and aldehyde), aldo-keto reductases, azo-reductases, epoxide hydrolase, and a variety of esterases and amidases. See **Drug metabolism** for further information.

Phase 2 reactions is a term used for conjugation reactions such as glucuronidation, glutathione conjugation, and amino acid conjugation in the process of drug metabolism. See **Drug metabolism** for further information.

Phase 3 metabolism is a term applied to transport of drugs and metabolites across cell membranes into and out of tissues. See **Drug transporters** and **Drug metabolism** for further information for further information.

Phase I clinical trial is the first clinical test of a drug usually on healthy subjects to assess safety, tolerability, and pharmacokinetics of the compound. Such trials generally include single ascending dose (SAD) and multiple ascending dose (MAD) portions. In the SAD phase, small cohorts of 8–12 subjects are initially given an experimental drug at a very low dose or a placebo. If the drug is well tolerated, it is administered in increasing doses to different cohorts until the maximal foreseen dose is reached or there are tolerability issues. Based on the results of this study, doses are selected for the multiple-dose phase in which daily doses are given for a limited period of time. If the initial dose is well tolerated, increasing dose levels are given to different cohorts, tolerability and pharmacokinetics are monitored in these studies; biomarkers of efficacy may also be monitored. The doses for subsequent Phase II clinical studies are selected based on the results of these Phase I studies.

Phase II clinical trial is generally the first clinical trial in patients. The experimental drugs are usually administered over 3–6 months at several dose levels to cohorts of 20–100 patients. The studies are designed to demonstrate initial clinical efficacy, and to select doses for larger pivotal trials. They also contribute to the continued collection of clinical safety data.

Phase III clinical trial is a more extensive clinical trial conducted under conditions that reflect daily clinical use of the experimental drug. Such a trial generally involves large patient cohorts, a limited number of doses, and may also contain comparator cohorts receiving the standard disease therapy. Generally, two such pivotal trials are required for drug registration. The trials should demonstrate the efficacy of the drug in a disease population and the benefit against the current standard therapy, if such therapy exists. They are also the main safety studies that determine the risk-benefit assessment of the therapy. Duration of a Phase III clinical trial is variable depending upon the disease outcome to be monitored, but can be up to several years.

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Phase IV clinical trials are any clinical trial performed with a marketed drug after registration, to enhance knowledge of the use or safety of the drug within the approved indication.

Pheochromocytoma, benign is a neuroendocrine neoplasm of the chromaffin cells from the adrenal medulla. See **Endocrine Glands** in Appendix 2 for more information.

Pheochromocytoma, malignant is a neuroendocrine neoplasm of the chromaffin cells from the adrenal medulla with increased pleomorphism or atypia, and an increased mitotic rate as compared to the benign counterpart. See **Endocrine Glands** in Appendix 2 for more information.

Phospholipidosis is the accumulation of phospholipid-xenobiotic complexes within lysosomes of various cell types. This accumulation occurs due to drug-induced disruption of the normal removal of cell membrane components. These phospholipid-containing complexes appear on routine hematoxylin and eosin (H&E) sections as cytoplasmic vacuoles. Confirmation of these whorled structures, termed "multilamellar bodies," is conducted via ultrastructural analysis and/or with immunohistochemical staining for LAMP-2. Cationic amphophilic compounds can produce this lesion. See **Multilamellar bodies** for further information.

Differential diagnoses: **Fatty change**; **Glycogen accumulation**.

Photoallergy test is a photosafety assay which is conducted to evaluate an immunologically mediated reaction to a chemical initiated by the formation of photochemicals acting as, or producing, antigens. According to ICH S10, "for dermal products where the API or any new excipient has a MEC (Molar Extinction Coefficient) value greater than 1000 L/mol/cm at any wavelength between 290 and 700 nm, a photoallergy assessment is generally warranted in addition to phototoxicity testing. As the predictivity of nonclinical photoallergy tests is unknown, this would typically be a clinical assessment using the to–be-marketed formulation and conducted during Phase 3." EMEA 2002 guidance mentions the use of a guinea pig photoallergy test and in vitro models but qualifies these as having limited validation. Photoallergy tests for systemically-administered drugs or chemicals and photogenotoxicity testing are not considered warranted under ICH S10.

Photoreceptor displaced nuclei, see the preferred term **Retinal photoreceptor nuclei displacement**.

Phototoxicity is defined as the pathological consequences of the action of ultraviolet radiation on photoreactive compounds. Photoreactive chemicals absorb light at wavelengths between 290 and 700 nm. These chemicals can be locally applied or distributed to the skin after systemic administration. Light absorption usually occurs after sun exposure but can also be observed after exposure to artificial light. The absorbed light through energy transfer results in the generation of reactive oxygen and nitrogen species responsible for the pathology observed. If the light is absorbed by the administered chemical or metabolites, the toxicity is called direct phototoxicity, while generation of endogenous photoreactive compounds (e.g., porphyrin) is called indirect phototoxicity. Compounds such as sparfloxacin and other fluoroquinones or 8-methoxypsoralen are known photoreactants. Clinically, acute phototoxicity generally manifests after a few hours and can last for a few hours to a few days. The classic acute reaction of phototoxicity is erythema, edema, and hyperkeratosis and flaky skin involving the light-exposed regions of the body followed by desquamation, erosions, ulcerations, and/or hyperpigmentation. Under the microscope, affected areas of the skin show epidermal and/or dermal edema, congestion, hemorrhage, and inflammation associated with erosions, ulcerations, epidermal degeneration, and necrosis. The presence of intraepidermal inflammatory cells in the form of transmigrating cells, pustules, or superficial serocellular crusts, hyperkeratosis and increased melanin secretion, with or without pigmentary incontinence, can also be observed. Chronic repeated light exposure involving coal tar, psoralens, and fluoroquinones can lead to neoplastic changes in animals.

Phototoxicity tests are any number of photosafety tests to evaluate the potential of a drug or chemical to produce toxicity following photoactivation. They are best described in ICH S10 (Photosafety Evaluation of Pharmaceuticals), using the criteria for phototoxicity and/or photoallergy testing as any chemical that:

- absorbs light within the range of natural sunlight (290–700 nm);
- generates a reactive species following absorption of UV-visible light;
- distributes sufficiently to light-exposed tissues (e.g., skin, eye);

Tests include chemical assays (e.g., reactive oxygen species [ROS]), in vitro assays (e.g., 3T3 neutral red uptake phototoxicity test [3T3 NRU-PT], endorsed by OECD), and in vivo systemic and local (dermal) short-term administration studies in rodents with (and without) irradiation. A decision-tree approach is recommended, with in vitro testing possibly eliminating the necessity of follow-up in vivo test, depending on the results obtained and acceptability of the test system employed.

Phthisis bulbi is a terminal state after damage to the eye causes atrophy, distortion of ocular compartments, and destruction of the ocular tissues, thickened posterior sclera, and macroscopic shrinkage of the globe. Intraocular mineralization is common, and bone or cartilage metaplasia sometimes occurs. Causes include severe ocular insults such as trauma, retrobulbar blood sampling, infections, autoimmunity, neoplasia, and surgery.

Differential diagnoses: **Microphthalmia**; **Anophthalmia**. See **Harderian gland adenocarcinoma** for illustration.

Physeal atrophy, see the preferred term **Physeal thickness decreased**.

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Physeal dysplasia is alteration of the organization of chondrocytes in the physis of growing animals with or without a concurrent change in the thickness of the physis. There can also be abnormal cartilage matrix formation and fracture observed with this finding. Special stains are useful to assess for matrix alteration (e.g., toluidine blue, safranin O). Administration of compounds associated with increased physeal thickness can also cause physeal dysplasia, including VEGF inhibitors and MMP inhibitors.

Synonym(s): **Cartilage dysplasia**.

Physeal dystrophy, see the preferred term **Physeal thickness decreased**.

Physeal expansion, see the preferred term **Physeal thickness increased**.

Physeal hypertrophy, see the preferred term **Physeal thickness increased**.

Physeal thickness decreased occurs if the normal progression of physeal chondrocyte proliferation or hypertrophy is impaired. Physes are at their thickest during bone development and become thinner as bone growth slows as an animal approaches its adult size. Decreased chondrocyte proliferation is the most common cause of decreased physeal thickness. Inanition, corticosteroids, and elevated FGF-21 (leading to decreased IGF-1) can all lead to decreased physeal thickness. Longitudinal bone growth will be impaired. Decreased physeal thickness is easiest to appreciate in the proximal tibial physis and the costochondral junction in the rib.

Synonym(s): **Physeal dystrophy**; **physeal atrophy**.

Physeal thickness increased occurs in growing animals with an open growth plate and indicates a failure of the transition from hypertrophic chondrocytes at the growth plate into primary spongiosa. A multitude of mechanisms can impair this process including VEGF inhibitors, MMP inhibitors, and other tyrosine kinase inhibitors. The growth plate can be dramatically thickened with loss of normal orthogonal chondrocyte orientation (physeal dysplasia). Removal of the cause of impairment can also lead to a dramatic resolution of the increased thickness, although some irregularity in chondrocyte orientation may remain.

Synonym(s): **Physeal hypertrophy**; **physeal expansion**; **endochondral hypertrophy**.

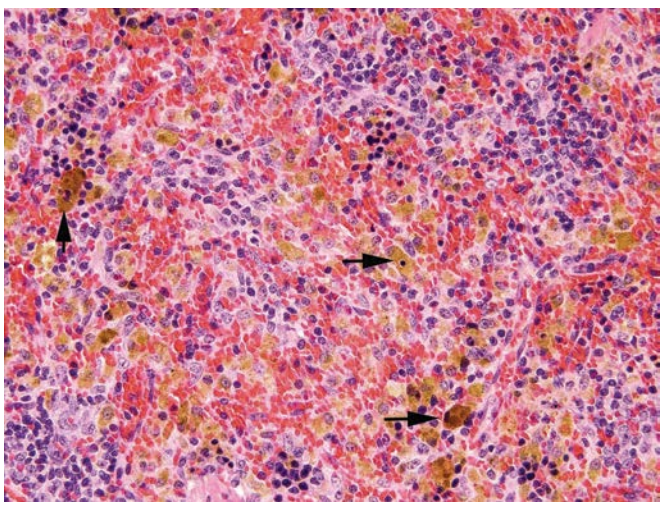
Physiological effects affecting toxicity study outcomes can refer to either (1) the effects of aging/maturation, or (2) to the alteration of normal physiological processes by chronic administration of a drug or chemical, ameliorating or potentiating adverse effects in a given species. Examples of (1) include age-related effects on reproductive organ target toxicities, or metabolism of drugs to inactive or reactive species, and (2) thyroid adenomas in rats as a result of chronic administration of drugs or chemicals that induce microsomal UDP-glucuronyl transferases responsible for thyroxine metabolism in rodents. Further examples include mammary tumors in rodents that are considered related to physiologic increases in serum prolactin from age-related pituitary neoplasms that may be exacerbated by chronic administration of drugs or chemicals that alter circulating prolactin, and an age-related increased incidence of hyaline droplet nephropathy in male rats that may become more pronounced with chronic treatment of an otherwise non-nephrotoxic agent.

Physiological tolerance describes an observed phenomenon, where after repeated exposure to a drug or chemical, larger doses are required to produce the desired effect. This has been observed with several classes of chemicals such as analgesics, drugs, pesticides, and toxins. It can be caused by receptor down-regulation, which reduces the ability to respond, or enzyme induction, which increases the clearance of the drug (e.g., carbamazepine).

Physis is the growth plate of bone where new bone is created through a process called endochondral ossification, contributing to longitudinal growth. The normal physis in skeletally immature animals is complex and composed of multiple cell types arranged in an orderly manner that participate in this ossification process. The physis of young rodents is an important system where compound-mediated bone growth changes may be observed and should be included for evaluation in toxicology studies.

Pigment is material that imparts color to tissues or cells. Examples include endogenous (e.g., melanin, hemosiderin, lipofuscin), and exogenous (e.g., tattoo components, carbon dust, dietary carotenoids) materials. See **Ceroid pigment**; **Hemosiderin pigment**; **Lipofuscin pigment**; and **Wear and tear pigment** for further information.

Pigment accumulation is an intracellular accumulation of pigmented material. The pigment may be endogenous or exogenous. Endogenous pigments are typically byproducts of cellular metabolism, such as lipofuscin, bilirubin, or hemosiderin. These pigments are most often brown to yellow, and

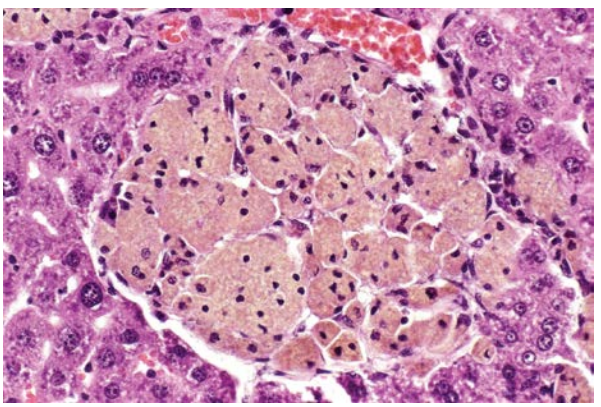


Pigment accumulation in the spleen of a rat, H&E. Arrows indicate macrophages with brown pigment accumulation (hemosiderin). (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

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granular to globular. Special stains are required to definitively identify the pigment. There are a wide variety of exogenous pigments resulting from pharmacological or environmental xenobiotics. The color, shape, and location of the pigment depends on the xenobiotic. See also **Pigment**; **Wear and tear pigment**; **Hemosiderin pigment**; **Ceroid pigment**; and **Lipofuscin pigment** for further information.

Pigmented macrophage is characterized by an intracytoplasmic accumulation of pigment particles or clumps that may be due to accumulation of drug or its metabolites, phagocytosis of cellular pigments or debris, or secondary to a breakdown of phagocytosed cells or materials within macrophage lysosomes, particularly in the spleen, liver, lymph node sinuses and mucosa-associated lymphoid tissue (MALT), or in reactive tissue-resident macrophages in tissues and body compartments. Hemosiderin secondary to hemorrhage, inhaled carbon, and tattoo ink as an incidental finding and melanin (in pigmented animals) or lipofuscin increases during aging are the most common intracytoplasmic pigments. Special histochemical stains for iron, lipids, copper, and carbohydrates, immunohistochemistry, and imaging mass spectrometry may assist in identification of these pigments in tissues. See **Hemosiderin pigment** and **Wear and tear pigment** for further information.

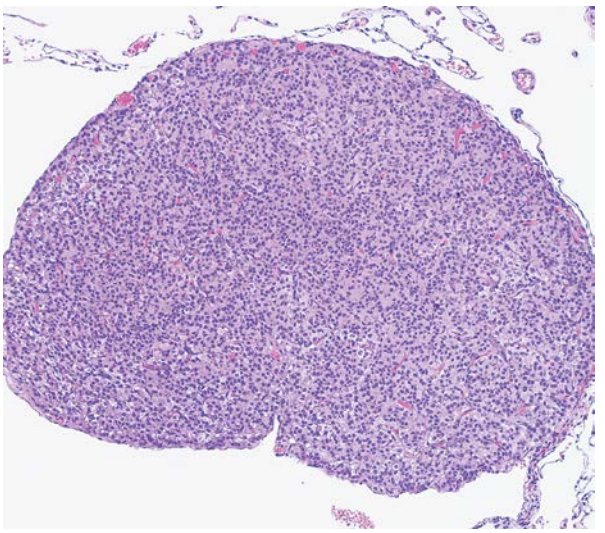


Pigmented macrophages in the liver of a rat, H&E. Macrophages are distended with amorphous to globular golden-brown pigment within the cytoplasm. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

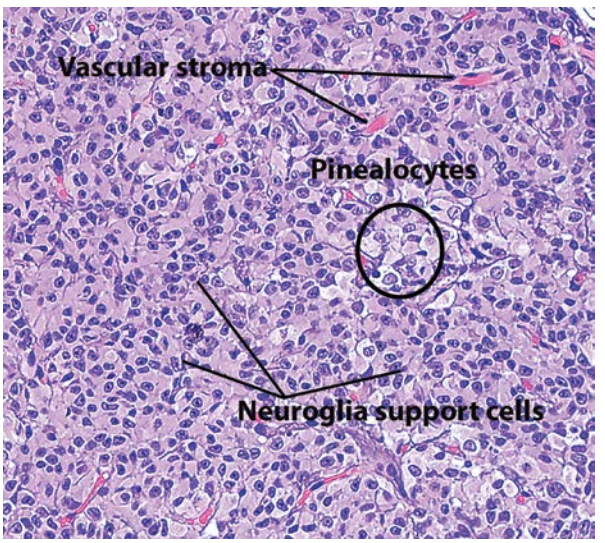
Pilomatricoma, see the preferred term **Hair follicle tumor, benign**.

Pilomatrix carcinoma, see the preferred term **Hair follicle tumor, malignant**.

Pineal gland is an endocrine organ that produces and secretes melanin from pinealocytes and contains additional support tissues (vascular and collagenous) and cells (neuroglia). The pineal gland is located above the third ventricle of the brain and is central to management of the circadian rhythm. It is intimately connected to the hypothalamus and sympathetic nervous system through neural connections that reach to the cervical ganglia and back to the pineal gland. See Appendix 3 for more information.



Pineal gland, Sprague Dawley rat, H&E.



Pineal gland, Cynomolgus monkey, H&E.

Pineal gland tumor, see the preferred terms **Pineocytoma**; **Pineoblastoma**.

Pineal parenchymal tumors are uncommon primary neoplasms composed of pineal gland cells. Pinealomas are benign pineal tumors (terminology used in rats) but are also known as pineocytomas. Pineoblastoma is a less differentiated pineal neoplasm. Refer to **Nervous System** and **Endocrine system** in Appendix 2 for more information.

Pineoblastoma, malignant is a rare neoplasm that originates from cells (pinealocytes) in the pineal gland that may be infiltrative with the presence of necrosis and hemorrhage. See **Endocrine Glands** in Appendix 2 for more information.

Pineocytoma, benign is a rare neoplasm that originates from cells (pinealocytes) in the pineal gland and are noninvasive. See **Endocrine Glands** in Appendix 2 for more information.

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Pituicytoma is a benign primary astrocytic tumor of the pars nervosa of the pituitary gland. See **Endocrine Glands** in Appendix 2 for more information.

Pituitary acidophil cell is found in the pars distalis of the anterior pituitary gland. These cells are named for their brightly eosinophilic cytoplasm when processed by hematoxylin and eosin (H&E) staining. There are two types of acidophils: somatotrophs, which produce somatotropin (growth hormone), and mammotrophs, (lactotrophs) which produce prolactin (luteotropin). See Appendix 3 for more information.

Synonym(s): **Somatotroph**; **mammotroph**.

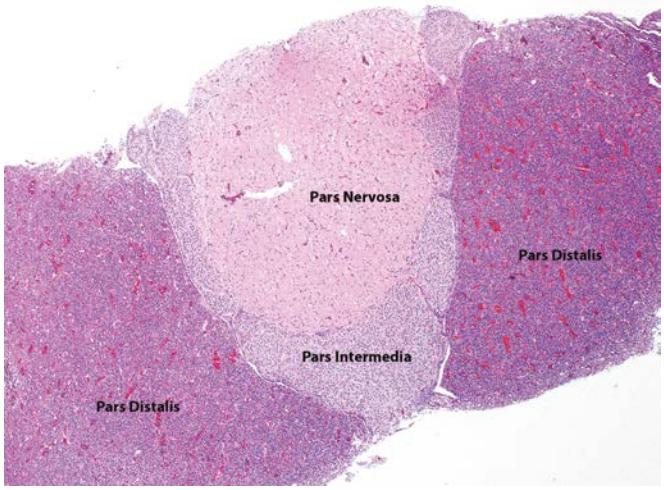
Pituitary basophil cell is found in the pars distalis of the anterior pituitary gland. These cells are named for their blue or purple cytoplasm when stained with hematoxylin and eosin (H&E). There are three types of basophils: corticotrophs, gonadotrophs, and thyrotrophs. Corticotrophs produce adrenocorticotropic hormone (ACTH), and gonadotrophs produce follicle stimulating hormone (FSH), luteinizing hormone (LH) and in humans, human chorionic gonadotropin (hCG). Thyrotrophs produce thyrotropin-releasing hormone (TRH). See Appendix 3 for more information.

Synonym(s): **Corticotrophs**; **gonadotrophs**; **thyrotrophs**.

Pituitary chromophobe cell is found in the pars distalis of the pituitary gland. These cells are named for their clear cytoplasm when processed by hematoxylin and eosin (H&E) staining. Chromophobes are considered resting or degranulated cells, capable of producing adrenocorticotropic hormone (ACTH) and prolactin. These cells may also serve a support function within the pituitary gland, participating in intralobular extracellular hormone transport. See Appendix 3 for more information.

Synonym(s): **Corticotroph**; **mammotroph**.

Pituitary gland is a neuroendocrine organ located within the pituitary fossa (sella turcica) of the cranium and attached to the ventral brain by the pituitary stalk. During organogenesis, the pituitary gland develops from oropharyngeal ectoderm (Rathke's pouch). The pituitary gland consists of two divisions, the neurohypophysis (pars nervosa) and adenohypophysis (pars distalis, pars intermedia, pars tuberalis). While the adenohypophysis is completely contained within the pituitary gland, the neurohypophysis extends to include the hypothalamic neurons and the infundibular stalk. The pituitary gland is a complicated endocrine organ that manufactures and secretes multiple hormones in response to signals received from the brain (hypothalamic-releasing hormones or neural input) and from peripheral endocrine organs, and is involved in many homeostatic and reproductive body functions. Hormones from the pituitary gland are generally trophic, leading to stimulation of glands and peripheral organs, and are strictly regulated by feedback neuroendocrine signals. The feedback systems are generally organ specific and denoted as "axis" when referenced an example being the hypothalamic-pituitary-adrenal (HPA) axis. In addition to the adrenal gland, the pituitary gland is part of axes regulating the thyroid gland (hypothalamic-pituitary-thyroid [HTA] axis), ovary, and testes (hypothalamic-pituitary-gonadal [HPG] axis). See Appendix 3 for more information.



Pituitary gland and pituitary gland subdivisions. Sprague Dawley rat, H&E.

Pituitary gland toxicity describes any effects related to drug or chemical treatment that alter the structure or function of the pituitary gland. Most commonly evidenced as endocrine disruption in adrenal, thyroid, or reproductive organ functions, the effects can be direct or indirect, owing largely to the feedback regulation of hypothalamic-pituitary-endocrine organ systemic physiology.

Pituitary gland tumor, see the preferred terms **Pars distalis adenoma, benign**; **Pars distalis carcinoma, malignant**.

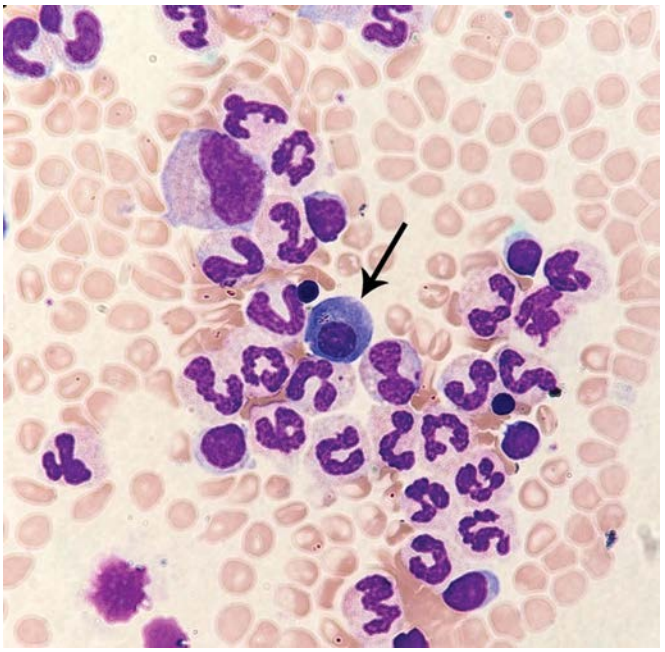
Pituitary hormones refers to any of the nine vital hormones released from either the anterior, intermediate, or posterior segments/lobes of the pituitary gland, including the "trophic hormones" from the anterior pituitary: growth hormone (GH/somatotrophin), thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), prolactin, luteinizing hormone (LH), and follicle-stimulating hormone (FSH); melanocyte-stimulating hormone (MSH) from the intermediate lobe, and antidiuretic hormone (ADH) and oxytocin from the posterior lobe. See the description for each of these hormones under their respective names, including **Female sex hormones** for further information.

Placenta is a feto-maternal organ in the uterus joining the mother to the embryo/fetus allowing nourishment, gas exchange, and excretion of waste products.

Placental transfer across the placental barrier is sometimes assessed in reproductive toxicity studies. It may involve special studies with radiolabeled compound in which the uptake of radioactivity into to the fetus is assessed, or the use of cold methodology in satellite animals in a toxicology study to assess the concentration of parent compound, and sometimes major metabolites in fetal tissues.

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Plasma cells are ovoid, mononuclear white blood cells, ~15 to 20 μm in diameter, with an eccentrically located, round nucleus containing densely clumped chromatin. The cytoplasm is abundant and darkly basophilic with a clear perinuclear Golgi area. They are observed mostly in tissues and rarely in the circulation; when in the circulation, their presence is usually associated with an infectious process. They represent approximately 2% of the bone marrow cell population. Plasma cells are specialized B lymphocytes that produce immunoglobulins. While most plasma cells appear as above, Mott cells (a type of plasma cell) contain many clear, round cytoplasmic inclusions called Russell bodies. Russell bodies correspond to endoplasmic reticulum filled with aberrant proteins.



Plasma cell (arrow), bone marrow smear, monkey.

Plasmacytic lymphoma is a systemic tumor composed of mature or immature plasma cells with an obvious plasmacytoid differentiation. Refer to **Hematopoietic System** in Appendix 2 for further information.

Plasmacytoma, see the preferred term **Plasmacytic lymphoma**.

Plasma protein binding is the noncovalent binding of drugs to plasma proteins. Many acidic and neutral drugs bind to serum albumin, which has several potential binding sites, while basic drugs may bind to α-1-acid glycoprotein. The extent of plasma protein binding of marketed drugs varies greatly. Several different methods are available to assess the extent of protein binding, including ultracentrifugation, equilibrium dialysis, and size exclusion chromatography. Plasma protein binding affects the clearance of a drug from the plasma such that highly bound compounds tend to be less rapidly cleared. Since the plasma protein binding is noncovalent, it is freely reversible.

Plasma proteins is a collective term for any of the circulating proteins found in the blood, including albumin (~55%), fibrinogen (~7%), and globulins (~38%). These proteins help maintain osmotic pressure, blood viscosity, and blood pressure. All plasma proteins are synthesized by the liver, except for gamma globulins, which are produced by lymphocytes and plasma cells. Plasma proteins play an important role in the transport of drugs, lipids, vitamins, minerals, and steroid hormones. Serum contains the same proteins as plasma except for fibrinogen, which forms insoluble fibrin during the clotting process.

Plasmid is a circular DNA molecule that is separate from a cell's chromosomal DNA. Plasmids are naturally present in bacteria and in some eukaryotes. Often plasmids contain genes that provide some benefit to the host cell (e.g., antibiotics resistance). Plasmids are often-used tools in molecular biology that can be used as vectors to incorporate recombinant DNA into various cell types.

Platelet component distribution width (PCDW) is the distribution width of the mean platelet component (MPC) and is expressed as grams per deciliter (g/dL). PCDW has been reported to be useful for monitoring shape change of platelets in low concentrations of thrombin. As for MPC, its clinical utility is limited.

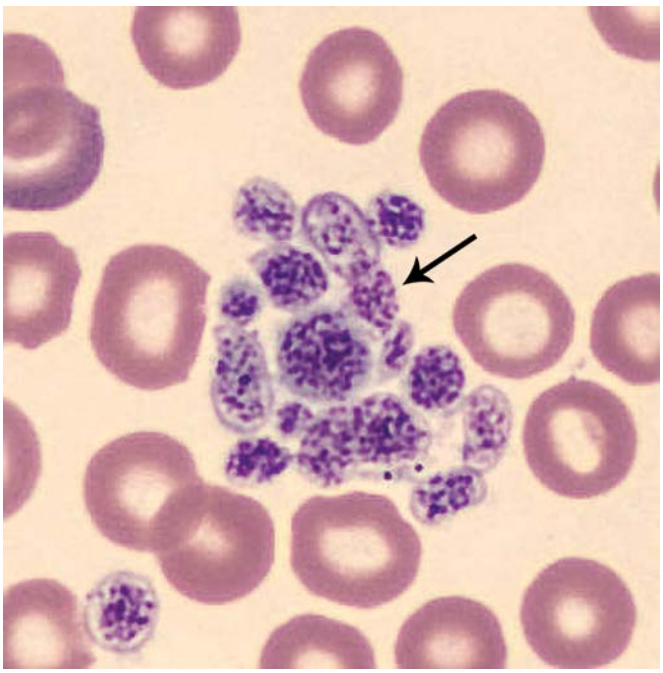
Platelet count is the calculated number of platelets in a volume of whole blood. It is determined on EDTA blood samples with automated instruments by either voltage pulse counting, electro-optical counting, or flow cytometry. Platelet counts are quite variable due to platelet intrinsic property to adhere to foreign surface, other cells, and each other. In addition, the small size of the platelet makes them difficult to distinguish from cellular debris or small erythrocytes. Sampling technique has a negligible impact on the accuracy of the platelet count. Most sampling artifacts are due to platelet activation, and delay in reaching the anticoagulant during sampling resulting in a spuriously low platelet count. Collecting samples from a large peripheral vein helps. Examination of a blood smear prepared shortly after blood collection may help in identification of small platelet clumps and cellular debris that may have affected the counts. In addition, a platelet number estimate can be obtained from a blood smear examination to confirm count accuracy. Blood samples in EDTA are acceptable for platelet count analysis for ~5 hours at room temperature and 24 hours at 4°C. The reference range value in human, dog, and nonhuman primate is ~150–400 $\times$ 10^9/L and 800–1200 $\times$ 10^9/L in rodents.

Platelets are small (1–3 μm in diameter), anuclear cytoplasmic fragments present in the blood. They are discoid in shape and contain cytoplasmic granules. They are generated in the bone marrow from megakaryocytes. The primary role of platelets is hemostasis, coagulation, and thrombosis. Upon exposure to collagen of the extracellular membrane, platelets adhere to the site of vascular injury via von Willebrand factor (vWF), glycoprotein Ib, and collagen interactions, and secrete

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adenosine phosphate (ADP) and other mediators from alpha granules which lead to platelet aggregation and activation of the coagulation cascade, thrombin formation, and formation of organized thrombi stabilized in place by fibrin. Hemostatic function is dependent on adequate platelet numbers and function. Activity (i.e., aggregation potential and adhesion molecule expression) of platelets is linked to their size, wherein the increased size (mean platelet volume [MPV]) means greater activity. The role of platelets is far more complex than once thought, and extends far beyond hemostasis to inflammation, wound healing, angiogenesis, and immune function.

Synonym(s): **Thrombocytes**.



Clumps of platelets, blood smear, rat.

Platelet volume distribution width (PDW) represents the distribution width of the mean platelet volume (MPV), and is expressed as a percent (%). It should be interpreted in the context of MPV. It is considered more sensitive than MPV to detect early bone marrow platelet production.

Pleomorphic carcinoma is a malignant growth of epithelial cells that contains extensive areas of spindle and/or giant cells. The spindle cells are often positive for vimentin, which is uncommon for carcinomas. In some cases, the vimentin-positive spindle cells are also positive for smooth muscle actin, suggesting a myoepithelial origin. This variant of carcinoma has been reported in the lung, mammary gland, and pancreas in animals and humans.

Pleomorphic lymphoma, see the preferred term **Lymphoma follicular center cell**.

Pleomorphic mixed cell lymphoma, see the preferred term **Lymphoma follicular center cell**.

Pleomorphic sarcoma is defined as a malignant mesenchymal neoplasm characterized by prominent cellular pleomorphism and often robust mitotic activity. There may or may not be an identifiable line of differentiation. The cellular pleomorphism is characterized by considerable variation in size and shape of individual cells with high variability in nuclear and cytoplasmic morphology. Cellular pleomorphism may be present in lesions encompassing a broad spectrum of biologic behavior and is not itself an indicator of aggressive behavior. Similarly, mitotic activity alone is not an indicator of aggressiveness; however, the combination of cellular pleomorphism and mitotic activity is often associated with malignant soft tissue neoplasms.

Plethysmography (head out or whole body plethysmography) is used to assess pulmonary function in small animals, usually rodents, as part of the battery of safety pharmacology studies. Basically, animals are placed in a chamber that allows assessment of breaths per minute, inspiratory time, expiratory time, minute volume, tidal volume, etc. Measuring these parameters in control and treated animals allows an assessment of the effects of a compound (test article) on pulmonary function.

Ploidy is a term that denotes the count of chromosome sets in a cell. For example, typical cells in the body have two, and are described as "diploid." Germ cells contain half the chromosomes ("haploid"). Cells containing three or greater the number of chromosome sets, as in a haploid cell, are described as "polyploid." Normal hepatocytes are often polyploid. Cells with "aneuploidy" have an abnormal chromosome count that does not reflect a multiple of the haploid cell chromosome number.

***Pneumocystis* spp**. is a rare source of mycotic infection of the lung. Infections are usually asymptomatic and are associated with *Pneumocystis jiroveci* (formerly known as *P. carinii*); however, in rats there are also infections with *P. wakefieldii*, and in mice *P. murina*. Macroscopically, there is consolidation of the lung, which typically does not collapse on opening the thoracic cavity. In addition, the alveolar air spaces contain foamy eosinophilic material (in hematoxylin and eosin [H&E]-stained sections), which may be accompanied by inflammatory cell infiltration, type II pneumocyte hypertrophy, and interstitial fibrosis. In addition, perivascular lymphocytic inflammatory cell infiltrates and lymphohistiocytic interstitial pneumonia in the lungs of rats, previously linked to a "rat respiratory virus," have also been associated with *P. jiroveci* infection. Infections can result in high mortality in colonies of immunodeficient mice, and pneumocystosis is reportedly common as a subclinical infection of domestic rabbits. The fungi may be demonstrated using Grocott's or Gomori methenamine silver stains.

Pneumocyte type II cell hyperplasia is characterized by a continuous, single cuboidal epithelial cell lining of the alveolar walls within the lungs. It is observed as part of the repair process following injury that leads to re-epithelialization by transdifferentiation into type I cells. Refer to **Respiratory System** in Appendix 2 for further information.

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POC (proof of concept) trial is an early clinical trial, usually during Phase I or early Phase II, which is designed to investigate safety and establish the relationship between the dose and desired drug activity, usually using a surrogate clinical endpoint.

Poikilocytosis refers to increased numbers of abnormally shaped red blood cells on blood smear examination. Poikilocytes include schizocytes, acanthocytes, keratocytes, echinocytes, spherocytes, echinocytes, codocytes, and any other abnormal red blood cell shape type. The term poikilocytosis is nonspecific, implying that there is a mixture of abnormally shaped red blood cells present without clear overrepresentation of one poikilocyte type over another. The combination of poikilocytes present may help identify the underlying pathological cause.

Point mutation is a single base pair change in the DNA sequence. Point mutations can occur spontaneously or can be induced by physical or chemical agents. Such mutations can result in single amino acid alterations, premature termination of transcription, or translation or no effect at all, particularly if the mutation occurs in the third position of the codon.

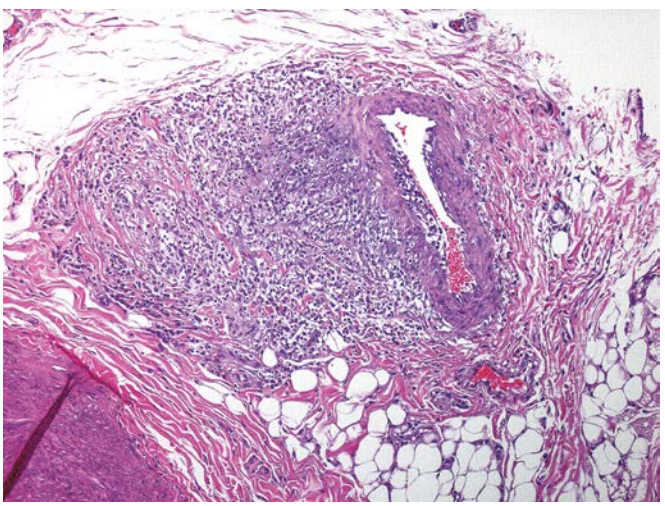
Polioencephalitis is inflammation of the gray matter of the brain. One cause of polioencephalitis is an enterovirus for which one of the early vaccines was developed and is still in use.

Polioencephalomalacia is cerebrocortical necrosis in the brain that presents as a laminar (layered) pattern.

Polyarteritis, see the preferred terms **Arterial inflammation** and **Polyarteritis nodosa**.

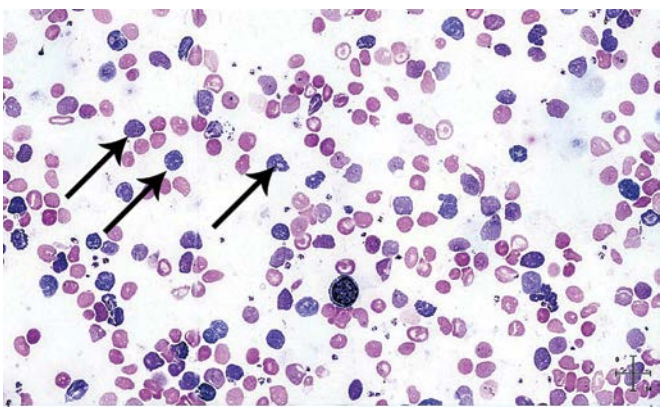
Polyarteritis nodosa is a syndrome that commonly affects the mesenteric, pancreatic, splenic, and testicular arteries of rats, and is associated with hypertension (spontaneously hypertensive rats), renal disease, and aging in male Sprague Dawley rats. It has also been reported in humans and nonhuman primates. Affected arteries are firm and segmentally thickened, forming tortuous, adherent, nodular masses. Histologically, there is fibrinoid necrosis of the tunica intima and media followed by extensive inflammatory reaction and subsequent fibrosis of all layers of the vessel wall. In general, the term polyarteritis nodosa should not be used in toxicity studies and a more specific, descriptive term for the lesions is preferred.

Synonym(s): **Periarteritis nodosa**; **panarteritis**; **systemic necrotizing vasculitis**.



Polyarteritis nodosa, artery, cynomolgus monkey, H&E.

Polychromasia is observed on routine blood smear examination by an increased number of blue-gray colored red blood cells, or polychromatophils. It indicates the release of immature red blood cells that still contain ribosomes, which are not present in mature red blood cells. The presence of ribosomes in the cytoplasm of these immature red blood cells affects their staining properties and makes them appear blue-gray. These immature polychromatic cells are reticulocytes; however, not all reticulocytes are polychromatophils. Only the younger reticulocytes with enough ribosomes in their cytoplasm to affect the cell staining affinity for basic dyes will be seem as polychromatophils. Polychromasia on blood smear examination is correlated with increased reticulocytes, mean corpuscular volume (MCV), and hemoglobin distribution width (HDW), and decreased mean corpuscular hemoglobin concentration (MCHC) on automated analyzers. Polychromasia signals the bone marrow release of immature red blood cells, either secondary to anemia as part of a physiological response to erythropoietin, or an inappropriate release secondary to bone marrow injury.

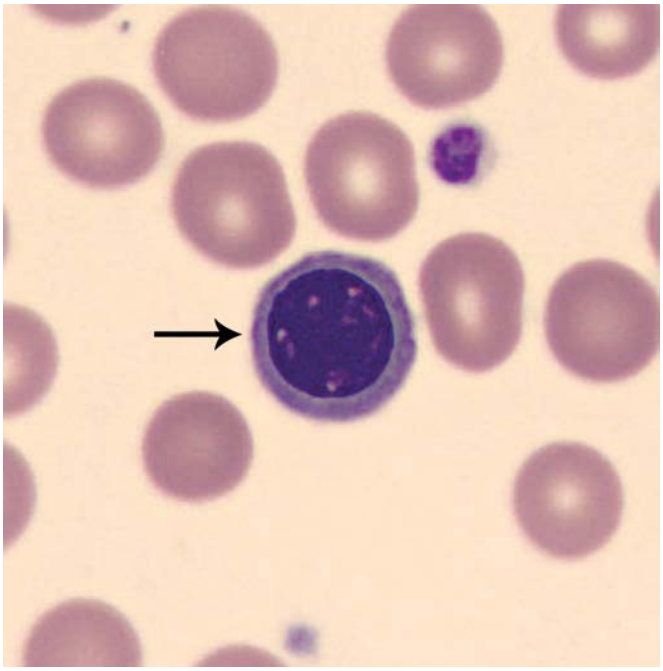


Marked polychromasia (gray cells, arrows); blood smear, sickle cell mouse model.

Polychromatophilic rubricyte is produced during the third development stage of erythrocyte production within the bone marrow, and stem from the basophilic rubricyte. Polychromatophilic rubricytes range in size from 10–15 μm in diameter and have a nuclear:cytoplasmic (N:C) ratio of approximately 4:1. Both the cell and the nucleus are round. The nucleus may be central or eccentric. Chromatin is highly clumped, and nucleoli are absent. The cytoplasm is blue-gray due to increased acidophilic staining from increasing levels of hemoglobin. This is the last erythroid precursor still capable of undergoing mitosis.

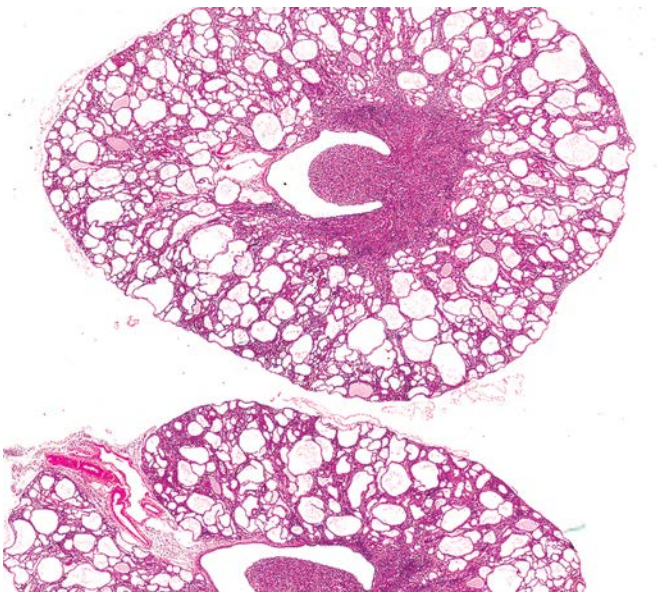
Synonym(s): **Polychromatophilic normoblast**; **polychromatophilic erythroblast**.

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Polychromatophilic rubricyte (arrow), blood smear, monkey.

Polycystic kidney is characterized by the bilateral presence of multiple cysts within the kidney. In humans, it is an autosomal dominant hereditary disorder associated with mutations in the PKD-1 and/or PKD-2 genes. In the rat, the condition is a rare congenital disorder but has been induced by exposure to diphenylthiazole.



Polycystic kidney disease, rat kidney, H&E.

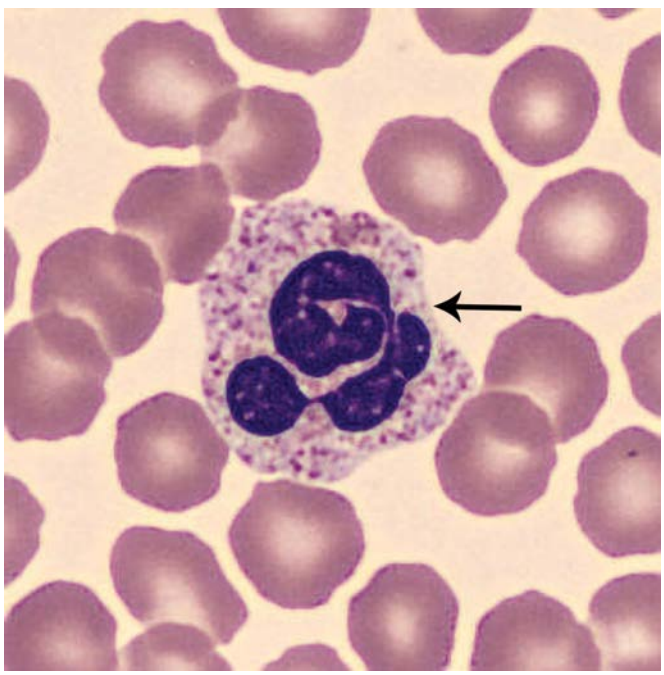
Polycystic ovary syndrome (PCOS) is a condition in the human female characterized by increased numbers of small antral follicles in the ovaries (i.e., polycystic ovaries), increased androgens and luteinizing hormones, and irregular menses. When testosterone is administered to mice, rats, or macaques in early to mid gestation, overt PCOS develops in the female offspring. In macaques, PCOS can also occur sporadically and may follow a similar heritable pattern as is observed in humans.

Polycythemia is an increase in red blood cell mass as evidenced by red blood cell count, hemoglobin, and/or hematocrit above the reference range for the particular species. This condition may be due to hemoconcentration, splenic contraction, or increased production (i.e., neoplastic or physiologic). Refer to **Hematopoietic System** in Appendix 2 for further information.

Polycythemia vera is a myeloproliferative disorder associated with increased red blood cell mass, thrombocytosis, and increased white blood cell count. As opposed to polycythemia, it is not associated with evidence of dehydration, and levels of erythropoietin are low normal to low. It has been described in most animal species. Refer to **Hematopoietic System** in Appendix 2 for further information.

Polymerase chain reaction (PCR) is a technique to amplify particular DNA segments. The principal of PCR is based on the use of a Taq polymerase, DNA nucleotide bases (A, C, G, and T), primers, and DNA template to be copied. PCR involves a thermal cycling (heating and cooling) that allows three main stages (denaturing, annealing, and extending) necessary for PCR amplification.

Polymorphonuclear leukocyte (also known as granulocyte) is a general term for white blood cells, including neutrophils, eosinophils, and basophils, and comprise 40–75% of leukocytes in the peripheral blood. Polymorphonuclear leukocytes are activated and recruited to sites of infection and/or inflammation by IL-8, c5a, leukotriene LTB_4, and platelet-activating factor.



Polymorphonuclear neutrophil (arrow), blood smear, monkey.

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These cells are part of the innate immune system and provide the first line of defense through phagocytosis and degranulation.

Polyp is a tissue mass protruding from an epithelial surface. Polyps generally have a vascularized stromal body covered by an epithelium native to the organ of origin. These growths are generally considered benign, but in some cases are considered preneoplastic, as in human colorectal cancer development.

Polyp (gastrointestinal) is an abnormal growth of tissue projecting from a mucous membrane. It may be attached by a narrow stalk (pedunculated) or have a more flattened, nodular appearance (sessile). Refer to **Gastrointestinal Tract** in Appendix 2 for further information.

Polyploidy is a condition in which a cell contains the multiple of the normal diploid set of chromosomes. Polyploidy is common in plants and in some animals, or in some specific mammalian tissues such as liver or muscle. Polyploidy can also be induced by some chemicals that interfere with normal chromosome segregation during mitosis (e.g., mitotic spindle inhibitors).

Porphyrin granuloma, see the preferred term **Harderian gland granulomatous inflammation**.

Portio vaginalis hypertrophy is the uniform thickening or expansion of the fibromuscular stroma in the part of the cervix that extends into the vagina. This lesion does not distort the surrounding tissue architecture. A similar change may occur in the vagina proper (see **Vaginal stromal hypertrophy** for more information).

Differential diagnoses: **Stromal hyperplasia**; **Fibroma**; **leiomyoma**.

Synonym(s): **Cervical stromal hypertrophy**.

Posterior pituitary gland is the anatomic region of the pituitary gland (pars nervosa) that lies within the neurohypophysis. It contains microvessels supported by pituicytes (glial cells) and serves as the terminus of the hypothalamic neurosecretory hormone delivery system. The pars nervosa mediates the release of oxytocin and antidiuretic hormone (ADH) from the hypothalamus into the circulation. See image under **Pituitary gland**. See Appendix 3 for more information.

Synonym(s): **Pars nervosa**.



Posterior pituitary gland with microvasculature in section, cynomolgus monkey, H&E.

Posterior synechia (lens), is a clinical term for adhesions; see the preferred term **Iris adhesion**.

Postnatal period is the stage of development of the individual after birth.

PPAR (peroxisome proliferator activated receptor) is a group of nuclear receptors which regulate cellular metabolism and differentiation. Three types of PPAR (α-,β-, and δ-) are known, with different effects on drug metabolism and endogenous lipid metabolism. All PPARs form heterodimers with retinoid receptor (RXR) and bind to DNA response element inducing pleiotropic responses. The endogenous ligands are fatty acids and eicosanoids.

32P post labeling is an electrophoretic method to detect DNA adducts. DNA is cleaved into nucleotides and those containing adducts are separated and subsequently radiolabeled for visualization.

Preclinical safety evaluation is a synonym for nonclinical safety evaluation. See **Nonclinical safety evaluation** for information.

Precoital interval is a term used in fertility studies to assess the number of days of cohabitation before insemination of the female(s).

Precorneal membranous occlusion, see the preferred term **Conjunctiva overgrowth**.

Pre-Descemet's membrane corneal opacity is a discrete focus of activated and possibly ectopic endothelial cells that has been reported to occur spontaneously in the deep corneal stroma above Descemet's membrane in New Zealand white rabbits. These foci may occur early in life, are not progressive, and have not been reported in other laboratory animals. Usually identified as deep corneal opacities by optical coherence tomography, the focal and small size of these opacities may result in difficulties in sampling for histologic characterization. Although these foci are not well characterized, they probably represent proliferation over a defect in the endothelial monolayer, as corneal endothelium in rabbits can regenerate (endothelium is non-regenerative in other species) and can form multinucleated cells. These foci are not equivalent to pre-Descemet's corneal dystrophy in humans, dogs, and mice. See the preferred term **Corneal endothelium hyperplasia**.

See **Optical coherence tomography** for illustration.

Pregnancy index (%) is a parameter assessed in fertility studies that describes the percentage of the mated animals

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that become pregnant or number pregnant/number mated or inseminated ×100.

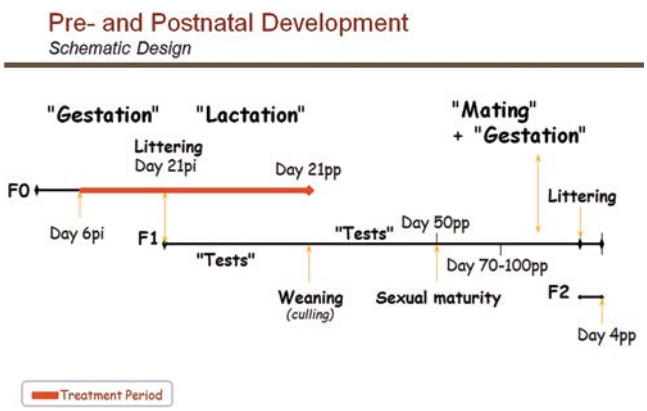
Pre-Manufacture Notification (PMN) is a notification to the Environmental Protection Agency (EPA) that a laboratory intends to manufacture a new chemical substance that is not on the Toxic Substance Control Act (TSCA) inventory.

Premarket Notification [510(K)], is a submission to the FDA to demonstrate that the device to be marketed is at least as safe and effective, that is, substantially equivalent, to a legally marketed device that is not subject to premarket approval.

Premature physeal closure, see the preferred term **Growth plate closed**.

Prenatal period is the stage of development of the fetus just prior to birth.

Prenatal/postnatal developmental toxicity studies are performed in rodents to evaluate the effects of substances on parturition, weaning, and maternal nursing ability. They are conducted using a battery of tests before and after weaning to assess physical development (with developmental landmarks), sensory functions, reflexes (including motor coordination), and behavior (learning and memory) of the offspring.



Preputial gland is an accessory male sex organ of rodents. They are paired, modified subcutaneous sebaceous glands located at the end of the prepuce. The acini of the preputial glands consist of basal cells with basophilic cytoplasm and secretory cells. Each preputial gland has a long excretory duct with a wide lumen lined by stratified squamous epithelium, and empty into the preputial cavity. Preputial glands contribute to pheromone production and are referred to as clitoral glands in the female.

Preputial gland (female), see the preferred term **Clitoral gland**.

Preputial gland adenocarcinoma is a malignant neoplasm of acinar cells of the preputial gland, consisting of irregular nests of acinar cells with nuclear and cellular atypia and high mitotic activity. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Preputial gland adenoma is a rare spontaneous neoplasm of acinar cells. Grossly, the tumor is firm, tan, and multilobulated, and is often bilateral on the lower abdominal wall near prepuce. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Preputial gland apoptosis, see the preferred term **Preputial gland single cell epithelial necrosis**.

Preputial gland atrophy is characterized by acini of reduced size that are lined by a single layer of cuboidal or squamous sebaceous cells. Atrophic changes are associated with sebaceous cell degeneration and intracytoplasmic yellow-brown granular pigmentation. The gland stroma has prominent interstitial collagen with infiltration by inflammatory cells. Ducts may be dilated and filled with inspissated secretory material and inflammatory cells.

Preputial gland basal cell carcinoma, see the preferred term **Preputial gland basal cell tumor, malignant**.

Preputial gland basal cell tumor, benign is a rare neoplasm arising from basal cells lining the preputial gland ducts composed of well-differentiated cells arranged in circumscribed nests. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Preputial gland basal cell tumor, malignant is a rare neoplasm arising from basal cells lining the preputial gland ducts composed of circumscribed nests of basophilic cells with elongated to oval nuclei and a high mitotic rate. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Preputial gland cystadenocarcinoma, see the preferred term **Preputial gland adenocarcinoma**.

Preputial gland cystadenoma, see the preferred term **Preputial gland adenoma**.

Preputial gland cystic change, see the preferred term **Preputial gland ductal dilation**.

Preputial gland cystic degeneration, see the preferred term **Preputial gland ductal dilation**.

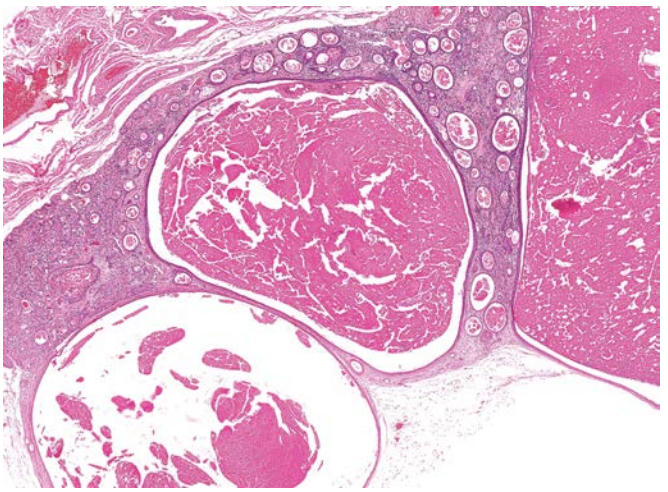
Preputial gland degeneration may affect sebaceous epithelial cells, ductular epithelial cells, or both, and result in dilatation or ectasia and accumulation of secretory material. The affected cells are swollen with epithelial vacuolization and bleb formation.

Differential diagnosis: **Preputial gland atrophy**.

Preputial gland ductal dilation is a common background finding in aging rodents. Cystic dilated ducts are lined by flattened epithelium with luminal keratin or cell debris. Ductal dilation is often associated with inflammation, with or without epithelial hypertrophy, or hyperplasia.

Synonym(s): **Preputial gland cystic degeneration**; **preputial gland cystic change**.

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Dilated preputial gland ducts with inflammation, F344/N rat, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

Preputial gland epidermoid carcinoma, see the preferred term **Preputial gland, squamous cell carcinoma**.

Preputial gland hyperplasia is a spontaneous, age-related lesion in the rat and mouse, and typically stems from reactive hyperplasia due to inflammation. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Preputial gland single cell epithelial necrosis is characterized by epithelium of reduced size containing shrunken nuclei but with intact cellular membranes (i.e., apoptosis). This is typically present without accompanying inflammation. Ductal or acinar cells may be affected.

Synonym(s): **Preputial gland apoptosis**.

Preputial gland squamous cell carcinoma is a malignant tumor derived from squamous epithelial cells.

Preputial gland squamous cell papilloma is an uncommon benign tumor in the rodent which arises from the ductal cells of the preputial gland.

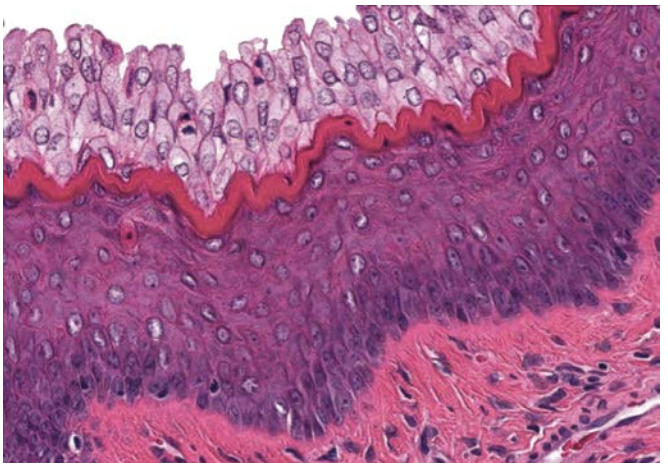
Primary adenoid cystic carcinoma, see the preferred term **Eccrine gland carcinoma**.

Primary lung irritant is a corrosive inhaled substance that affects the upper respiratory tract only, has no toxic metabolite(s) or breakdown product(s), and produces no systemic toxicities.

Primitive neuroectodermal tumor (PNET), see the preferred term **Neuroectodermal tumor**.

Proestrus is the phase of the estrus cycle preceding estrus. It is the period where one or multiple follicles begin to grow. See **Estrous cycle** for further information.

Proestrus vagina refers to the histologic features of the vagina that are typical for the proestrus phase of the estrus cycle. In rodents, initiation of proestrus coincides with the development of the granular cell layer in the vaginal mucosa and continues as the mucosa further thickens with the appearance of a surface mucus layer. Cornification of the vaginal mucosa indicates progression to the estrus phase of the cycle in rodents.



Proestral vaginal epithelium, rat, H&E.

Progesterone is a steroid hormone secreted by the corpus luteum in the ovaries and the placenta. Progesterone prepares the uterus for pregnancy. It maintains the uterus after fertilization and then throughout the pregnancy as well as prevents further release of eggs from the ovaries during pregnancy. See **Female sex hormones** for further information.

Prolactin is a hormone produced by the luteotroph cells of the anterior pituitary gland that is responsible for multiple effects in the female reproductive tract.

Synonym(s): **Luteotropin**.

Prolactin cell hyperplasia is a nonneoplastic increase in the number of prolactin cells (i.e., lactotroph, mammotroph) in the pars distalis of the pituitary gland that often occurs in conjunction with hypertrophy. See **Endocrine Glands** in Appendix 2 for more information.

Prolactin-inhibiting hormone (PIH) is dopamine, a hormone that inhibits prolactin secretion among other functions, and which normally remains in homeostatic concentration as a constant inhibitor of anterior pituitary gland prolactin secretion. Loss or depression of hypothalamic PIH release is required for prolactin to be produced and released from the anterior pituitary gland. PIH is decreased during conditions that require mammary gland development (i.e., increased estrogen during late pregnancy and physical activity of the nursing infant) in conjunction with an increase in prolactin-stimulating hormones from the hypothalamus.

Synonym(s): **Dopamine**.

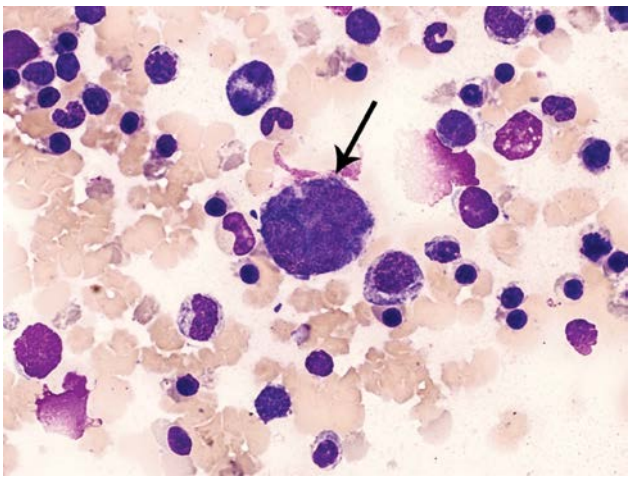
Prolapse is used to indicate protrusion of a tissue from a body orifice, or to an abnormal site. It may occur in a wide variety of tissues and structures including the rectum, urinary bladder, uterus, third eyelid, intervertebral disk, and heart valve. The significance and outcome of the prolapse depends upon the tissue involved, extent of compromise of the prolapsed tissue, and

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impact on the affected tissue (e.g., prolapse of a heart valve, prolapse of an intervertebral disk toward the spinal cord).

Proliferating cell nuclear antigen (PCNA) is a nuclear nonhistone protein expressed during DNA synthesis. Immunohistochemical staining for PCNA in tumor cells correlates with mitotic activity, and in some cases, tumor grade.

Promegakaryocytes are megakaryocyte precursor cells that are ~20–80 μm in diameter that replicate through endomitosis, and typically contain 2–4 nuclei without nucleoli that are separate or connected via a thin strand of nuclear material. They contain moderate amounts of basophilic cytoplasm with developing azurophilic granules. Promegakaryocytes are most responsive to thrombopoietin but are also stimulated by stem cell factor (SCF), IL-3, GM-CSF, IL-11, and erythropoietin, and express CD38, CD41, CD42 (±), and CD61.

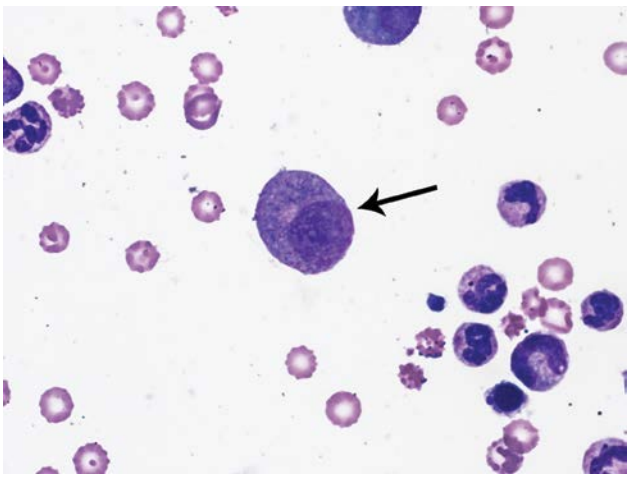


Promegakaryocyte (arrow), blood smear, minipig.

Promonocyte is a monocyte precursor ~12–20 μm in diameter that resides in the bone marrow. Promonocyte nuclei are elongated and have lace-like chromatin with one or more nucleoli and small amounts of medium blue cytoplasm that often has pseudopods. They are difficult to separate from early granulocytic precursors; however, they lack the primary granules that develop in promyelocytes. Promonocytes express CD4, CD11b, CD13, CD14, CD15, CD33, and HLA-DR. Promonocytes are not observed on blood smears but may be seen in cases of acute myelomonocytic (AML-M4) or monocytic leukemia (AML-M5).

Promotion is a step in the carcinogenic process where the cells, after initiation, can proliferate and expand in number to form a tumor.

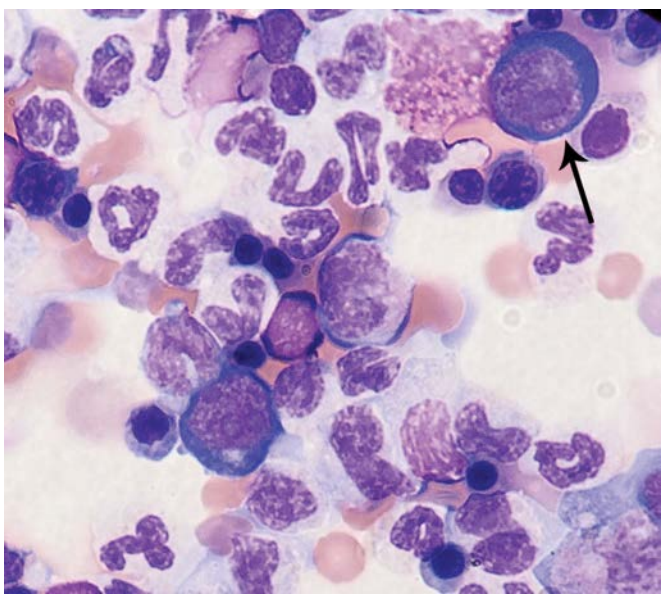
Promyelocyte (also known as progranulocyte) is ~15–25 μm in diameter and is a granulocyte precursor cell that resides in the bone marrow. Promyelocyte nuclei are generally round with coarse, clumping chromatin, one or more nucleoli, and small amounts of light blue cytoplasm containing variable numbers of reddish-purple primary granules that may overlie the nucleus. Promyelocytes can be identified microscopically in the bone marrow but are rarely observed on blood smears except in cases of severe inflammation or leukemia.



Promyelocyte (arrow), bone marrow, monkey.

Proopiomelanocortin (POMP) is a protein produced by the pituitary gland and is the common precursor for melanocyte-stimulating hormone (MSH), β-endorphin, and adrenocorticotrophic hormone (ACTH). Post-translational processing is tissue-specific, with ACTH and β-endorphin production in the pars distalis and MSH production in the pars intermedia.

Prorubricyte is the first erythrocyte precursor in the four stages of erythrocyte development within the bone marrow. The prorubricyte is produced directly from the CFU-GEMM–specific stem cell and driven by erythropoietin stimulus. Prorubricytes are large (17–24 μm in diameter), round, deeply basophilic cells with a large central round nucleus. Cytoplasm may range from medium to dark blue. Prorubricytes have a high nuclear-to-cytoplasmic ratio (approximately 6:1) and contain prominent nucleoli. They express high levels of transferrin receptors for iron



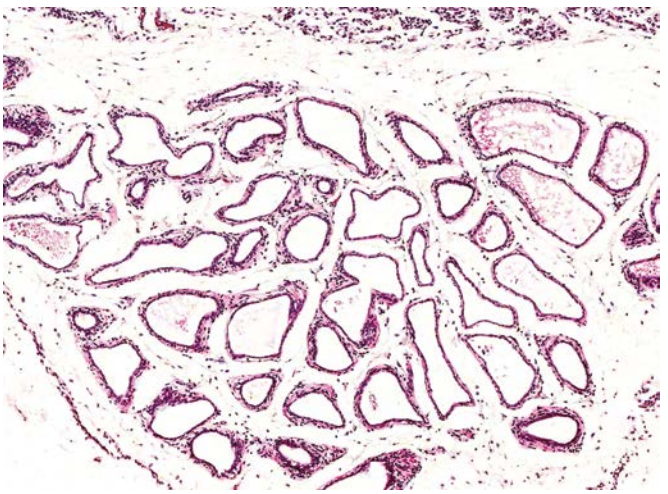
Prorubricyte (arrow), bone marrow, cynomolgus monkey.

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acquisition and erythropoietin receptors, demonstrating their sensitivity to this erythroid-stimulating growth factor.

Synonym(s): **Rubriblast**; **pronormoblast**.

Prostate atrophy is characterized by glandular shrinkage, which may be reflected in decreased prostate gland weights. Microscopically, acini are reduced in size, with attenuation of the lining epithelium, reduced secretory material, and increased stromal prominence. Atrophy often involves all lobes of the prostate. The pathogenesis relates to inhibition of gonadal steroid and pituitary hormones and may involve any one or combination of the following: (1) inhibition of testosterone synthesis and secretion; (2) inhibition of 5α-reductase, the enzyme within the prostate that converts testosterone into the more active growth factor dihydrotestosterone (DHT); and/or (3) competitive antagonism of the androgen receptor. Known inducers of prostatic atrophy include finasteride, epristeride, and hydroxyflutamide. Estrogens decrease the volume of glandular epithelium and increase the fibromuscular stroma in both the ventral prostate and seminal vesicle. Deficiency of the Egr family of zinc finger transcription factors such as Egr4 and Egr1, as in *Egr4-Egr1* double-mutant mice, leads to atrophy of the prostate, testis, epididymis, and seminal vesicle. Spontaneous prostatic atrophy is also observed as an age-related change in rodents.



Atrophic prostatic acinae, F344/N rat, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

Prostate gland is a male accessory gland found in all placental mammals. It differs considerably among species anatomically and physiologically. The structure of the prostate varies, ranging from tubuloalveolar (as in humans) to branched tubular. In rats and mice, it is composed of distinct lobes, while in humans and dogs, the prostate is a compact, solitary structure. In the dog, the gland is particularly well developed, and the dog is a useful animal model for studying spontaneous prostate cancer that metastasizes to bone.

Prostatic adenocarcinoma, see the preferred term **Accessory male sex organs, adenocarcinoma**.

Prostatic adenoma, see the preferred term **Accessory male sex organs, adenoma**.

Prostatic carcinoma (with neuroepithelial differentiation), see the preferred term **Prostatic neuroendocrine tumor, malignant**.

Prostatic carcinosarcoma, see the preferred term **Accessory male sex organs, carcinosarcoma**.

Prostatic epithelial mesenchymal tumor, see the preferred term **Accessory male sex organs, carcinosarcoma**.

Prostatic intraepithelial neoplasia (PIN), see the preferred term **Accessory male sex organs, atypical hyperplasia**.

Prostatic neuroendocrine tumor, malignant is observed in the ventral lobe of the prostate or within submucosal glands of urethra and consists of accumulations of small round cells of neuroectodermal origin. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Prostatic poorly differentiated adenocarcinoma, see the preferred term **Accessory male sex organs, carcinosarcoma**.

Prostatic sarcomatoid carcinoma, see the preferred term **Accessory male sex organs, carcinosarcoma**.

Proteasomes are cellular protein complexes that degrade targeted proteins by proteolysis.

Proteinaceous plug may result in obstruction of the urethra in the rodent (particularly male mice) and may be mixed with desquamated epithelial cells, spermatozoa, and/or inflammatory cells. A proteinaceous plug may also be found as a postmortem finding in rodents (particularly male rats), which represents an agonal secretion from the accessory sex glands occurring during euthanasia and may fill the entire urinary bladder. Unless there are pathologic effects associated with the protein plug, they are generally not diagnosed.

Protein-losing gastropathy, see the preferred term **Hypertrophic gastritis**.

Proteinuria is a synonym for albuminuria. See the preferred term **Albuminuria**.

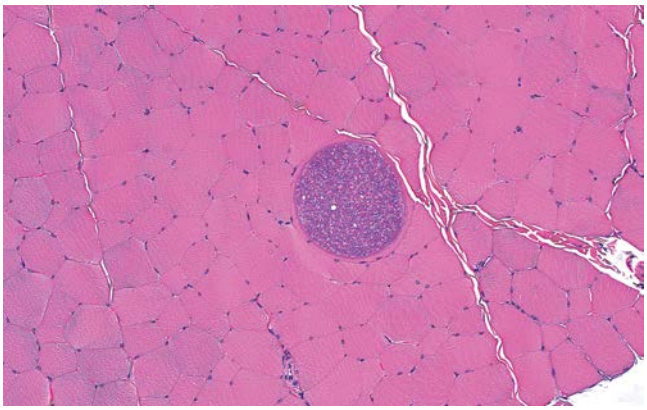
Proteomics is the analysis of the entire content of proteins in a cell, organ, or organism. Proteomic analysis is not used in routine toxicology studies but is often included in exploratory studies to determine the mechanisms of toxicity by looking at alterations of cellular protein patterns induced during the course of a pathological change.

Proto-oncogenes are genes that when modified (mutated) give rise to oncogenes. Oncogenes are genes associated with tumor formation, which often provide a proliferative advantage to the cell and are a characteristic of the cancer cell.

Protozoa is the phylogenic kingdom containing microscopic eukaryotic single cell organisms that includes flagellates,

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ciliates, sporozoans and amoeba. Protozoans are abundant in soil and water environments, and some are pathogenic parasites of multicellular organisms.



Protozoal cyst of *Sarcocystis* sp. in the skeletal muscle of a cynomolgus macaque, H&E.

Pseudocyesis, see the preferred term **pseudopregnancy**.

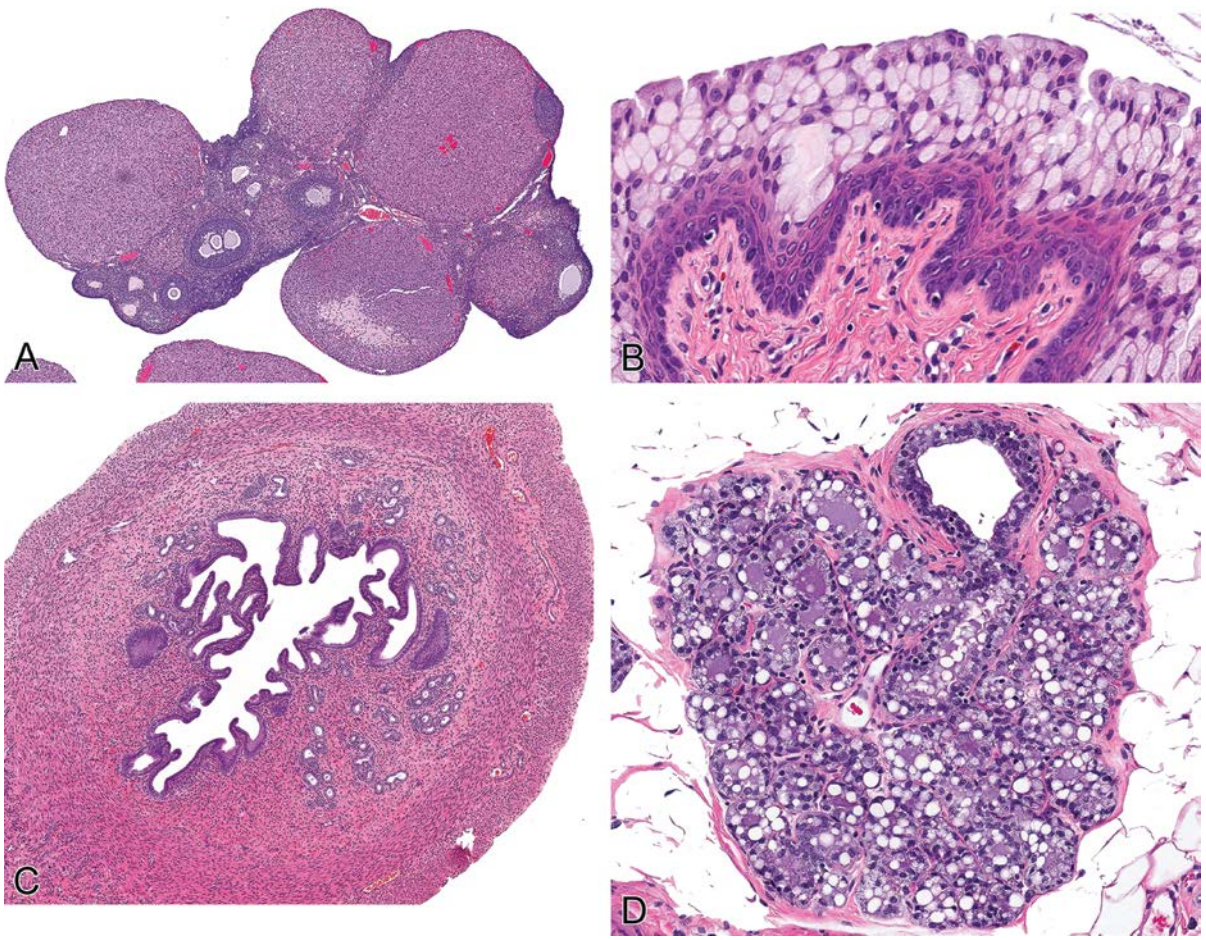
Pseudocyst is an accumulation of fluid in a cyst-like structure but is differentiated from a true cyst as it does not have an epithelial or other membranous lining. It may also be referred to as an "adventitious" or "false" cyst.

Pseudoglandular formation as it pertains to neoplasms is a morphologic change in which a tumor derived of epithelial cells undergoes structural alteration resulting in the appearance of a glandular structure. If pronounced, the pseudoglandular formation may result in the morphology resembling a primary or metastatic adenocarcinoma. Pseudoglandular formation may be noted in neoplasms such as hepatocellular carcinoma. Pseudoglandular formation also refers to a normal stage of development of the fetal lung characterized by the formation of the bronchial portion of the lung.

Pseudohermaphrodite, see the preferred term **Male reproductive tract feminization**.

Pseudomembrane is a layer of exudate (i.e., a mass of cells and proteinaceous fluid that exudes from blood vessels or an organ, especially as a feature of inflammation) resembling a membrane on the mucosal surface of an organ.

Pseudopregnancy is also referred to as pseudocyesis or false pregnancy. In this condition, hormonal signaling is consistent



Prominent ovarian CL (A), increased vaginal mucification (B), diffuse endometrial hyperplasia (C), and mammary lobuloalveolar hyperplasia (D), rat, H&E. (Reproduced with permission of the Academic Press from Rudmann, D.G. and Foley, G.L. 2013. In: Haschek, W.M. et al. (eds.) *Haschek and Rousseaux's Handbook of Toxicologic Pathology*, 3rd ed. Elsevier, Academic Press, pp. 2599–2660.)

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with pregnancy, but there is a lack of developing embryo or fetus. In rats and mice, pseudopregnancy is often accompanied by increased prolactin signaling, as well as persistent, large androgen- and progesterone-producing corpora lutea in the ovary, mammary gland lobuloalveolar hyperplasia, and vaginal mucification. Pseudopregnant cycles are common during reproductive senescence in rats and mice and can also occur spontaneously or in response to some xenobiotics. In dogs, the normal, long ovarian cycle reflects a physiologic pseudopregnancy (see figures at the previous page bottom).

Synonym(s): **Pseudocyesis**.

Pseudopterygium, see the preferred term **Conjunctiva overgrowth**.

Pulmonary acariasis, caused by infection with *Pneumonyssus simicola*, is a frequent parasitic infection of Old World nonhuman primates, with infection rates in wild-caught rhesus monkeys approaching 100%. Although the incidence in laboratory-bred animals is very low, it may be a rare cause of debilitation, cough, sneezing, and dyspnea, and with a superimposed lung infection can result in significant morbidity and death. Other potential complications include pulmonary arteritis and pneumothorax; however, most cases are incidental findings at necropsy. Macroscopic findings include cystic lesions up to several millimeters in diameter, and air-filled bullae, often in the hilar region of lung lobes. Microscopically, there is multifocal pyogranulomatous inflammation centered on bronchi and bronchioles, frequently containing pigmented material including siliceous components of the mite exoskeleton. Pigmented material persists after the death of mites and plays an important role in perpetuating lung lesions. Although pulmonary acariasis can confound microscopic examination of the lung, it has also been used as a model for various conditions, including asthma and silicosis. Transmission requires close contact, does not require a vector, and is likely to occur by inhalation of a respiratory aerosol. One must differentiate this condition from other causes of inflammation in the respiratory system.

Pulmonary acinar carcinoma is a malignant neoplasm originating from club cells (i.e., bronchiolar exocrine cells). The neoplasm has a predominantly acinar cell pattern containing cells that may contain eosinophilic cytoplasmic globules. Refer to **Respiratory System** in Appendix 2 for further information.

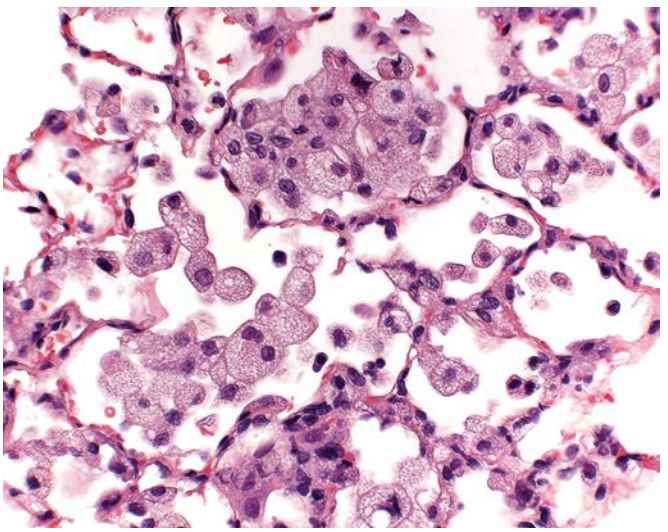
Pulmonary adenocarcinoma, see the preferred term **Bronchioloalveolar carcinoma**.

Pulmonary adenosquamous carcinoma is a malignant neoplasm arising from a clonal shift within a carcinoma (e.g., adenocarcinoma) to include a malignant squamous phenotype. They share common pathological features with squamous cell carcinomas. Refer to **Respiratory System** in Appendix 2 for further information.

Pulmonary alveolar macrophage aggregation is a common background finding in the lungs of most laboratory animal species and is particularly frequent in rats. Macrophages are responsible for the removal of excess alveolar surfactant, and therefore aggregations may be associated with conditions favoring increased surfactant secretion. They are also commonly seen following inhalation of poorly soluble drugs, in which case there is a distinct predilection for aggregations at the respiratory bronchioles and the bronchioloalveolar junctions. The cells often have a foamy appearance, dependent on the nature of the phagocytosed particulate. Most often the macrophages appear unaffected by the ingested material; however, if cell damage and necrosis ensue, they may become associated with an influx of neutrophils or lymphocytes, formation of cholesterol clefts, or even granulomatous inflammation, granulomas, and fibrosis.

Differential diagnoses: **Eosinophilic crystalline pneumonia**; **Pulmonary alveolar proteinosis**; **Pulmonary inflammation**.

Synonym(s): **Lung (alveolar) histiocytosis**.



Alveolar macrophage aggregation, lung rat, H&E.

Pulmonary alveolar macrophage interstitial aggregation is characterized by the presence of densely packed, foamy or pigmented macrophages in the alveolar interstitium, or pleural, perivascular, and peribronchiolar connective tissues. This change is generally associated with the inhalation of insoluble particles. Aggregation of macrophages at these sites is more commonly seen in dogs and nonhuman primates than in rodents due to differences in lung clearance routes. The aggregations are believed to be a consequence of overwhelmed lymphatic clearance, and as such tend to become chronic, being regarded as "pulmonary sumps." Macrophages in these locations rarely elicit an additional inflammatory reaction and appear to be static.

Differential diagnoses: **Pulmonary alveolar proteinosis**; **Pulmonary inflammation** (i.e., in response to inhaled material).

Synonym(s): **Lung (alveolar) histiocytosis**.

Pulmonary alveolar phospholipidosis is by common usage a term that refers specifically to a condition induced in the

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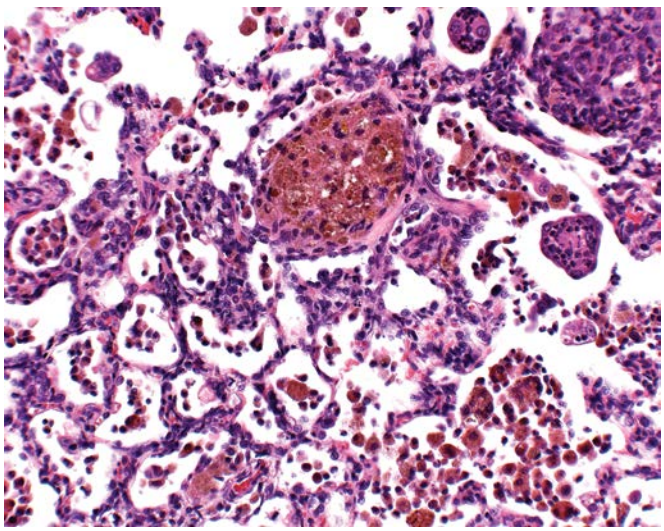
lung by treatment with cationic amphiphilic drugs (CADs) and is characterized by the presence of variable numbers of foamy macrophages in the alveolar spaces. The fundamental lesion in phospholipidosis is the excessive accumulation of phospholipids in lysosomes, due to interference with synthesis or decreased breakdown. The foamy macrophages become enlarged, and progressively increase in number with duration of CAD exposure, in severe cases appearing to almost entirely fill the alveolar spaces. The macrophages may be associated with traces of eosinophilic, intra-alveolar material (surfactant). Phospholipidosis does not usually invoke an inflammatory reaction, but in some cases the foamy macrophages may be associated with a neutrophilic infiltrate, and in exceptional instances, abscessation may develop. By conventional light microscopy, phospholipidosis often appears confined to macrophages, but careful examination may reveal increased vacuolation of Type II pneumocytes. In addition, ultrastructural examination or immunohistochemistry with a lysosome-associated membrane protein (LAMP)-2 antibody often demonstrates increased numbers of lysosomal inclusions in other cell types, such as Type I pneumocytes, endothelial cells, and circulating lymphocytes. By transmission electron microscopy (TEM), the condition is characterized by the presence of lamellar bodies, which are regarded as lysosomal in origin; these are referred to as (lysosomal) lamellar bodies. As phospholipid is produced by Type II pneumocytes, and phagocytosed by alveolar macrophages, under normal conditions there is a background level of phospholipid visible as lysosomal membranous whorls within these cells. The term lamellar body refers to the excessive accumulation associated with phospholipidosis. Phospholipidosis is most common in rats but may also be seen in other laboratory species.

Differential diagnoses: **Pulmonary alveolar proteinosis**; **Pulmonary inflammation**.



Pulmonary alveolar phospholipidosis, alveolar macrophage, lung rat, transmission electron micrograph.

Pulmonary alveolar pigmented macrophages reflect the phagocytic function of alveolar macrophages leading to engulfment of any inhaled dusts or particulates deposited in the alveoli. These phagocytosed particles often cannot be broken down by the macrophage's lysosomal degradation pathways, and thus accumulate within the cytoplasm. If they are innocuous, they remain within the macrophage until the cell itself is either cleared via the mucociliary escalator or lymphatics, or they accumulate in aggregates within the interstitium, referred to as "pulmonary sumps."



Pigmented alveolar macrophage aggregation, lung, rat H&E.

Pulmonary alveolar proteinosis (PAP) is a condition characterized by the progressive accumulation of amorphous, eosinophilic, periodic acid-Schiff (PAS)-positive, granular material in the alveoli. This is associated with relatively sparse numbers of foamy macrophages that stain positively for neutral lipids. Focal proliferation of Type II pneumocytes may also be seen. In chronic examples, there is usually an associated lymphocytic inflammatory response, and sometimes focal fibrosis. Ultrastructurally, the intra-alveolar material is composed of lamellar bodies and tubular myelin (i.e., surfactant). In its advanced stage, the condition may be readily distinguished from phospholipidosis by the predominance of eosinophilic material, relatively few foamy macrophages, and the presence of neutral lipid within macrophages. However, in the early stage both conditions are characterized by focal accumulations of foamy macrophages, and a differential diagnosis relies on the presence of neutral lipid in PAP and phospholipid in phospholipidosis. The etiologies involve exposure to dusts such as

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quartz, or immunosuppression with inhibition of GM-CSF (granulocyte-macrophage colony-stimulating factor, including therapeutic monoclonal antibodies), the cytokine essential for macrophage catabolism of excess surfactant.

Differential diagnoses: **Pulmonary alveolar phospholipidosis**; **Pulmonary edema**.

Synonym(s): **Alveolar lipoproteinosis**.



Pulmonary alveolar proteinosis, lung rat, H&E.

Pulmonary arteriolar medial hypertrophy as a result of pulmonary hypertension causes a thickening of the tunica media due to smooth muscle hypertrophy and may extend beyond to include thickening of the tunica adventitia due to increased connective tissue. There may also be a reduction in the number of smaller, peripheral arterioles that appear non-muscular. Pulmonary arteriolar hypertrophy should not be confused with the normal presence of cardiac muscle around the major branches of pulmonary veins in rodents and the normally thick walls of the oblique zone of the pulmonary arteries, particularly in rats. Pulmonary arteriolar medial hypertrophy must be differentiated from sectioning artifact (e.g., tangential section).

Pulmonary arteriopathy typically occurs secondary to intravenous (i.v.) injection or infusion studies that result in the production of thromboemboli or embolized fragments of hair shaft or bacteria which, due to the extensive, fine vascular bed of the lung, become entrapped in the pulmonary vasculature. Once lodged, they provoke an inflammatory reaction; thus the lungs in animals from i.v. studies often show a range of pathologies including arterial endothelial hypertrophy/hyperplasia, medial thickening, perivascular eosinophils, bacteria-induced inflammation, granulomas, and macrophage accumulation.

Pulmonary atelectasis in laboratory animals is generally recognized at necropsy and is seen as an area of collapsed lung or a collapsed lobe. It usually develops secondary to an airway obstruction; thus the extent of the collapse is determined by the anatomical location of the affected airway. The airway obstruction may be due to the presence of a foreign body, inflammatory exudate, bronchiolitis obliterans, or mucus plug. Once the obstruction forms, the distal alveoli become deflated, collapse, and the lack of airflow prevents their subsequent re-expansion. As the condition must be distinguished from inadequate inflation-fixation, particularly in the case of the lobar form, the initial necropsy observation is of diagnostic value. Pulmonary atelectasis must differentiated from artifactual collapse of the lung.

Synonym(s): **Pulmonary fetalization**.

Pulmonary choristoma is a rare congenital tumor-like proliferation of cells characterized by the presence of normal cells or tissues at a location other than their usual site. An example is poorly circumscribed bundles of skeletal muscle fibers within the pulmonary parenchyma. Refer to **Respiratory System** in Appendix 2 for further information.

Pulmonary club cell degeneration/necrosis may be observed in the small airways (bronchioles) of the lungs. As these cells contain abundant xenobiotic metabolizing enzyme systems, they are subject to species differences and are vulnerable to chemical-induced metabolic activation via P450, with a potential for the production of toxic metabolites and consequent cell degeneration and necrosis.

Pulmonary club cell eosinophilic inclusions may be observed in the small airways (bronchioles) of the lungs. Careful examination of the terminal bronchiolar epithelium from control rats occasionally reveals the presence of single, large, eosinophilic inclusions, which occupy most of the characteristic apical cytoplasmic bleb. The numbers of these inclusions have been shown to increase by inhalation exposure to corticosteroids. The inclusions demonstrate strong, positive immunoreactivity for surfactant protein D (SP-D), a protein domain predominantly found in lung surfactant. These inclusions have not been reported in other laboratory species.

Pulmonary club cell regeneration and hyperplasia is characterized by nascent cells that are basophilic, lack the characteristic apical bleb of mature club cells, and have the ability to self-renew or differentiate into ciliated or goblet cells. Club cells (i.e., bronchiolar exocrine cells) are the progenitor cells found in the terminal and respiratory bronchioles. They are largely responsible for epithelial repair. Following damage, they become hyperplastic and may undergo squamous metaplasia. Refer to **Respiratory System** in Appendix 2 for further information.

Pulmonary club cells (formerly known as Clara cells) are a cell type that is generally confined to the terminal and respiratory bronchioles, although in the mouse they are found throughout the airways, including the trachea. The cells have a characteristic apical bleb, which suggests apocrine secretion capability. In most species, club cells contain large amounts of drug-metabolizing enzymes, and are also thought to be involved in the synthesis of airway surfactant; however, in the dog, the cell cytoplasm is mostly occupied by glycogen

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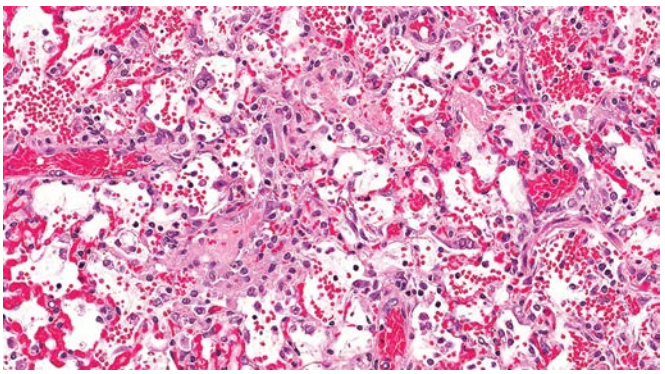
granules. The cells are readily identified immunohistochemically with a CC16 antibody.

Synonym(s): **Clara cell**.

Pulmonary club cell vacuolation may be observed in the small airways (bronchioles) of the lungs and may occur due to the presence of cytoplasmic phospholipid or neutral lipid. The former is inevitably associated with pulmonary alveolar phospholipidosis, and the latter is seen in dogs given inhaled corticosteroids. Immunohistochemistry using adipophilin (neutral lipids) and lysosome-associated membrane protein2 (LAMP2; lysosomes) antibodies readily distinguishes between the two etiologies.

Pulmonary cystic keratinizing epithelioma is more complex than the simple pulmonary keratinizing cyst in that it manifests greater keratinization and extends into the adjacent airways. Refer to **Respiratory System** in Appendix 2 for further information.

Pulmonary diffuse alveolar damage is a generalized term which may be applied to a sequence of changes that occur following alveolar wall injury, characterized by distinct pathological phases: exudative, proliferative, and fibrotic. The exudative phase is characterized by congestion, interstitial edema, alveolar edema, endothelial and epithelial necrosis, and hyaline membrane formation overlying sites of alveolar epithelial denudation. The proliferative phase involves Type II pneumocyte hyperplasia and early fibroblast proliferation; the

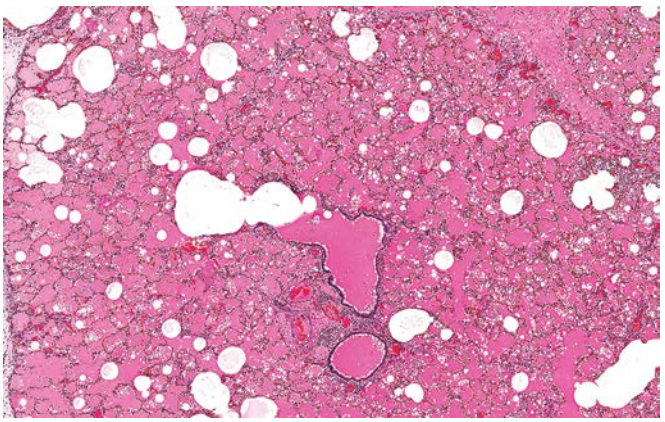


Pulmonary diffuse alveolar damage, lung rat, H&E.

fibrotic phase involves interstitial myofibroblast activity and collagen deposition.

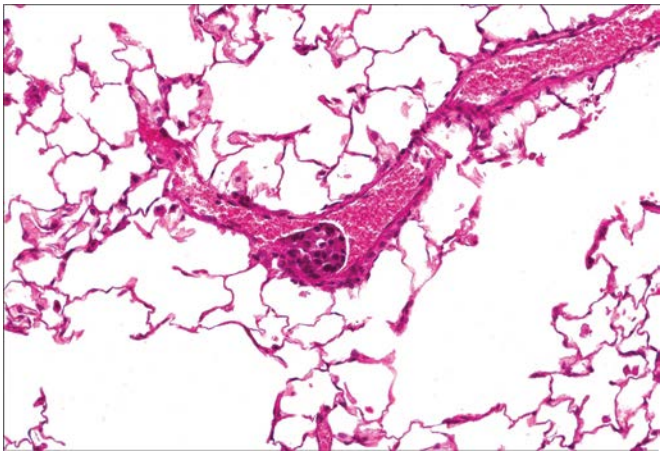
Pulmonary edema appears as acellular, amorphous eosinophilic material, either expanding perivascular loose connective tissue (i.e., pulmonary interstitial edema), or in more severe cases, within the air spaces themselves (i.e., pulmonary alveolar edema). The lack of cellularity allows differentiation from pulmonary alveolar proteinosis, and fibrin may be differentiated by the use of a phosphotungstic acid hematoxylin (PTAH) stain.

Differential diagnoses: **Pulmonary alveolar proteinosis**; **Pulmonary diffuse alveolar damage**.



Pulmonary edema, lung rat, H&E.

Pulmonary emboli are often thromboemboli originating in the systemic circulation distant from the lung, such as from a jugular thrombus following intravenous catheterization, and these may be sterile or septic. Intravenous dosing may also introduce fragments of skin or hair into the circulation by passage of the needle, resulting in pulmonary emboli consisting of foreign material. Such emboli will produce a suppurative or granulomatous inflammatory response which often includes multinucleate giant cells, and those containing keratin may be best visualized by polarized light. Occasionally, tumor emboli may occur in the lung. The dual arterial supply to the lung means that in otherwise healthy tissue, pulmonary emboli rarely result in infarction. Pulmonary emboli must be differentiated from artifact (i.e., postmortem clot).



Pulmonary tumor embolus, lung, rat, H&E.

Pulmonary excretion is the removal of drugs or drug-related products via the lung. See **Excretion** for further information.

Pulmonary fetalization is a synonym for pulmonary atelectasis. See the preferred term **Pulmonary atelectasis**.

Pulmonary fibrosis is an increase in the amount of collagen present or abnormal distribution of collagen within the lung. The presence of mature collagen may be demonstrated by Masson's trichrome or Van Gieson histologic stains. Established pulmonary

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fibrosis is frequently accompanied by hypertrophy of the overlying epithelial cells. A low-grade mononuclear inflammatory cell infiltration may also be present. Classic models of lung fibrosis in rodents include inhalation of crystalline silica and installation of bleomycin. Oxidative stress is believed to be important to the process of fibrogenesis in the lung, and there is evidence that within the respirable range, smaller particles (with higher surface area) have greater proinflammatory effects; hence fibrogenic potential. For example, intratracheal instillation of ultrafine (20 nm) titanium dioxide nanoparticles induces a greater inflammatory response than fine particles (250 nm) at the same mass dose.

Differential diagnosis: **Fibrosing alveolitis**.

Pulmonary hypoplasia is a failure to complete the alveolar stage of lung development, resulting in a primitive appearance closely resembling the saccular stage. A rodent model of human pulmonary hypoplasia has been developed using the herbicide nitrofen.

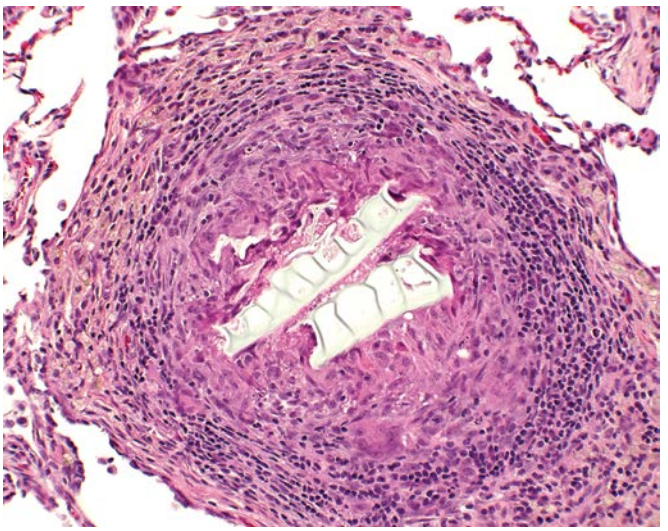
Differential diagnosis: **Pneumocyte Type II cell hyperplasia**.

Pulmonary infarction is rarely observed in laboratory animals, since lungs of most laboratory species are supplied by a dual anastomosing circulation (i.e., pulmonary and bronchial); thus vascular occlusion does not inevitably induce ischemia and consequent infarction. However, pulmonary infarction may be observed as a consequence of thromboembolic conditions, intravascular foreign bodies, and circulating malignant neoplastic emboli. The infarcted area undergoes necrosis and takes on a "ghost-like" appearance. Pulmonary infarction must be differentiated from autolysis.



Pulmonary infarction, lung rat, H&E.

Pulmonary inflammation may be seen in response to inhaled irritants, whether test article–related or due to foreign bodies. The type of inflammation can be categorized by duration (i.e., acute or chronic) defined by the primary cellular response seen. Acute inflammation is characterized by the presence of neutrophils, and may be accompanied by vascular congestion, edema, and exudates. The presence of eosinophils may indicate an immunologic response. If the primary cellular response is mononuclear, with a variable cell population that may include lymphocytes, macrophages, and plasma cells, then the inflammation is defined as subchronic or chronic. Chronic pulmonary inflammation is also associated with an increase in cellularity of the BALT. The type of cellular infiltrate may also indicate that the inciting cause is persistent or immunogenic. The presence of a persistent irritant invokes an inflammatory response termed chronic active that may progress to granulomatous inflammation. Chronic active inflammation is characterized by the presence of significant granulocytic and mononuclear cell populations comprising the infiltrate, indicating continued stimulation of granulocytes against a background of chronic inflammation, or resolution of the acute phase. Granulomatous inflammation is characterized by the presence of large macrophages with abundant cytoplasm (epithelioid cells), lymphocytes, and plasma cells, and in longstanding lesions, the presence of fibrosis.



Pulmonary (granulomatous) inflammation with foreign material, lung, dog, H&E.

Pulmonary keratinizing cyst is a rat-specific lesion composed of a simple, well differentiated, keratin-filled cyst. Refer to **Respiratory System** in Appendix 2 for further information.

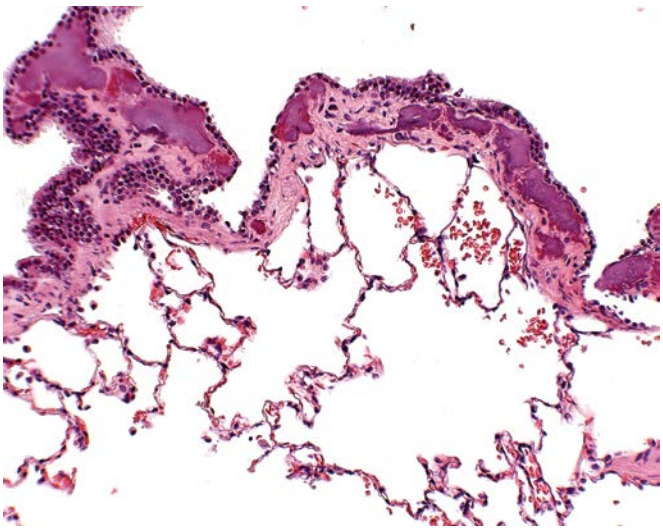
Pulmonary mesothelial hyperplasia is characterized by an increased thickness of the single cell mesothelial layer of the pleura, and may manifest papillary outgrowths. It is usually associated with inflammation, neoplasia, or can be aggravated by mechanical abrasion against the parietal pleura. Refer to **Respiratory System** in Appendix 2 for further information.

Pulmonary mineralization of the alveolar septa, bronchioles, and pulmonary vasculature appears in hematoxylin and eosin (H&E) staining as basophilic concretions along the basal lamina of affected epithelia, and occurs in a primarily intimal or subintimal location in the affected vasculature. Concretions are usually linear, but rarely appear as rounded to irregular, laminated bodies referred to as microliths. Pulmonary mineralization is associated with chronic renal disease (e.g., advanced cases of chronic progressive nephropathy

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in the rat) and has been seen following dosing of vitamin D analogs or excessive supplementation of marmosets with vitamin D as prophylaxis against simian bone disease. In addition, pulmonary mineralization has been noted in dogs following chronic inhalation administration of corticosteroids, producing a Cushing's disease–like syndrome. Must be differentiated from inhaled mineral or bone.

Differential diagnosis: **Pulmonary osseous metaplasia**.



Pulmonary mineralization, lung, dog, H&E.

Pulmonary osseous metaplasia is characterized by the presence of eosinophilic osseous material in alveoli. The etiology is uncertain, but it is not associated with inflammation. Refer to **Respiratory System** in Appendix 2 for further information.

Pulmonary perivascular eosinophil accumulation may be seen as a spontaneous lesion of unknown etiology in rats, and as its name suggests, is characterized by the accumulation of eosinophils in the perivascular connective tissues. A severe form of this condition, characterized by localized alveolar involvement, may be seen in the lungs of brown Norway rats.

Pulmonary resistance (airway) is the resistance of airflow in the respiratory system causing a pressure gradient during inspiration or expiration. Airway resistance is mainly influenced by the friction encountered when moving air into and out of the lungs. This friction can be increased by decreasing the radius of the airway or disrupting the laminar flow (assuming the length of the airway and the viscosity of the air remain constant). For laminar flow, the respiratory system fluid dynamics can be quantified by the Hagen-Poiseuille equation (analogous to Ohm's law). The pressure difference is determined by the length and radius of the tube, the viscosity of the fluid (air), and the flow rate. Factors affecting resistance are therefore any change in these parameters. The pressure gradient is also affected by turbulent flow. Turbulent flow dramatically increases resistance compared to laminar flow. Currently, there are no equations that can accurately describe resistance during turbulent flow. Whenever there is an increase in resistance, a much larger driving pressure is required to produce the same ventilation (labored breathing). Therefore, any disruption inside the respiratory system to decrease the size of the tube or the laminar flow will add to difficulty in breathing. The elasticity of the lungs will also impact respiratory efficiency and is a critical component in measured respiratory airway resistance. Fibrosis can significantly decrease compliance, while emphysema increases compliance.

Pulmonary resistance (vascular) is resistance that is influenced by the length and diameter (radius) of the blood vessels, as well as blood viscosity. In particular, pulmonary vascular resistance (PVR) is inversely proportional to pulmonary blood flow and lung volume (inspiration or expiration), and directly proportional to arterial oxygen concentration (hypoxia = vasoconstriction). Chronic PVR (pulmonary hypertension) is associated with pulmonary, cardiac, or systemic disease. Physical signs are often absent, and if left unchecked can lead to enlargement of the right ventricle of the heart with a shift in the electrical axis that may lead to heart failure. Some of the reported symptoms are edema, weakness, fatigue, syncope, and angina.

Pulmonary segmental fibrosis, see the preferred term **Fibrosing alveolitis**.

Pulmonary squamous cell carcinoma is a rare malignant neoplasm that is believed to arise from alveolar or bronchiolar epithelium. It is characterized by variable keratinization, cellular atypia, increased mitoses, and areas of necrosis. Invasion of adjacent pulmonary structures may occur. Refer to **Respiratory System** in Appendix 2 for further information.

Pulmonary squamous cyst, see the preferred term **Pulmonary cystic keratinizing epithelioma**.

Pulmonary squamous epithelioma, see the preferred term **Pulmonary cystic keratinizing epithelioma**.

Pulmonary squamous metaplasia is a replacement of alveolar epithelium by squamous cells. Refer to **Respiratory System** in Appendix 2 for further information.

Pulmonary surfactant is a mixture of approximately 90% lipids (mostly phospholipids), and approximately 10% proteins (A–D), and is responsible for reducing alveolar surface tension. It is synthesized and secreted by the alveolar Type II cells as lamellar bodies which unravel to form tubular myelin. The tubular myelin subsequently disaggregates to form an alveolar surface film. Most surfactant is recycled by Type II cells with the remainder being catabolized by alveolar macrophages. Of the surfactant proteins, SP-B and SP-C become incorporated into the phospholipid membranes and stabilize the alveolar surface film; SP-A has a role in the formation of tubular myelin, while SP-D regulates the size of the surfactant lipid pool. In addition, SP-A and SP-D are components of the innate immune system, functioning as collectins (i.e., collagenous Ca2+-dependent defense lectins), binding to a broad spectrum of microorganisms.

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Pulmonary surfactant dysfunction (PSD) may be detected in acute alveolar injuries as an early change before being subsequently obscured as other more visible pathologies develop. It can be detected by transmission electron microscopy (TEM), manifesting as changes in either the intracellular or alveolar surfactant pools, or both. The alveolar pool is normally composed of recently secreted lamellar bodies, tubular myelin, a lining film, and a few unilamellar vesicles, whereas in dysfunction there are decreases in the first three, but greatly increased numbers of the unilamellar vesicles. The intracellular pool is stored as lamellar bodies within the Type II pneumocytes, and dysfunction may manifest as increased or decreased numbers or size or configuration of these bodies. Dysfunction may also be detected by measurement of surface tension or by the detection of surfactant gelation characterized by changes in rheology (i.e., elasticity and viscosity) of surfactant obtained by bronchoalveolar lavage (BAL).

Pulmonary toxicity is an adverse effect of a drug or chemical on the lungs. It may occur as a direct result of inhalation of a toxicant (e.g., asbestos), or as a target organ of a systemically available drug or chemical (e.g., amiodarone).

Pulp concretion is a mineralized structure arising in the pulp cavity. These discrete calcified bodies may be single or multiple within one tooth. Generated among necrotic cells or connective tissue, these structures must be differentiated from denticles, which are composed of dentin and variable cellular components. Pulp concretions have been reported in rodent incisors as well as in other types of teeth.

Differential diagnosis: **Denticle**.

Synonym(s): **Pulp stone**.



Pulp concretion in the tooth of a rat. Decalcified tooth, H&E.

Pulp stone, see the preferred term **Pulp concretion**.

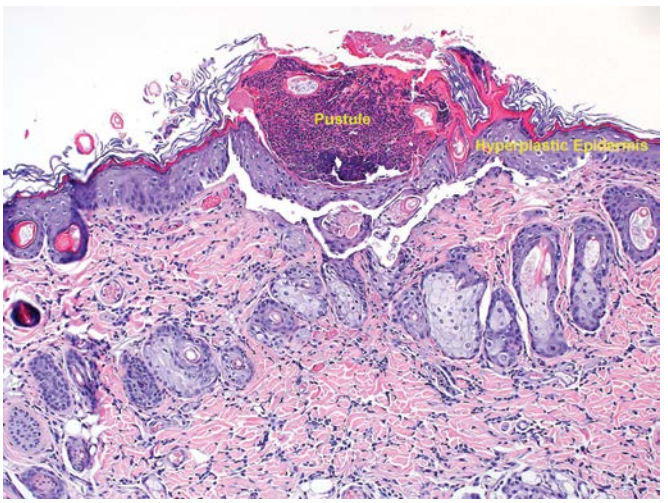
Pure red cell aplasia (PRCA) is an uncommon disorder that may occur in the development of red blood cells. Erythroblasts are extremely low or absent in the bone marrow, but white blood cell and platelet production remain normal. This is different from aplastic anemia, where all cell types are depleted. The bone marrow is usually normocellular, but individuals have a severe anemia and very low reticulocyte counts. Typically, there are less than 0.5% erythroblasts in the bone marrow. PRCA can be a congenital or an acquired condition. Congenital disorders have limited survival. Acquired PRCA has been associated with viral infections and as an adverse reaction to medications, and are often reversible. Chronic PCRA is also associated with hematologic malignancies, solid tumors, autoimmune disorders, and thymomas.

Purkinje cell necrosis is a subtype of neuronal necrosis affecting Purkinje cells (neurons) in the cerebellum of the brain. See **Neuronal necrosis** for further information.

Purpura is a term for hemorrhage, larger than a petechial or ecchymosis. See **Petechia** for further information.

Purulent inflammation, see the preferred term **Suppurative inflammation**.

Pustule is a well-demarcated, raised, focal localized accumulation of largely degenerate/variably viable inflammatory cells and cell debris below the stratum corneum of the epidermis (subcorneal), within the stratum corneum (intracorneal), within the cellular epidermis (intraepidermal/suprabasilar), or immediately below the epidermis (subepidermal). The lesion

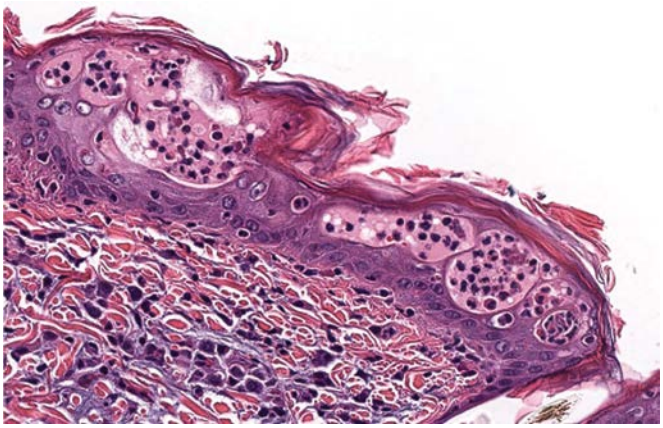


Pustule in skin of CD hairless rat; H&E. Underlying epidermis is hyperplastic.

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can be further subcategorized by the primary inflammatory cell population present being neutrophilic, lymphocytic, eosinophilic, or mononuclear. Pustules are typical of many infections and immune-mediated diseases (e.g., pemphigus foliaceus and pemphigus vulgaris).

Synonym(s): **Microabscess**.



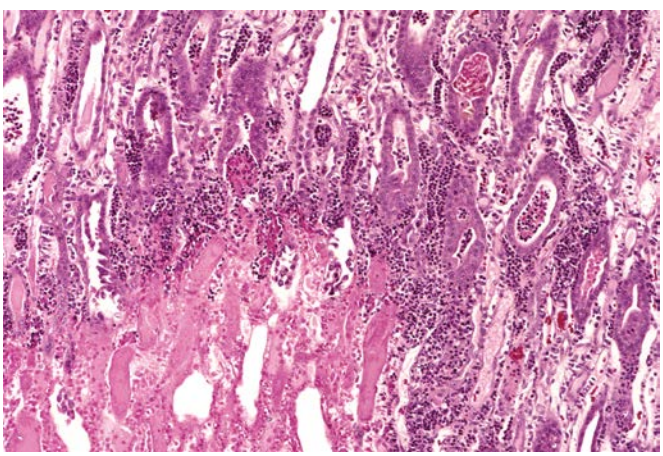
Pustule in the skin of a cat, H&E. Note also the underlying inflammation within the dermis; these cells are making their way to the epidermis.

PXR (pregnane X receptor) is a member of the nuclear receptor superfamily, which together with constitutive androgen receptor (CAR) acts as a sensor for xenobiotic compounds and induces the synthesis of enzymes involved in their metabolism. Many drugs induce metabolizing enzymes through interaction with PXR, which binds to DNA response elements as a functional heterodimer with the retinoid receptor (RXR). Endogenous agonists include progesterone, 17α-hydroxyprogesterone, 17α-hydroxypregnenolone, 5α-dihydroprogesterone, 5β-dihydroprogesterone; xenobiotic agonists include rifampicin, St. John's wort, and paclitaxel.

Pyelitis, see the preferred term **Renal pelvic inflammation**.

Pyelonephritis is an acute inflammatory process involving the parenchyma of the kidney and is particularly evident in the cortex. It is usually a result of bacterial infection which can be either bloodborne, or more commonly arises as an ascending infection from the urinary tract. Rats are particularly prone to the latter due to a propensity for spontaneous vesicoureteral reflux. Other initiating factors include renal pelvic calculi and papillary necrosis. Histologically, the lesion is characterized by tubule basophilia and infiltration of the cortex and medulla interstitium with neutrophils. Plugs of neutrophils may also be present in tubule lumens. Over time the acute phase is followed by a more chronic form of inflammatory change with mononuclear cell infiltration and minimal fibrosis.

Synonym(s): **Ascending pyelonephritis**.

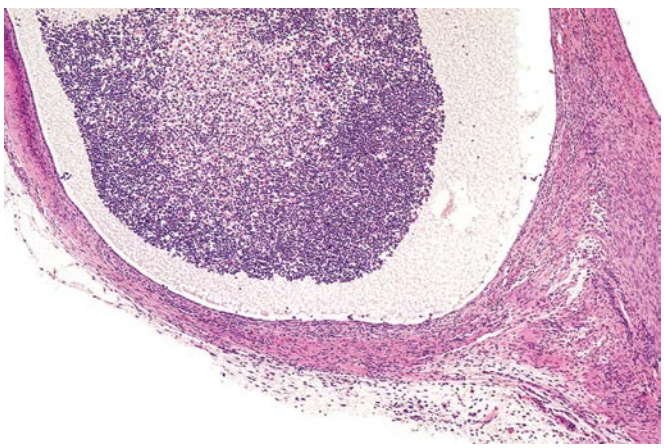


Papillary necrosis with pyelonephritis, rat kidney, H&E.

Pyknosis is shrinkage or condensation of the nucleus during necrosis and apoptosis.

Pyometra is suppurative inflammation of the uterus. The uterus is grossly filled or distended with a suppurative exudate (pus). Pyometra may occur with an open (draining) or closed cervix. Microscopically the exudate is composed of endometrial secretions with numerous activated and degenerative neutrophils, necrotic cellular debris, and (often) hemorrhage. Abundant bacteria may be evident. The endometrium may be ulcerated and have areas of squamous metaplasia.

Differential diagnoses: **Endometrial inflammation**; **Mucometra**.



Accumulation of uterine luminal neutrophils, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Dixon, D. et al. 2014. *J Toxicol Pathol* 26(3 Suppl):1S–107S.)

Pyothorax is the accumulation of suppurative exudates within the thoracic cavity and pleura, and often extends to involve the lung parenchyma. It is differentiated from other fluid accumulations within the thoracic cavity by the presence of inflammatory cells.

Differential diagnoses: **Hydrothorax**; **Hemothorax**; **Chylothorax**.

Synonym(s): **Suppurative pleuritis**.

Pyramidal necrosis is a subtype of neuronal necrosis affecting pyramidal cells (neurons) in the brain, usually the cortex, hippocampus, or amygdala. Pyramidal neurons have a pyramidal-shaped body. See **neuronal necrosis** for further information.

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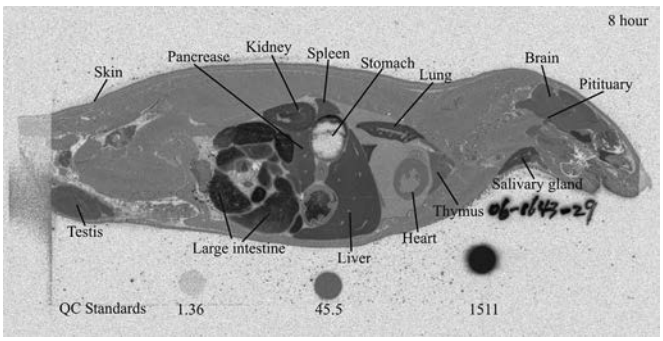
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Quality assurance (QA) encompasses all the planned and systematic activities implemented within the quality system, and demonstrated as needed, to provide adequate confidence that an entity will fulfill requirements for quality.

Quality control (QC) involves the operational techniques and activities that are used to fulfill requirements for quality.

Quantitative structure-activity relationship (QSAR) is a method of quantitative modeling relating to variation in measures of activity in a series of chemical compounds based on variation in chemical structure between compounds in a series. The use of QSAR in the study and identification of potentially toxic chemicals has recently garnered considerable interest as a means of the early selection (and attrition) of compounds of similar structure and activity in preclinical drug development.

Quantitative whole-body autoradiography (QWBA) a technique to visualize the distribution of a radiolabeled drug within organs and tissue of laboratory animals, usually rodents. At various time points after administration of the radiolabeled drug animals are sacrificed and frozen in a suitable medium. Once frozen, thin whole-body sections are prepared and exposed to a phosphor imaging plate, which generates a digital image showing distribution of radioactivity throughout the section. The tissue residence times may be determined by sacrificing animals at various times after a single dose. Studies are usually performed in the rat strain used for toxicology studies, which are usually albino rats, to assess whether potential binding to melanin groups of pigmented rats may be included. A typical autoradiogram is shown below.



Quiescent uterus, see the preferred term **Endometrial atrophy**.

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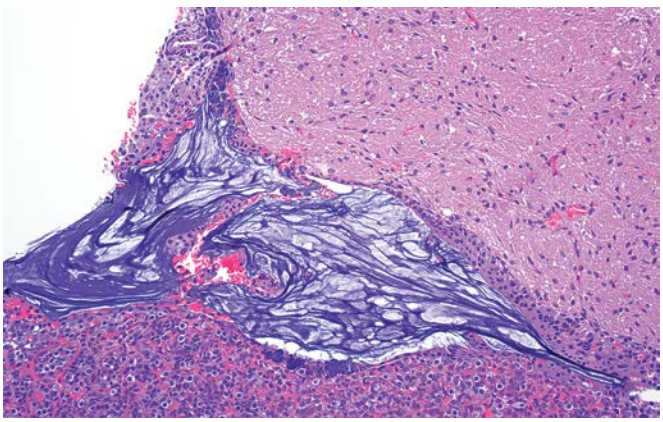
Randomization is the process of making something random, that is, removing or reducing bias from a selection process. Randomization is typically used to empower statistical analyses in both nonclinical and human drug studies. In toxicology studies, it is particularly important when allocating animals to the various groups in order to avoid bias.

Ranula, see the preferred term **Mucocele**.

Rapid acetylators are persons capable of rapid acetylation of certain amine-, sulfonamide-, or hydrazine-containing drugs. See **Acetylator phenotype**, **Slow acetylators**, and **Acetylation** for further information.

Rathke's pouch is an embryologic structure involved in the formation of the pituitary gland that originates from pharyngeal roof ectoderm. During development, an invagination of the pharyngeal roof ectoderm (Rathke's pouch) forms and comes in contact with the neural ectoderm of the developing brain. Over the course of development, this invagination separates from the oral epithelium but retains communication with the neural ectoderm, ultimately giving rise to the adenohypophysis, while the neural ectoderm develops into the neurohypophysis. The point of contact between these two structures gives rise to the pars intermedia. In the postnatal animal, failure of closure of Rathke's pouch results in an embryologic remnant that can result in dilation of this space or become cysts.

Rathke's pouch persistence represents an embryologic remnant of Rathke's pouch (an embryologic structure involved in the formation of the pituitary gland that originates from pharyngeal roof ectoderm) that is located between the pars distalis and pars intermedia of the pituitary gland. Persistent Rathke's pouch can be a source of nonneoplastic cysts (pars intermedia cysts, Rathke's cleft cysts, congenital pituitary cysts) or dilation (dilated persistent Rathke's clefts) that are typically incidental, but in some instances, particularly if large, can compress surrounding structures such as the optic chiasm and pituitary gland. Histologically, the cysts can be lined by variably ciliated, pseudostratified to columnar epithelium, which can exhibit goblet cell differentiation, and contain mucin, eosinophilic proteinaceous material, and/or sloughed cells. In cases of ruptured cysts, associated inflammation and fibrosis may be present. Dilation of a persistent Rathke's pouch is observed as expansion of the space between the pars distalis and pars intermedia that often contains eosinophilic proteinaceous material and, less commonly, hemorrhage and cholesterol clefts. Both can occur in multiple species, including rodents, dogs, and nonhuman primates. Dilated persistent Rathke's pouches are relatively common in rodents.



Rathke's cleft cyst lined by ciliated columnar epithelium and containing red cells and mucin; cynomolgus monkey, H&E.

Raw data includes all original test facility records and documentation, or verified copies thereof that are the result of original observations and activities in a nonclinical laboratory study.

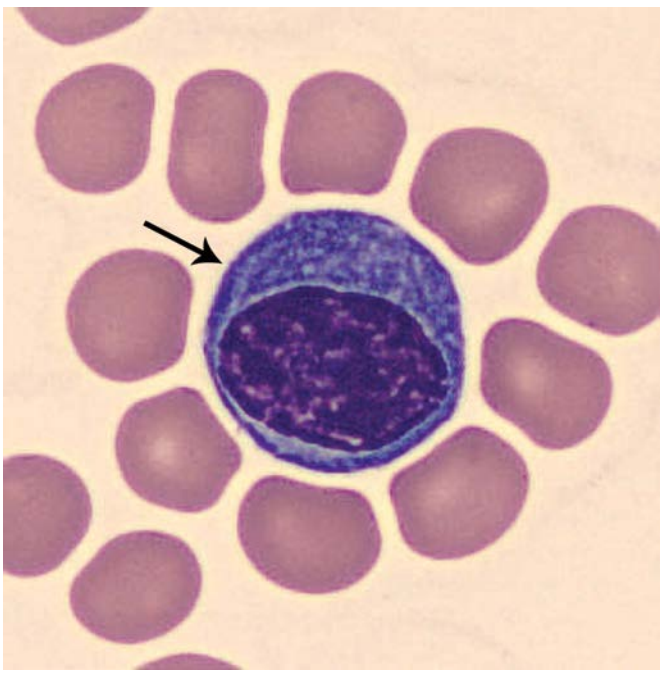
Reactive bone involves all bone cell types. After an insult to a bone structure (such as trauma), damaged osteocytes signal osteoclast recruitment to begin the healing process by removing damaged bone concurrent with temporary stabilization with new fibrous connective tissue and cartilage. Osteoblasts follow and create bone by intramembranous ossification; this new bone is woven. Over time, remodeling occurs, which results in normal trabecular bone of appropriate dimensions to meet biomechanical requirements. A classic example is the fracture healing process.

Reactive hyperplasia of lymph nodes occurs following a variety of stimuli. Different regions of the lymph node may be affected including the paracortex, germinal centers, and/or medullary cords. Reactive hyperplasia involving the follicles is characterized by prominent, active germinal centers that remain normal in appearance, without effacement of the normal nodal architecture. Reactive hyperplasia involving the paracortex (deep cortex, T-cell zone) is characterized by small, dark lymphocytes accompanied by scattered immunoblasts and plasma cells.

Reactive lymphocytes are highly variable in size, nuclear shape, and cytoplasmic characteristics. On blood smear examination, they tend to be larger than typical lymphocytes,

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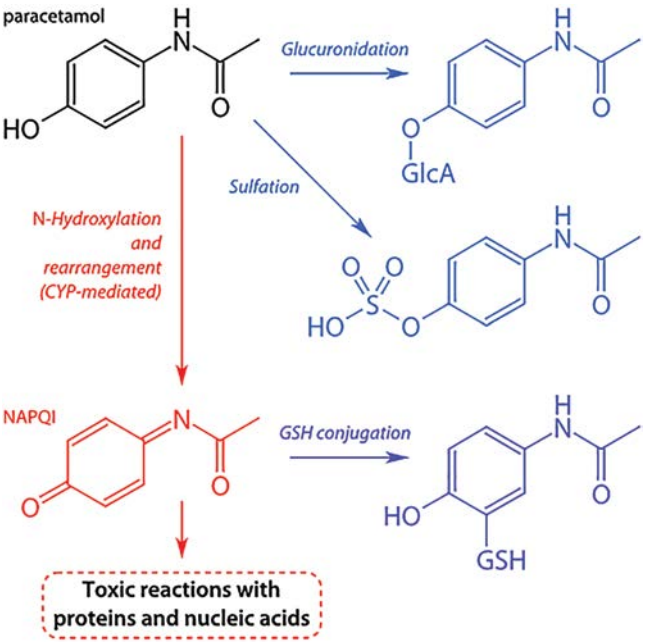
sometimes even larger than neutrophils. Their cytoplasm is more abundant and ranges from pale to darkly basophilic, occasionally containing small clear vacuoles, which make them sometimes difficult to differentiate from monocytes. Some reactive lymphocytes have a plasma cell–like appearance with a perinuclear, lighter-staining Golgi area. The nuclei of reactive lymphocytes are also variable in shape (e.g., round, ovoid to multilobulated) and location (central to eccentric). The nucleus chromatin, although less dense than in small lymphocytes, still exhibits a mature pattern without the presence of nucleoli. Reactive lymphocytes are nonspecific indicators of an ongoing immune response and tend to be observed commonly in younger animals that are exposed to new antigens. Their pleomorphism and frequent hyperactive appearance may be mistaken for a hematological malignancy.



Reactive lymphocyte (arrow), blood smear, monkey.

Reactive metabolites (reactive intermediates) are generally electrophilic metabolites formed by the oxidative metabolism of drugs. These reactive intermediates may interact with cellular macromolecules, such as proteins or DNA, resulting in toxicity or mutagenicity. The toxicity resulting from reactive metabolites is a function of several factors, including the chemical reactivity of the intermediate (i.e., the extent of metabolism by alternative routes which do not result in reactive intermediates and the inactivation [detoxification] of the reactive intermediates). This may be exemplified by the production of reactive intermediates from the metabolism of paracetamol (acetaminophen).

At low therapeutic doses paracetamol is metabolized by glucuronidation and sulfation, and only small quantities, if any, of the reactive intermediate (*N*-acetyl-*p*-benzoquinone imine [NAPQI]) are formed. At higher toxic



Metabolism of paracetamol and production of reactive intermediates.

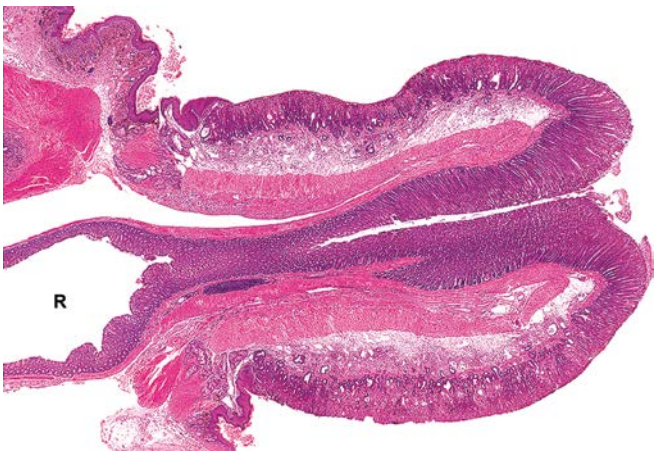
doses, the conjugation reactions are partially saturated, and the *N*-hydroxylation reaction becomes more predominant, forming greater amounts of the reactive metabolite NAPQI. However, this quinonimine is effectively inactivated by glutathione conjugation such that hepatotoxicity only occurs at very high doses when the hepatocellular glutathione is largely depleted. This example illustrates that although reactive metabolites may be formed from a drug or drug candidate, the extent to which this results in toxicity is a consequence of the balance between metabolic activation, the inactivation of the reactive intermediate, and metabolism by alternative routes. Examination of reactive intermediate formation has, however, become common practice as part of the profiling of drug candidates during drug discovery , often by screening for glutathione conjugates.

Reactive oligodendroglia, see the preferred term **Satellitosis**.

Reactive oxygen species are reactive molecules containing oxygen such as peroxides, superoxide, and hydroxyl radical. They are produced during normal oxidative biological processes and rapidly detoxified. Oxygen may be reduced to superoxide, which is converted to hydrogen peroxide by superoxide dismutase. The hydrogen peroxide in turn is reduced to water by catalase or glutathione peroxidase. If not reduced, it may generate hydroxyl radicals. Under conditions of oxidative stress, these detoxification reactions may be overwhelmed, and oxidative damage may occur.

Rectal prolapse is the term most commonly used for intestines protruding through the rectum. It is typically a macroscopic observation confirmed by microscopic findings of displaced anatomy, typically accompanied by varying degrees of inflammation, fibrinous adhesions, and necrosis.

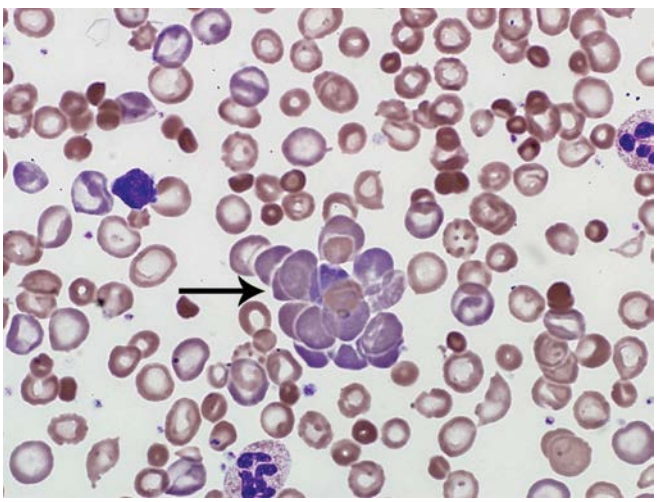
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Rectum, mouse (Bouin's fixed). H&E. Prolapse, longitudinal section. R = rectum. (Image reproduced with permission of the Japanese Society of Toxicologic Pathology from Nolte et al., 2016.)

Red blood cell, see the preferred term **Erythrocyte**.

Red blood cell agglutination or autoagglutination is seen with autoimmune disorders or transfusion reactions. Red blood cells form packets of three or more red blood cells in the absence of a clear organization pattern unlike rouleaux (see **Rouleaux** for further information), and occurs in autoimmune disorders and transfusion reactions. Red blood cells are bound together by immunoglobulins (mostly IgM, occasionally IgG) via irreversible bonds, which means that the red blood cell packets do not disappear upon mixing with saline. Red blood cell agglutination is usually associated with the presence of spherocytes on blood smear examination. Red blood cell agglutination is due to IgM or IgG directed against red blood cell membrane molecules, drug or infectious agents attached to the red blood cell membrane, or a combination of both red blood cell membrane component and a foreign hapten. As red blood cell agglutination is due to an immune response, it can take 10 days to a month to develop. If severe enough, red blood cell agglutination can be seen in the EDTA collection tubes. Visual red blood agglutination is used to assess matching for blood transfusion.



Red blood cell agglutination (arrow), peripheral blood smear, monkey.

Red cell distribution width (RDW) is automatically determined with the generation of the CBC using an automated hematology analyzer. RDW provides an objective assessment of anisocytosis, or size variation, in populations of red blood cells. Mathematically, the RDW is the coefficient of variation of the MCV and is shown in the following formula:

$$\text{RDW (\%)} = \text{(Standard deviation/mean) MCV} \times 100$$

High RDW values indicate that red blood cells are more variable in size. High RDW values are seen in regenerative anemia associated with higher numbers of immature red blood cells, reticulocytes. In contrast, a higher number of smaller red blood cells such as in iron deficiency anemia, or larger red blood cells such as in folate or B_{12} deficiency will also increase RDW values. The RDW may have higher sensitivity than MCV, so that lower numbers of smaller or larger red blood cells in a population may be observed as an increase in RDW before a change in MCV is observed. There is no clinical relevance associated with a decrease in RDW.

Red cell mass is the total mass of erythrocytes in circulation. Red cell mass is reduced in anemia and increased in polycythemia. Red cell mass can be quantitated by tagging an aliquot of blood with a radioisotope, reinfusing the tagged sample, and then determining the dilution of tagged cells in a sample obtained 1–3 hours later. Determination of red cell mass is used to differentiate between absolute and relative polycythemia. Total red cell mass takes into account both the red cell number and the red cell size. Red cell number varies with species. In general, smaller animals have higher red blood cell counts. Red cell size also varies with species, and in general, the smaller the animal, the smaller the mean cell volume (MCV). This variability in RBC and MCV across species allows red cell mass to remain fairly constant across species. Oxygen association/dissociation curves remain similar across species due to constant red cell mass.

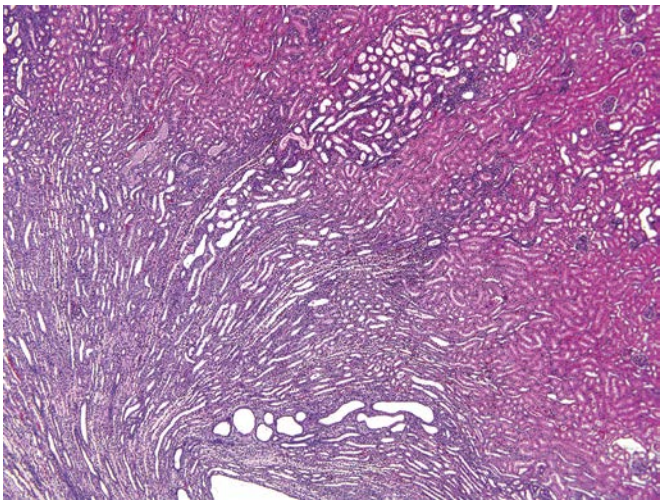
Red dead neurons, see the preferred term **Neurons, red dead**.

Reflex tachycardia is an increase in heart rate that is driven by the autonomic nervous system in response to a decrease in systemic blood pressure detected by baroreceptors. Baroreceptors detect changes in blood pressure, and atrial stretch receptors detect changes in blood volume; both can trigger changes in sympathetic and parasympathetic inputs to the sinoatrial (SA) node, which directly regulates the rate of stimulation of cardiac contraction and thus heart rate. Mammalian species vary in their sensitivity and responses to autonomic tone, with dogs notably sensitive to induction of reflex tachycardia. In nonclinical safety studies, test compounds that have direct effects on vascular resistance or autonomic tone may present with cardiac pathology findings attributable to reflex tachycardia. However, decreased blood volume and pressure during terminal exsanguination may also stimulate reflex tachycardia, which is not related to the test article, and contributes to

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peracute cardiac changes such as contraction bands in heart sections evaluated microscopically.

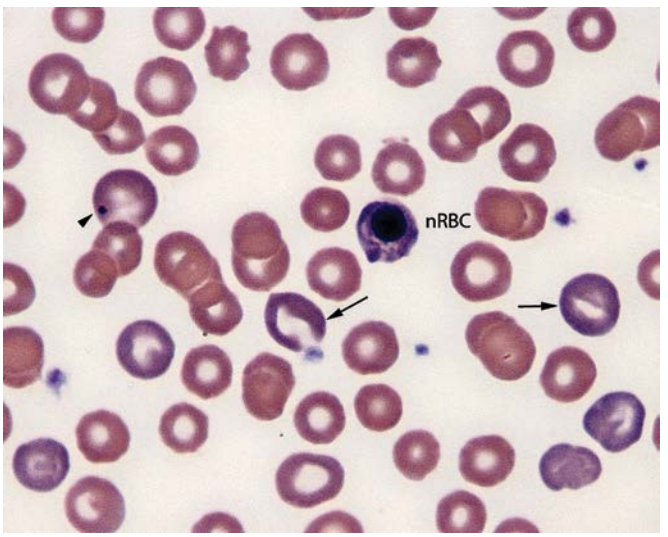
Reflux nephropathy is an ascending injury of the renal parenchyma. It comprises a constellation of renal tubule changes emanating from effects in the urinary tract, such as infection, inflammation, chemical-induced irritation, increased pressure, or transient obstruction. The renal changes consist predominantly of tubule dilation, running from the papillary and medullary collecting system into the cortex where the most prominent alteration is observed. Areas of tubule basophilia are prominent in the renal cortex, with dilation of the distal tubules and over time, atrophy of the proximal tubules. Chronically, the lesions resolve into fibrotic scars running from the subcapsular cortex down to the papilla. An example of reflux nephropathy is caused by chronic administration of melamine in rats, probably associated with pressure effects induced by melamine precipitation in the lower urinary tract.



Reflux nephropathy, rat kidney, H&E.

Regeneration involves the reconstitution of damaged tissue and/or lost cells by cells of the same type. For tissues to undergo this process, the cell type involved must be capable of regeneration (e.g., typical epithelia versus non-regenerative neurons). Also, for some tissues, the connective tissue infrastructure (e.g., basement membrane of renal tubule) must remain intact. This is to be contrasted with repair by fibrosis, in which there is replacement of damaged tissue by nonfunctional, fibrous connective tissue (scarring).

Regenerative anemia is caused by a loss of erythrocytes through bleeding or hemolytic anemia. In cases of anemia it is important to evaluate bone marrow function to classify as either regenerative anemia, where erythropoiesis is active and effective, or non-regenerative anemia, which has reduced or ineffective erythropoiesis. An increase in the absolute reticulocyte count best reflects the effectiveness of bone marrow erythropoiesis. The timing of reticulocyte assessment is important, as it takes 4 to 6 days for reticulocytes to peak, but reticulocyte counts may decline within 10 days, so that peak erythropoietic response can be missed with inappropriate sample timing. Increases in macrocytosis, anisocytosis, and red cell distribution width (RDW) are usually present in regenerative anemia due to increased numbers of larger, immature, polychromatophilic red blood cells. The presence of nucleated red blood cells (nRBC) is also a useful indicator of a bone marrow regenerative response. Basophilic stippling and Howell-Jolly bodies may also suggest accelerated erythropoiesis but are not specific markers of regeneration.



Regenerative anemia, blood smear, Wistar rat. Hallmarks of regenerative anemia include increases in polychromasia (arrow), nRBCs, and Howell-Jolly bodies (arrowhead) in the peripheral blood.

Regenerative hyperplasia, see the preferred term **Hepatocellular hyperplasia, regenerative**.

Regenerative renal tubule, see the preferred term **Renal tubular epithelial regeneration**.

Regional necrosis, see the preferred term **Infarct**.

Regurgitation, see the preferred term **Gavage-related reflux and aspiration**.

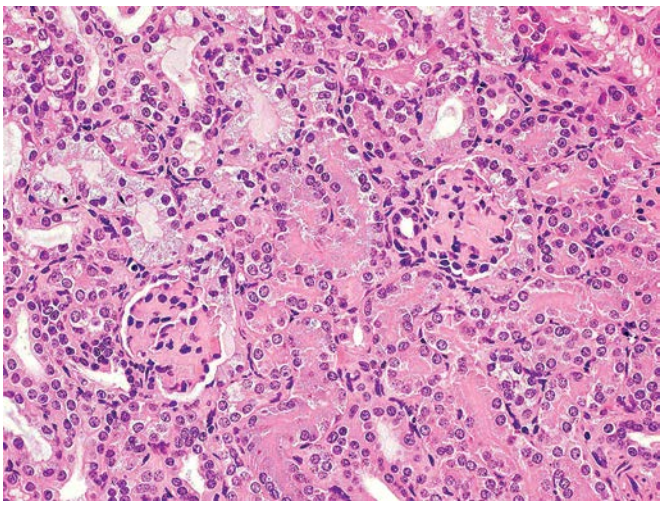
Renal abscess is a focal accumulation of neutrophils and necrotic debris in the renal parenchyma that is large enough to be visible grossly.

Renal agenesis, see the preferred term **Renal aplasia**.

Renal amyloidosis is a disease in which there is an accumulation of homogeneous eosinophilic material in the glomeruli. Accumulation of this material can also be prominent in the intertubular interstitium. The condition is common in laboratory mice, such as the CD-1 strain, and Syrian golden hamsters, but is rare in the rat kidney. The accumulating material stains negatively with periodic-acid Schiff (PAS) stain, but characteristically stains positively with Congo red and shows an apple-green birefringence under polarized light. Ultrastructurally,

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the accumulating material is composed of amyloid fibrils that are believed to represent misfolded protein or peptide. Small-molecule drugs or chemicals are not known to induce this alteration, but some may modify its development. Human monoclonal antibodies administered to cynomolgus monkeys and other species of laboratory animals can be associated with renal amyloidosis. See **Amyloid** for further information.



Amyloidosis, tubular and interstitial, mouse kidney, H&E.

Renal aplasia is congenital absence of a kidney, usually unilateral and occasionally seen in laboratory animals of all species.

Synonym(s): **Renal agenesis**.

Renal cell adenoma, see the preferred term **Renal tubular adenoma**.

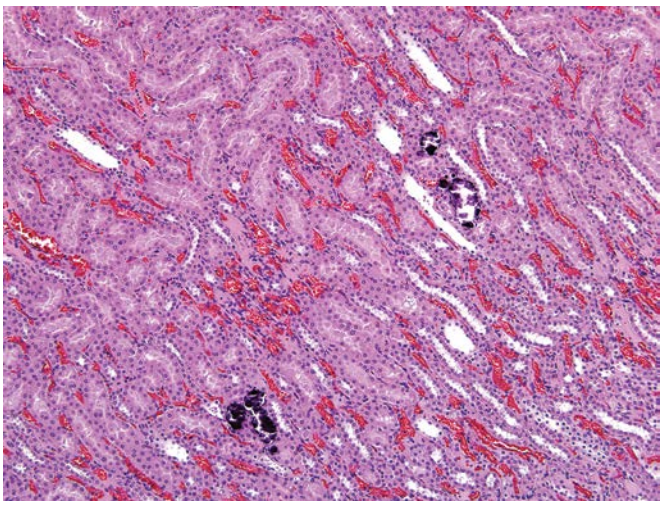
Renal cell carcinoma, see the preferred term **Renal tubular carcinoma**.

Renal clearance reflects the excretion of drug or drug products in the urine. It is the result of glomerular filtration, direct tubular excretion, and tubular uptake.

Renal collecting duct necrosis is death of the epithelial cells lining the collecting duct. See **Renal ductular necrosis** for more information.

Renal congenital pelvic dilation is the expansion in size of the renal pelvis present at the time of birth. Pelvic dilation may also be observed in toxicology studies and is likely linked with spontaneous vesicoureteral reflux in the rat, rather than being congenital.

Renal corticomedullary mineralization is deposition of large foci of mineral at the distal end of the pars recta proximal tubules near the junction of the outer and inner stripes of the outer medulla in the kidney. It is seen mainly in female rats when fed a diet with a calcium/phosphorus ratio imbalance, such as AIN-76. Corticomedullary (CM) junction is a misnomer, as the true CM junction in the rat is between the deep cortex and commencement of the outer stripe of the outer medulla. See Appendix 3 for more information.



Corticomedullary mineralization, kidney, rat, H&E.

Renal cystic tubule is a focal tubular dilation of increasing dimensions in the renal cortex or medulla, usually lined by flattened (or occasionally cuboidal) tubule epithelium. In rodents, cystic tubules are usually spontaneous and solitary, with little or no stainable contents by hematoxylin and eosin (H&E) stain.

Renal cytoplasmic granules accumulate in the cytoplasm of proximal convoluted tubules in the kidneys, and result from the chronic administration of antisense oligonucleotides to mice, rats, and monkeys. The accumulating granules are thought to be parent compound or a metabolite(s), as these compounds are preferentially excreted through the kidney. The uptake into the renal tubule is via the brush border, and granules accumulate in the lysosomes. Small cytoplasmic granules have also been identified in proximal tubule cells of the rat after exposure to anthraquinone. In the latter case, the small granules were identified as myoglobin.

Renal distal tubular necrosis is death of the epithelial cells lining the distal tubule. See **Renal ductular necrosis** for more information.

Renal ductular necrosis is oncotic death of sheets of multiple epithelial cells in the proximal, distal, or collecting tubules resulting in epithelial disintegration leaving cell debris within the tubule lumens forming granular casts. It is usually seen in either the proximal convoluted tubule (S1 and/or S2 segments) or, more frequently, in the pars recta portion of the proximal tubule (S3 segment). Classic examples are the acute tubular responses in the S3 segment following administration of mercury salts or acetaminophen, and in ischemia, which usually involves the S3 proximal tubule. Acute tubular necrosis sometimes needs to be carefully distinguished from autolytic change in the proximal tubules. The latter can show a detachment of

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the degenerating cells from the basement membrane, and nuclei appear to fade (become "ghosted") in staining intensity rather than disintegrate. In acute tubular necrosis, tiny, densely staining fragments in the lumenal cellular debris represent disintegrating nuclei, and the cellular debris tends to be granular in texture. Acute tubular necrosis is rapidly followed by tubular cell regeneration. The presence of mitoses suggests prior genuine tubular necrosis versus autolytic change. See **Renal tubule epithelial regeneration** for further information.

Synonym(s): **Acute renal tubular necrosis**; **toxic nephrosis**; **renal tubular oncotic necrosis**; **renal tubular coagulative necrosis**.

Renal dysplasia is a developmental abnormality in rodents characterized by an intrarenal area of anomalous tissue including persistent primitive mesenchyme, altered tubules, cysts, and sometimes nonnative tissue such as cartilage. Renal dysplasia also occurs as a disorder in dogs and monkeys. This term has occasionally been used in the rat as nomenclature for preneoplastic tubule lesions but this usage is not recommended in rodent toxicologic pathology.

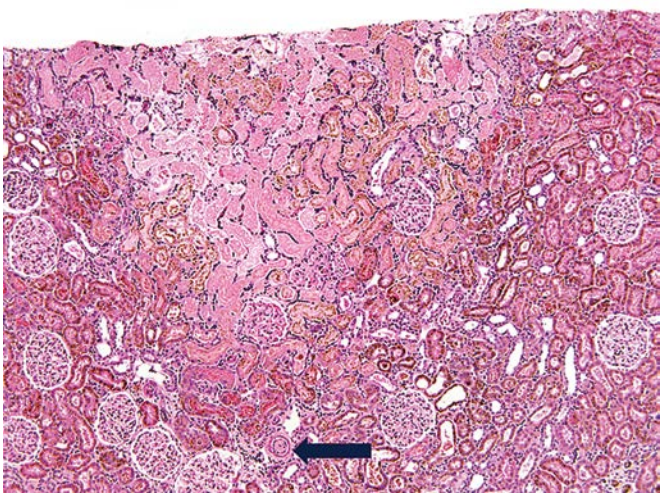
Renal eosinophilic droplets, see the preferred term **Hyaline droplet**.

Renal epithelioma, see the preferred term **Renal tubular adenoma**.

Renal excretion is the clearance of a drug or drug products via the kidney into the urine. See **Excretion** for further information.

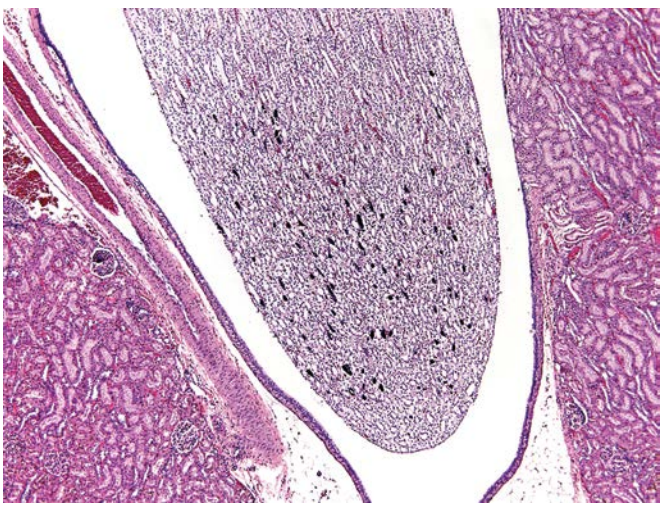
Renal inclusion bodies are rounded, variably sized, homogeneous profiles that can be intracytoplasmic or intranuclear. Intracytoplasmic inclusions due to D-amino acid oxidase have been observed in male and female rats as spontaneous occurrences, or following administration of propiverine hydrochloride or a norepinephrine/serotonin reuptake inhibitor. The bodies occurring in the proximal convoluted tubule or nucleus consist of finely granular, amorphous, eosinophilic material that have no limiting membrane. Intranuclear inclusions of this oxidase are surrounded by a clear halo consistent with chromatin margination. As D-amino acid oxidase is exclusively present in peroxisomes under normal conditions, it is likely that these intranuclear bodies are of peroxisome origin. Intranuclear inclusion bodies are also seen in the kidney of most species tested following chronic administration of lead salts. Lead-induced intranuclear inclusion bodies are eosinophilic and acid-fast, and consist of both lead and lead-binding proteins analogous to metallothionein. The latter are low-molecular-weight proteins that appear to sequester lead in a nontoxic form.

Renal infarct represents an area of dead kidney tissue resulting from failed blood perfusion to that specific renal tissue. The event may be acute or chronic. In the acute stage, it is a wedge-shaped lesion in the renal cortex characterized centrally by tubule necrosis, acute inflammatory infiltrates, and congestion. In the chronic stage, infarcts resolve into a scar-like lesion with capsular depression, tubule atrophy, and interstitial fibrosis. Although the vascular cause is not often found in a single histological section, thrombi or tumor emboli may sometimes be observed in kidney blood vessels as the etiology.



Renal infarct, rat kidney; arrow = tumor embolus, H&E.

Renal linear papillary mineralization is the presence of linear-shaped mineral deposits along the lumens of the thin descending limbs of Henle from the sharp U-bend in a proximal direction. This alteration is most prominent in the papilla but can also extend into the upper inner medulla. The mineral deposits have been shown to consist of calcium hydroxyapatite. This lesion is a hallmark of the chronic stage of α-2u-globulin nephropathy associated with renal tubule tumor development in male rats.



Linear papillary mineralization, rat kidney, H&E.

Renal lipomatous tumor of the kidney represents either a benign lipoma or a malignant liposarcoma. Lipomas are characterized by well-delineated aggregates of normal-appearing fat cells. Liposarcomas tend to be invasive and consist of adipocytes, adipoblasts, and undifferentiated mesenchymal cells. Lipomas

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and liposarcomas do not appear to be chemically induced. Refer to **Urinary System** in Appendix 2 for further information.

Renal mesenchymal tumor (RMT) is a malignant tumor of the rat kidney that generally contains a heterogenous population of mesenchymal cells. The main cell type is a fibroblast-like spindle cell, but RMTs can also contain smooth and striated muscle, cartilage, bone, or hemangiomatous cell types. RMTs frequently invade the renal pelvis and hilus. They can metastasize to the lungs or seed adjacent visceral organs in the abdomen. Refer to **Urinary System** in Appendix 2 for further information.

Renal microabscess is a discrete, focal aggregate of neutrophils in the interstitial tissue usually in the renal cortex, or in cortical tubule lumens. Microabscesses can be solitary, multifocal, or bilateral. They generally arise from systemic bacterial infections, but solitary microabscesses are sometimes seen in conjunction with end-stage chronic progressive nephropathy (CPN) in the rat.

Differential diagnosis: **Renal abscess**.

Synonym(s): **Renal tubulitis**.

Renal mineralization, see the preferred terms **Renal linear papillary mineralization** and **Renal pelvic mineralization**.

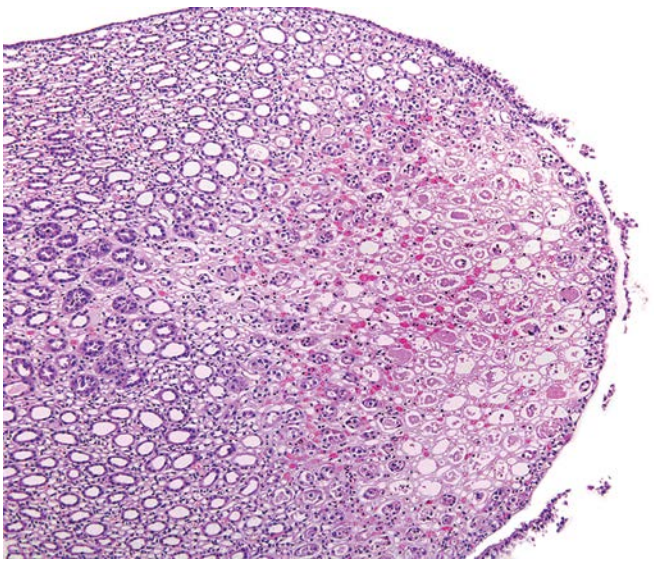
Renal osseous metaplasia is a spontaneous and discrete focus of osseous tissue, composed of osteoid and/or well-differentiated bone, occurring in the interstitium of the renal cortex or medulla.

Renal osteodystrophy, see the preferred term **Osteodystrophy fibrous**.

Renal papillary inflammation is the infiltration of inflammatory cells into the renal papilla. Renal papillary inflammation with neutrophils in the interstitium of the papilla or in lumens of the papillary collecting ducts is usually a precursor of pyelitis and/ or pyelonephritis.

Synonym(s): **Renal papillitis**.

Renal papillary necrosis is a term encompassing the early and late stages of degeneration and necrosis of the tip of the renal papilla. The early changes are characterized by loss of definition of structures at the papilla tip, particularly the interstitial cells between collecting ducts. Degenerative changes then involve the capillaries, and eventually the tubule epithelium. The degeneration can be restricted to the more distal parts of the papilla or involve all of this structure. The necrotic papilla stains lightly with hematoxylin and eosin (H&E) in comparison to the unaffected parenchyma, but remnants of the architecture can be visualized. Inflammatory cells and/ or mineral deposits accentuate the abscission zone between healthy and necrotic tissue, and in severe cases the necrotic papilla is sloughed into the renal pelvic space, where it is ultimately voided in the urine. A nodular form of urothelial hyperplasia often accompanies the injury associated with papillary necrosis. The rat is particularly prone to papillary necrosis, and a number of chemicals and drugs, including nonsteroidal anti-inflammatory drugs (NSAIDs) such as phenacetin and aspirin, are known to cause this lesion in humans. Phenacetin was withdrawn from the U.S. market in 1983 due to this risk. In some cases, as with ethoxyquin, there is a sex predisposition with male rats more affected than females. In dogs, severe dehydration may be associated with papillary necrosis.



Papillary necrosis, rat, H&E.

Renal papillitis, see the preferred term **Renal papillary inflammation**.

Renal parenchymal inflammation (also referred to as nephritis) is the infiltration of inflammatory cells into the interstitium of the kidney and may include both the medulla and the cortex. When acute, the predominant cell type is the neutrophil, while mononuclear cells predominate as lesions become chronic.

Synonym(s): **Chronic interstitial nephritis**; **nephritis**.

Renal parenchymal inflammation with neutrophils is an acute condition where polymorphonuclear neutrophils are the predominant cell type in the renal interstitium.

Synonym(s): **Suppurative nephritis**.

Renal pelvic inflammation is the infiltration of inflammatory cells into the renal pelvis. It is most commonly a sequela to an ascending bacterial infection from the lower urinary tract.

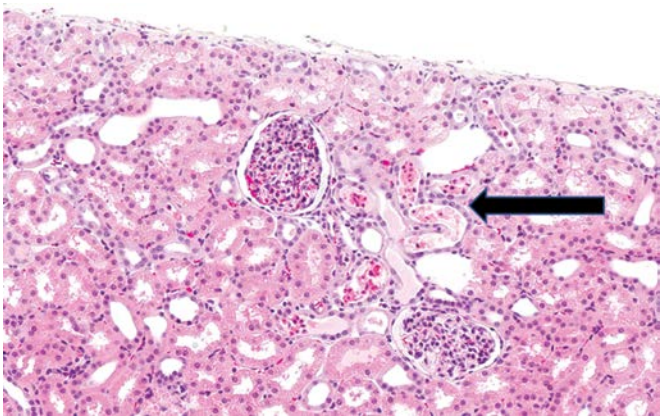
Renal pelvic mineralization refers to the presence of mineral deposits on the pelvic epithelium or in the renal pelvis lumen, particularly lodged in the blind ends of the fornices. This type of renal mineralization has occurred in association with the feeding of test articles that are poorly absorbed and osmotically active (e.g., sugar alcohols) that lead to altered mineral metabolism and increased excretion of urinary calcium. Accompanying clinical signs include soft stools or diarrhea,

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as well as cecal enlargement. The renal pelvic lesion is reversible only if the exposure is of short duration.

Differential diagnosis: **Renal corticomedullary mineralization**.

Renal proximal tubular necrosis is death of the epithelial cells lining the proximal tubule. See **Renal ductular necrosis** for more information.



Proximal tubular necrosis, acute, mouse kidney, H&E. (Reproduced with permission of Society of Toxicology from Frazier et al. 2012.)

Renal regenerative tubule, see the preferred term **Renal tubular cell regeneration**.

Renal sarcoma is a highly malignant tumor of the kidney. It is composed of fibroblast-like sarcoma cells that grow in fascicular patterns and are invasive. Renal sarcomas are rare neoplasms. Refer to **Urinary System** in Appendix 2 for further information.

Renal single cell necrosis is a term applied to scattered individual cells dying in the tubule lining or appearing as solitary, sloughed remnants within the tubule lumen. The cells can show various morphological forms, including apoptosis where the nuclei are fragmented, or as intact cells with condensed cytoplasm and contracted or pyknotic nuclei. Single cell necrosis is a common form of cell degeneration caused by toxic chemicals in other organs as well. See **Necrosis** for further information.

Renal toxicity describes any effect of a drug or chemical that adversely impacts kidney structure or function. Such toxicity can either be as a direct effect or indirectly through effects on hemodynamics, renal blood flow, or water-electrolyte balance.

Renal tubular adenoma (RTA) is a benign tumor of the kidney composed of a well-circumscribed proliferation of slightly pleomorphic tubular epithelial cells. Adenomas grow by expansion, lack a well-developed capsule or invasion, and show capillary ingrowth. They have the potential to develop into renal tubule carcinomas. Refer to **Urinary System** in Appendix 2 for further information.

Renal tubular calculi are small microcalculi (concretions of material, usually mineral salts) that form within individual nephrons or collecting ducts.

Renal tubular carcinoma is a malignant tumor of the kidney that is composed of tubular epithelial cells. They are generally large neoplasms that can be differentiated from adenomas by their larger size, pleomorphic to anaplastic cell morphology, areas of degeneration and hemorrhage, and increased numbers of mitoses. Carcinomas can invade the renal parenchyma and metastasize. Refer to **Urinary System** in Appendix 2 for further information.

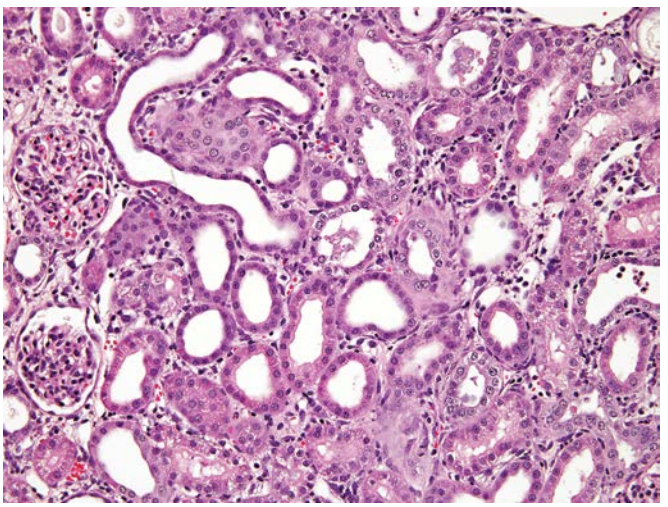
Renal tubular cast, see the preferred term **Hyaline cast**.

Renal tubular coagulative necrosis, see the preferred term **Renal ductular necrosis**.

Renal tubular dilatation, see the preferred term **Renal tubular dilation**.

Renal tubular dilation is an increase in the width of the lumens of renal tubules compared to their normal size for that age, strain, and species.

Synonym(s): **Renal tubular dilatation**; **renal tubular ectasia**.



Tubule dilation, rat kidney, H&E.

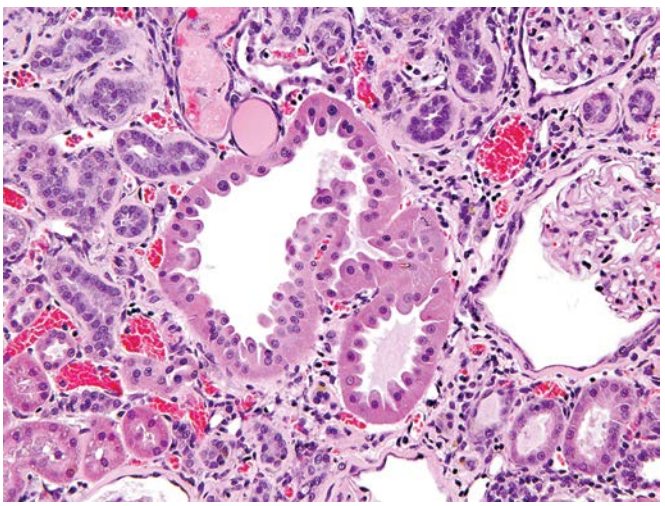
Renal tubular ectasia, see the preferred term **Renal tubular dilation**.

Renal tubular epithelial basophilia refers to an increase in basophilic staining of renal tubular epithelial cells as seen on a hematoxylin and eosin (H&E)-stained section. In most cases, basophilic tubules represent tubule regeneration; however, the term tubule basophilia can also be used for the early changes associated with chronic progressive nephropathy (CPN), renal tubule degeneration, and instances where there is an apparent absence of mitotic activity as in renal tubular atrophy.

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Renal tubular epithelial cell attenuation is the reduction in height and increase in width of epithelial cells, also referred to as flattening when viewed microscopically.

Renal tubular epithelial hypertrophy is considered an adaptive response characterized by an increase in volume and height of the tubule lining cells, with no increase in cell number or alteration of the single cell nature of the tubule lining. This is believed to occur in proximal convoluted tubules (PCT) in response to increased workload. It is frequently seen in the distal convoluted tubule (DCT) in response to sodium overload, and administration of diuretics such as furosemide. Renal tubule epithelial hypertrophy has also been observed in the collecting duct system in response to potassium depletion. Increase in kidney weight is a common finding in toxicology studies induced by agents metabolized in the kidney, implying tubule cell hypertrophy that is not histologically recognizable during routine microscopic evaluation.

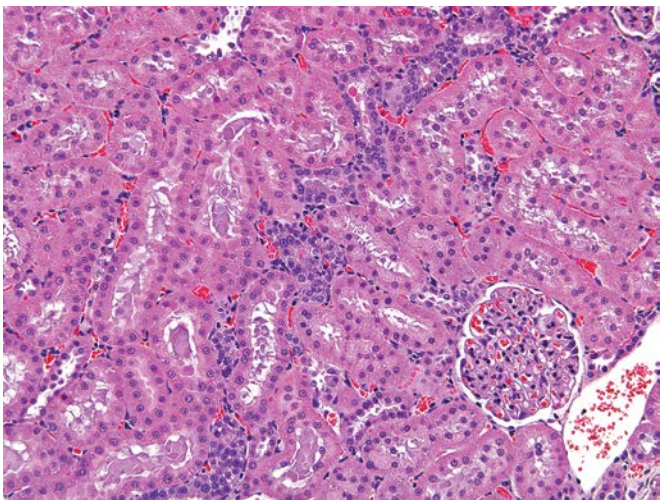


Tubule hypertrophy, rat kidney, H&E.

Renal tubular epithelial necrosis, see the preferred terms **Renal proximal tubular necrosis**; **Renal distal tubular necrosis**; or **Renal collecting duct necrosis**.

Renal tubular epithelial regeneration occurs following acute renal tubular necrosis; when attenuated, basophilic epithelium grows along the denuded basement membrane as the first stage of a regenerative process. The flattened regenerating cells become more cuboidal, and through proliferation, ultimately restore the tubule back to normal morphology. In tubules affected by single cell death, there is usually basophilia and an increase in scattered mitotic figures. Overproduction of cells during this regenerative period can lead to simple renal tubule hyperplasia when the injury is sustained by continued exposure to the toxic chemical. In toxicologic pathology, there is a tendency to diagnose basophilic tubules in general as regeneration, and either focal or multifocal in distribution.

Synonym(s): **Regenerative renal tubule**.



Tubule cell regeneration, rat kidney, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

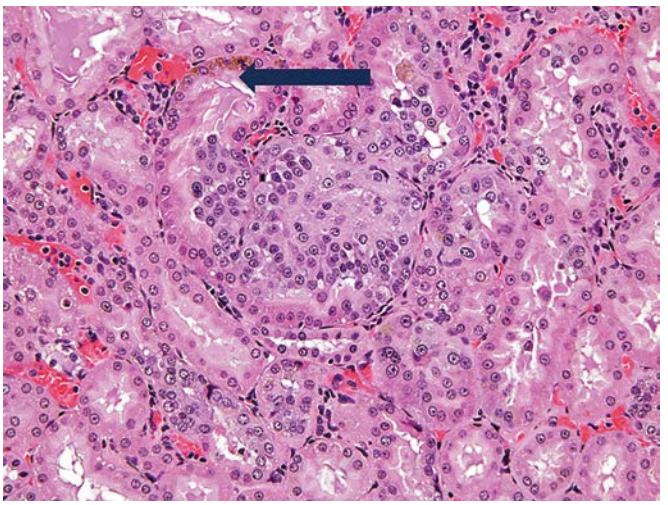
Renal tubular epithelial vacuolation is generally regarded as a degenerative alteration, but it is not a particularly common consequence of chemical-induced injury. It can affect any part of the nephron or urinary tract but is most commonly observed in the proximal convoluted tubule (PCT). It can also be a transient change. In the mouse and dog, renal tubule vacuolation is normal, and is also seen in the PCT of CD-1 male mice, and in the pars recta proximal tubules of beagle dogs. Renal tubule vacuolation is observed as scattered aggregates of clear, round cytoplasmic profiles of varying size, usually representing a hydropic change involving the lysosomal compartment of the proximal tubule epithelium, or lipid droplets which become clear or translucent spaces on histological processing. The most striking example of renal tubule epithelial vacuolation is seen in osmotic nephrosis. Gavage of oils such as mineral oil or dextrose results in tubular vacuolation that is transient and is not considered a degenerative change. Renal tubule epithelial vacuolation should be distinguished from artifactual, cytoplasmic rarefaction, which can occur as a tubule alteration caused by suboptimal histological processing, particularly in cells of the S3 segment of rats. See Appendix 3 for more information.

Renal tubular hyperplasia is a nonneoplastic proliferation of a single layer of tubule cells or can be a solid proliferation of tubular cells, termed atypical tubule hyperplasia (ATH), that is considered preneoplastic. Renal tubular hyperplasia is most often recognized as a component of the complex pattern of chronic progressive nephropathy (CPN). When part of CPN, it should not be diagnosed as a separate lesion. Renal tubular hyperplasia is generally not an induced lesion, while ATH is. Refer to **Urinary System** in Appendix 2 for further information.

Renal tubular oncotic necrosis, see the preferred term **Renal ductular necrosis**.

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Renal tubular pigmentation is the presence of yellow, brown, or eosinophilic fine or granular deposits within the tubule cytoplasm, most commonly in the proximal tubule. The pigment can be hemosiderin, lipofuscin (ceroid), bilirubin, or represent test article deposition. Hemosiderin accumulation results from intra- or extravascular hemolysis. Lipofuscin is a "wear-and-tear" pigment, and its accumulation in the kidney appears to have no functional or clinical significance. Bilirubin deposits can be associated with certain drugs that inhibit transporters and enzymes involved in hepatic uptake or biliary conjugation. See **Pigment** for further information.



Tubular pigmentation, rat kidney, H&E.

Renal tubular proteinosis, see the preferred term **Hyaline cast**.

Renal tubule is the functional unit of the kidney where resorption of water, electrolytes, and other molecules from the glomerular filtrate occurs.

Renal tubulitis, see the preferred term **Renal microabscess**.

Renin-angiotensin-aldosterone system (RAAS) is a complex multihormone system involved in the regulation of body fluid volume, plasma sodium concentration, and arterial blood pressure. Renin is a protein enzyme synthesized and stored by the juxtaglomerular (JG) cells of the kidneys as an inactive form called prorenin. When arterial pressure falls, the kidneys convert prorenin to its active form rennin, which enters the circulation and acts enzymatically to hydrolyze its plasma protein substrate, angiotensinogen, converting it to angiotensin I. Further conversion of angiotensin I to angiotensin II by angiotensin I-converting enzyme (ACE) occurs almost entirely within the lung. Angiotensin II causes intense vasoconstriction in arterioles, increasing peripheral resistance and raising systemic blood pressure. In addition to its vasoconstrictive properties, it also acts to decrease excretion of salt and water by the kidneys, thereby increasing interstitial fluid volume, and leading to a longer-lasting elevation of blood pressure. Angiotensin II also stimulates aldosterone secretion by the adrenal gland; a key function of aldosterone is to increase the sodium reabsorption in the kidney, thus increasing total body extracellular fluid sodium, and subsequent increased interstitial fluid retention. The balance between secretion, conversion, and degradation of the hormones of the RAAS maintains body homeostasis of fluid, sodium, and blood pressure. Disturbances of the RAAS occur when the organs responsible for production or conversion of the hormone elements become diseased, reducing their hormonal activity or receptivity to hormonal stimulation, such as in chronic kidney, heart, and lung disease or adrenal gland tumors.

Renin-angiotensin system (also termed the renin-angiotensin-aldosterone system [RAAS]) is a hormonal and signaling pathway regulating the body's blood flow and fluid balance. When renal blood flow is reduced, renin is released from the juxtaglomerular cell body, which splits the protein angiotensinogen to produce angiotensin I. This in turn is converted to angiotensin II by the angiotensin-converting-enzyme (ACE). Angiotensin II is multifunctional, but in particular is a powerful vasoconstrictor. It also stimulates release of aldosterone from the adrenal gland. Aldosterone influences the renal tubules to increasingly reabsorb sodium and fluid into the blood stream, at the same time decreasing potassium through renal excretion. The outcome is increased extracellular body fluid and increased blood pressure.

Reproductive cycle, see the preferred term **Estrous cycle**.

Reproductive System and Mammary Gland, Anatomy and Histology, see Appendix 3 for further information.

Reproductive toxicity, female involves adverse events caused by a substance (e.g., chemical, drug), a pathogen (e.g., microorganism, virus), or any other agent (e.g., radiation) that could affect the female reproductive function.

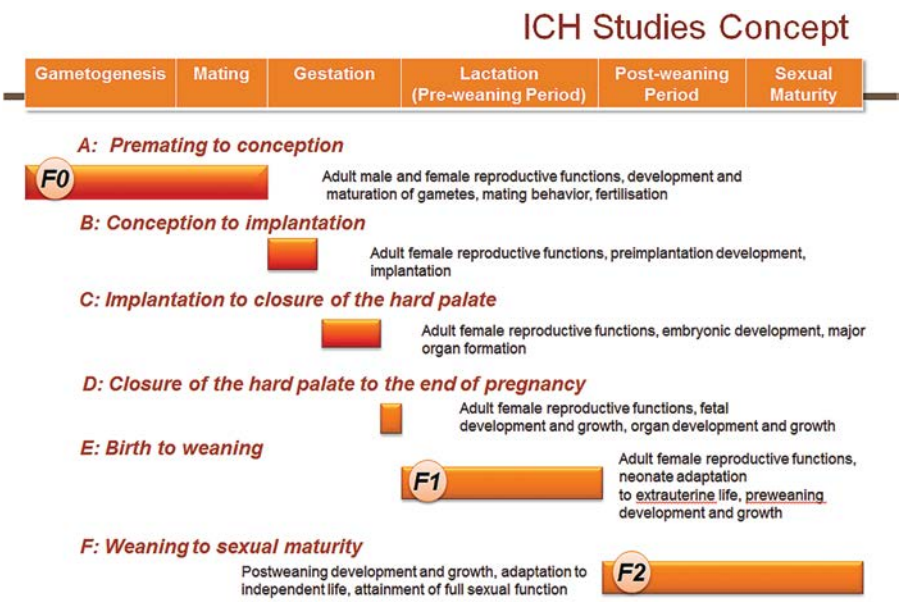
Reproductive toxicity, male involves adverse events caused by a substance (e.g., chemical, drug), a pathogen (e.g., microorganism, virus), or any other agent (e.g., radiation) that could affect the male reproductive function.

Reproductive toxicology testing involves investigation of all stages of the male and female reproductive cycle and development and occurs mainly in rats and rabbits. These testing stages are described in an ICH guideline [S5(R2)], Detection of Toxicity to Reproduction for Medicinal Products and Toxicity to Male Fertility; Parent: June 1993; Addendum: November 2000. A schematic view of the ICH concept (see figure at the next page top).

Resorption, see the preferred terms **Bone increased eroded surface** and **Osteoclasts increased**.

Respiratory acidosis is an acid-base imbalance in the blood caused by alveolar hypoventilation resulting in increased pCO_2 and reduced blood pH. Respiratory acidosis may be acute from

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Fertility studies assess stages A and B, embryo-fetal development studies assess stages C and D, and the peri-postnatal development study assesses stages E and F.

abrupt failure to ventilate resulting from central nervous system (CNS) depression, acute from sudden respiratory airway obstruction, or chronic from pulmonary disease (e.g., chronic obstructive pulmonary disease). Acute respiratory acidosis is considered a medical emergency with potentially fatal consequences if untreated. See **Acidosis** for further information.

Respiratory alkalosis is an acid-base imbalance in the blood caused by hyperventilation, resulting in reduced pCO_2. It may be either acute, with resulting increased blood pH, or chronic, with pH at or near normal levels. Respiratory alkalosis is often seen in conditions associated with high stress, anxiety or panic, and in conjunction with chronic diseases. This condition may result in a medical emergency if pCO_2 cannot be stabilized. See **Alkalosis** for further information.

Respiratory bronchiole is the most distal bronchiole and represents a transition between the functions of air conducting and gas exchange. It is present in nonhuman primates and carnivores but not other laboratory species. These airways are characterized by alveolar air spaces opening directly from their walls such that they have a conducting function but also contribute directly to gas exchange.

Respiratory dead space is the proportion of the total respiratory tract volume that is not active in the exchange of gases (O_2 and CO_2). Anatomical dead space includes the trachea and bronchi, where no gas exchange takes place. Physiological dead space refers to areas in the alveoli where there is ventilation but no perfusion, so the blood cannot eliminate CO_2.

Respiratory depression is a sustained reduction in the rate of breathing (respiration) to the point where it is inhibiting the delivery of oxygen and the removal of carbon dioxide.

Respiratory rate is the number of breaths taken in a given period of time. Generally, this is calculated as breaths per minute and can be measured by direct observation, by plethysmography, or by telemetry. Telemetry can be in the form of a jacket or implants that measure rate changes directly, or they can be derived from indirect methods, such as the pressure wave superimposed on blood pressure.

Respiratory sensitization is a localized allergic response in the airways of the lung to an inhaled or topically applied substance. Once sensitized, the response may result in either an immediate or delayed hypersensitivity reaction.

Respiratory System, Anatomy and Histology, see Appendix 3 for further information.

Restriction endonucleases are sequence-specific DNA cleavage enzymes. The specific sequences that are recognized by restriction endonucleases are called restriction sites. Originally of bacterial origin, these enzymes are widely used tools for genetic engineering and for the characterization of DNA fragments, referred to as restriction mapping.

Rete ovarii cyst is a cyst usually localized to the ovarian hilus and lined by a cuboidal or columnar, sometimes ciliated, epithelium.

Rete testis, located in the hilum of the testis, is an anastomosing network of ductular channels (called tubuli recti) lined by low epithelial cells, and functions as a site for fluid reabsorption. It is continuous with the efferent ductules and epididymis and carries sperm from the seminiferous tubules to the efferent ducts. Tubuli recti are joined to the seminiferous tubules by transitional tubules that are lined by Sertoli cells and occasional germ cells. Transitional tubules and the tubuli recti should not

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be mistaken for atrophic seminiferous tubules. In the dog, the rete testis is often microscopically visualized within the central part of the testis, while in the rodent, the rete testis lies subjacent to the capsule at the cranial pole of the testis.

Rete testis adenomas are composed of tubular and papillary structures lined by single or multiple layers of epithelial cells in the mediastinal testis, causing compression of the adjacent tissue. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

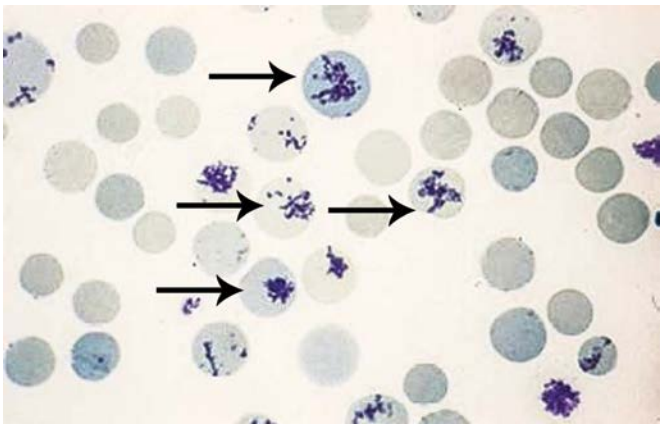
Rete testis carcinomas are characterized by invasion, marked atypia, a high mitotic rate, and sometimes hemorrhage, mucin, necrosis, and/or a schirrous response. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Rete testis dilation occurs most commonly in mice but may also be seen in other nonclinical species. It may be spontaneous or xenobiotic induced, and results from impaired fluid reabsorption in the efferent ducts/caput epididymis, distal obstruction in excurrent duct system (rete testis, efferent ducts, or epididymis), inhibition of peritubular contractions, and/or increased secretion of seminiferous tubule fluid by Sertoli cells. Rete testis dilation may be associated with sperm stasis or sperm granuloma(s) of the rete testis or efferent ducts, decreased (i.e., oligospermia) or absent (i.e., aspermia) epididymal sperm, seminiferous tubular dilation, and/or germinal epithelial atrophy. Dilated rete testis has been observed as an early event associated with seminiferous tubular dilation caused by 5-HT agonists.

Rete testis hyperplasia is a focal or multifocal change composed of tubules with hyperplastic epithelium. This change is most commonly observed in mice. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Reticulin fibrosis in bone marrow is an increase in reticulin fibers visualized by special stains, most commonly reticulin stain.

Reticulocyte is an immature red blood cell that contains constituent ribosomes that can be stained with vital stains such as methylene blue, brilliant cresyl blue, or azure blue. Stained reticulocytes contain a blue-black precipitate. Reticulocyte maturation can be recognized by the amount of precipitated material present. Cells with the largest amount of precipitate are the most immature, whereas those with the least amount of precipitate are the least immature. Reticulocyte counts are used to determine the percentage of reticulocytes observed per 100 mature erythrocytes and reflect the degree of erythropoiesis. The time from bone marrow release to complete elimination of ribosomes takes about 4 days. Increased erythropoietic activity results in premature release of reticulocytes into the peripheral blood so that they circulate for a longer period of time. In humans, the reference range for reticulocytes is approximately 0.5–1.5%. Large animals have a similar range, but rodents are substantially higher. Reticulocyte numbers are also elevated in newborns or young animals due to accelerated erythropoietic levels.



Reticulocytes (arrows), blood smear, rat (methylene blue stain). Higher levels of staining indicated increased numbers of ribosomes and more immature red blood cells.

Reticulosis, malignant is a malignant neoplasm of uncertain origin composed of a mix of mononuclear and glial cells, typically pleomorphic lymphoid to histiocytic cells within a stroma rich in reticulin fibers. Multinucleated giant cells and mitotic figures are common. Infiltration of meninges and perivascular and periventricular areas of the brain occurs typically. Refer to **Nervous System** in Appendix 2 for further information.

Reticulum cell sarcoma, see the preferred term **Lymphoma follicular center cell**.

Retina decreased cell layers, see the preferred term **Retinal atrophy**.

Retina decreased thickness, see the preferred term **Retinal atrophy**.

Retinal angiogenesis, see the preferred term **Retinal neovascularization**.

Retinal anomaly, see the preferred term **Retinal rosette**.

Retinal apoptosis is characterized by cytoplasmic hypereosinophilia, pyknosis, karyorrhexis, and membrane blebs that become apoptotic bodies that are often phagocytosed into other cells. Inner and outer nuclear cells, photoreceptor cells, and ganglion cells are most frequently affected. Inflammation is generally absent.

Differential diagnosis: **Retinal single cell necrosis**.

Retinal atrophy is focal, multifocal, to diffuse loss, collapse, and thinning of the retinal layers, which may be selective to the outer layers (outer retinal atrophy), inner layers (inner retinal atrophy), or global retinal atrophy. Outer retinal atrophy

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results in loss of the outer plexiform and outer nuclear and photoreceptor layers, and occurs as a spontaneous finding accompanying vascular abnormalities, retinal detachment, light-induced damage (refer to Appendix 3 for further information), and as a recessive trait in many strains of mice, particularly C3H and FVB. Inner retinal atrophy of the ganglion cells and retinal nerve fiber layer, with extension into the inner nuclear layer, occurs following exposure to toxins and radiation and as a result of infection, intravitreal inflammation, increased intraocular pressure, and vascular occlusion. Global retinal atrophy consists of loss of all defined retinal layers, leaving a fibrous remnant. Global atrophy can be a progression of inner or outer retinal atrophy, or increased severity of the underlying cause. Additional changes include proliferation of retinal glial cells, retinal folds, and rosettes, cysts, intraretinal migration of retinal pigment epithelium, and optic nerve atrophy. See **Lens capsule hypertrophy** for illustration.

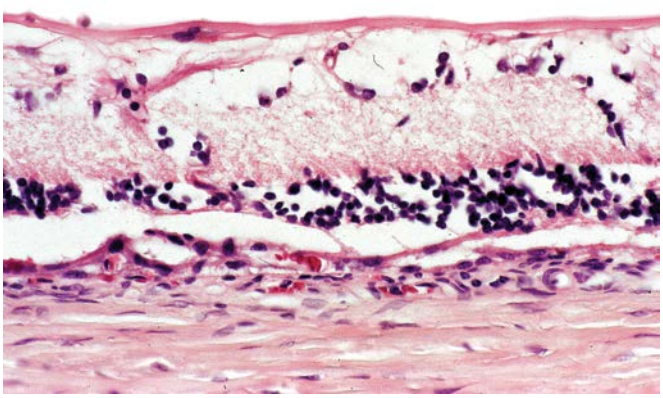
Synonym(s): **Retina decreased cell layers**; **retina decreased thickness**.

Retinal atrophy, global is an end-stage loss of all cell layers and collapse of the plexiform layers with loss of normal retinal architecture and replacement by a fibrous layer that may contain glial cells and a few neurons. See **Retinal atrophy**; **Retinal atrophy, inner**; **Retinal atrophy, outer** for further information.

Differential diagnoses: **Subretinal fibroplasia**; **Vitreal fibroplasia**.

Synonym(s): **Retinal scar**; **retinal glial scar**; **retinal diffuse gliosis**.

Retinal atrophy, inner consists of decreased ganglion cells, loss of nuclei in the inner nuclear layer, and thinning of nerve fiber and inner plexiform layers (refer to Appendix 3 for further information). This atrophy may be secondary to increased intraocular pressure, compressive lesions of the optic nerve causing ganglion cell death, or direct toxicity resulting in degeneration and loss of cells in the inner portion of the retina. Retinal ganglion cells are targeted by carbon disulfide, doxorubicin, glutamate, and lidocaine, and toxicants such as ethylcholine mustard aziridinium ion (AF64A) target the nuclei of the inner nuclear layer.



Retinal atrophy. Inner retinal atrophy with early outer retinal atrophy, F344/N rat, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

Retinal atrophy, outer consists of decreased numbers of nuclei in the outer nuclear layer, reduction and collapse of the outer plexiform layer causing fusion of the inner and outer nuclear layers, loss of the inner and outer segments of the photoreceptors, displacement of photoreceptor nuclei to the inner and outer segment layers, hypertrophy of retinal pigment epithelium (RPE), and migration of RPE cells and macrophages into the sensory retina (refer to Appendix 3 for further information). Causes include aging, hereditary (rodents and dogs), direct photoreceptor or RPE toxicity, nutritional deficiencies, retinal detachment, retinal inflammation, choroidal vascular disturbance, and subretinal injections of drugs as a part of gene therapy in laboratory animals. Unlike outer retinal atrophy, retina light-induced atrophy does not usually affect the RPE. See **Retinal atrophy, inner, Retinal pigment epithelium hypertrophy,** and **Subretinal fibroplasia** for illustrations.

Retinal calcification, see the preferred term **Retinal mineralization**.

Retinal cysts, see the preferred term **Retinal peripheral cystoid degeneration**.

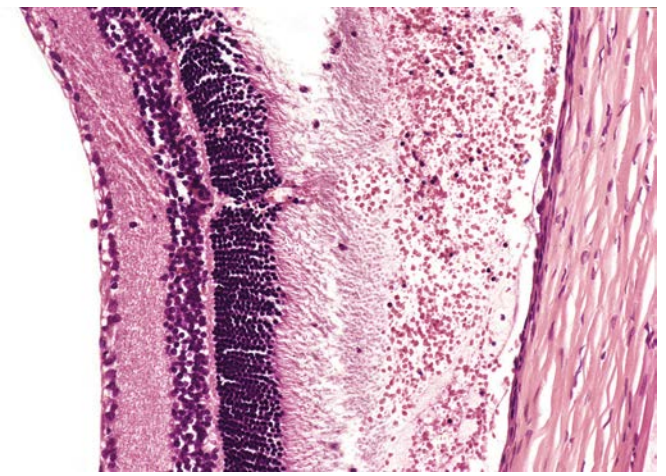
Retinal cytoplasmic vacuolation consists of clear or granular, round to oval cytoplasmic spaces of variable size and number in the cell cytoplasm, often in Müller cells, photoreceptors, and neurons. Vacuolation occurs as a spontaneous age-related finding, in chemical or xenobiotic injury and associated with necrosis and metabolic change. Hexachlorophene causes degeneration and vacuolation of photoreceptor outer segments, and chloroquine causes vacuolation in neurons and Müller cells. Phospholipidosis in the retina consists of foamy, lipid-like vacuoles containing bluish granules on hematoxylin and eosin (H&E) staining, irregular cytoplasmic inclusions on toluidine blue–stained thin sections, and lamellar whorls or crystalline inclusions ultrastructurally. Several cationic amphiphilic drugs produce phospholipidosis of the cornea, retina, and other tissues. The immunomodulator tilorone induces mucopolysaccharidosis and phospholipidosis in the cornea, retina, and other tissues of the rat. Vacuoles may be present in multiple ocular compartments (see **Corneal vacuolation**; **Ciliary body epithelial cytoplasmic vacuolation**; **Lens vacuolation**; **Iris epithelial cytoplasmic vacuolation**; **Retinal extracellular vacuolation**; **Retinal pigment epithelium vacuolation**). Vacuoles may also be an artifact from delays in fixation.

Differential diagnosis: **Retinal extracellular vacuolation**.

Retinal detachment is characterized by expansion of the subretinal space by fluid, macrophages, hemorrhage, or cellular debris, separation of the retina photoreceptor outer segment

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from the retinal pigment epithelium (RPE), hypertrophy of RPE ("tombstoning"), and retinal atrophy of the photoreceptor outer segments. Spontaneous retinal detachment is uncommon in laboratory animals but may occur with mutations of retinal cells or RPE and in the presence of trauma, vascular abnormalities, vitreal membranes, retinal holes or tears including intravitreal injections, fluid, hemorrhage, or inflammation within the subretinal space, infiltrating tumors, retinal atrophy, thinning of the sclera, and buphthalmos. The most common subtype of retinal detachment is rhegmatogenous, in which a tear allows fluid to accumulate and separate the retina from the RPE. Other subtypes include exudative, serous, or secondary retinal detachment due to tumors that cause separation but no retinal tears. The tractional subtype occurs when abnormal fibrous or fibrovascular tissue pulls the retina away from the RPE. Hypertrophy of RPE, hyperplasia, and separation of the RPE cells with photoreceptor degeneration, and pigment-laden macrophages help to distinguish detachment from artefactual separation. Artifactual shearing may create RPE "tenting" with the cells having an angular peak, and adherent fragments of photoreceptor outer segments.



Retinal detachment (rhegmatogenous due to hemorrhage) with retinal pigment epithelial hypertrophy, F344/N rat, H&E. See **Retinal pigment epithelium hypertrophy**, **Subretinal fibroplasia**, and **Vitreal inflammation** for additional illustrations. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

Retinal dystrophy, see the preferred term **Retinal rosette**.

Retinal edema, see the preferred term **Retinal extracellular vacuolation**.

Retinal extracellular vacuolation consists of clear spaces that separate or expand one or more retinal layers. Loss of nuclei in the nuclear layers and loss of dendrites and axons in the plexiform layers of the retina commonly lead to clear areas. Vacuolar changes may be extensive and lead to retinal splitting and retinal detachment with degenerative changes or toxic effects. Vacuoles may also be present in other ocular compartments (see **Corneal vacuolation**; **Ciliary body epithelial cytoplasmic vacuolation**; **Lens vacuolation**; **Iris epithelial cytoplasmic vacuolation**; **Retinal cytoplasmic vacuolation**; **Retinal pigment epithelium vacuolation**). Vacuoles may also be an artifact from delays in fixation.

Synonym(s): **Retinal edema**; **retinoschisis**.

Retinal fibroplasia is a fibrocellular layer over the inner (vitreal) surface of the retina that contains fibrocytes, glial cells, and retinal pigment epithelial cells as well as numerous vascular profiles. Inflammatory cells are usually present as a part of ocular or retinal inflammation, and small vascular profiles are present when retinal neovascularization occurs. Histochemical staining for collagen and immunohistochemistry staining for the potential cells of origin (hyalocytes, fibroblasts, astrocytes, glial cells, and Müller cells) or glial fibrillary acidic protein for glial cells are useful to characterize the components of the fibroblastic lesion. "Epiretinal membrane" is the clinical term for fibroplasia at or on the retinal surface, with idiopathic epiretinal membranes identified by fibroplasia on the internal limiting membrane.

Differential diagnoses: **Vitreal fibroplasia**; **Preretinal arteriolar loop**; **Retinal neovascularization**.

Synonym(s): **Epiretinal membranes**; **vitreal traction band**.

Retinal folds are focal to multifocal, irregular, often uplifted segments of retina that contain a disorganized infolding of the outer layers that may or may not affect the contour of the retinal surface, depending on the number of retinal layers involved and the extent of the finding. There may also be separation between the photoreceptors and the retinal pigment epithelium, accompanied by subretinal hemorrhage, macrophages, hypertrophy of retinal pigment epithelium, debris, and subretinal fibroplasia. Folds occur most frequently as a spontaneous malformation in certain strains of mice in association with microphthalmia. Similar changes, usually with concurrent degenerative changes of the retina or retinal pigmented epithelium, may be noted



Retinal fold, B6C3F1 mouse, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

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after damage to the retina. Folds may also occur in young animals due to fixation artifact, particularly if 70% ethanol is used as the fixative.

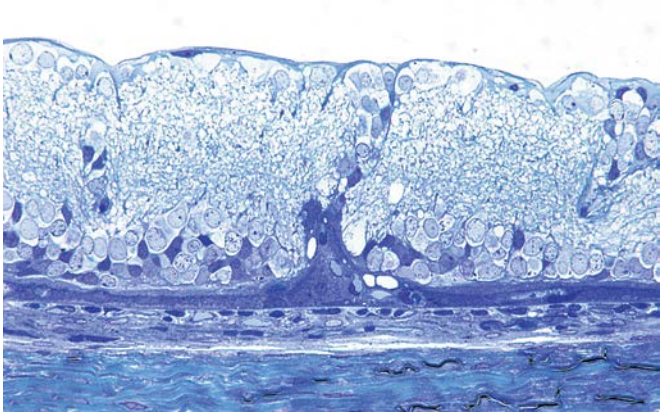
Differential diagnosis: **Retinal rosettes**.

Retinal gliosis, see the preferred term **Retina increased numbers glial cells**.

Retinal hemorrhage is the extravasation of blood cells into the retina, within retinal layers, or with leakage into the subretinal space, due to a blood vessel rupture. Hemorrhage may result from compression during handling of an animal, trauma, retinal detachment, hypertension, inflammation, infections, neoplasms, chemicals and xenobiotics, and alterations in vascular integrity. Free blood cells may also be a handling artifact. See **Retinal detachment** for illustration.

Retinal hyaline deposits, see the preferred term **Retinal extracellular matrix deposits**.

Retina light-induced atrophy is environmental phototoxicity which is a confounding retinal degeneration in albino rodents, rabbits, nonhuman primates, and minipigs due to ambient blue light exposure in vivaria, particularly during chronic studies. Retinal alterations include a decrease in the thickness of the outer nuclear layer, disorganization and thinning of the layers of the outer segments and inner segments, displacement of photoreceptor nuclei into the outer and inner segments and subretinal space, astrocyte proliferation, and Müller cell activation. The findings may progress to loss of photoreceptors, nuclear layers, and retinal pigment epithelium (RPE), and marked disruption of retinal architecture, particularly rods, which are more sensitive to light than cones. The predominant topography of the superior and temporal zone of the retina, vascular proliferation into the retina, and displacement of retinal nuclei help to distinguish phototoxicity from the diffuse pattern of retinal atrophy observed following administration of chemicals, xenobiotics, retinal detachment, photosensitivity, and spontaneous atrophy.



Retina light-induced atrophy, rat, toluidine blue stain on epoxy. (Image courtesy of L. Teixeira, University of Wisconsin.)

Chemicals and xenobiotics can also cause exacerbation of light-induced toxicity.

Synonym(s): **Retinal phototoxicity**; **light-induced retinopathy**; **light-induced photoreceptor degeneration**.

Retinal increased myelin is an acquired anomaly of ganglion cells consisting of abnormal myelinated axons in the nerve fiber layer of the central retina that causes focal thickening of the retina and sometimes clustering of axons on the retinal surface. This finding is most frequently observed as an incidental and probably developmental anomaly in pigmented rats.

Synonym(s): **Retinal myelin hypertrophy**.

Retinal increased numbers glial cells is a proliferation or migration of glial cells into the retina, localized to the optic nerve head as an incidental finding, but occurs throughout the retina as a response to injury. Immunohistochemistry for glial fibrillary acidic protein will identify these cells.

Synonym(s): **Retinal gliosis**.

Retinal increased pigment consists of yellow to dark brown, or sometimes eosinophilic pigment granules or clumps of brown pigment in retinal cells. Most frequently granules are observed in neurons, especially in ganglion cells, due to lipofuscin, which is sometimes called ceroid when the pigment is eosinophilic. This is an age-related change due to free radical damage. Lipofuscin as the basis for the pigmentation needs to be confirmed with special microscopy and stains (autofluorescence, periodic acid-Schiff, oil red O, Luxol fast blue, Schmorl's, Ziehl-Nielsen, or Lapham's method). Increased brown to black pigment granules or clumps in damaged areas of the retinal pigment epithelium, retinal layer, and vitreous are usually hemosiderin or melanin phagocytosed by cells following retinal detachment, atrophy, hemorrhage, and inflammation.

Synonym(s): **Retinal lipofuscinosis**.

Retinal inflammation consists of focal or diffuse accumulations of inflammatory cells (granulocytes or heterophils [rabbit], macrophages, lymphocytes, plasma cells, and multinucleated giant cells) within one or more layers of the retina, with the cell types dependent on the chronicity and initiating agent. Inflammation may occur in conjunction with cell necrosis from chemicals or xenobiotics, degenerative diseases, vascular abnormalities, age-related changes, and as a part of autoimmunity. Inflammation also contributes to retinal detachment and increased numbers of glial cells. Causes include trauma, extension from other ocular compartments, and infectious diseases.

Differential diagnosis: **Retinal inflammatory cell infiltrate**.

Synonym(s): **Retinitis**.

Retinal inflammatory cell infiltrate is often an incidental focal to multifocal accumulation of small clusters of usually lymphoid and sometimes myeloid cells, which may surround

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capillaries but in the absence of other changes of inflammation (edema, hemorrhage, necrosis and gliosis).

Differential diagnosis: **Retinal inflammation**.

Retinal lipidosis, see the preferred term **Retinal pigment epithelium vacuolation**.

Retinal lipofuscinosis, see the preferred term **Retinal increased pigment**.

Retinal malformation, see the preferred term **Optic fissure malformation**.

Retinal mineralization is intracellular granules or larger extracellular deposits of basophilic material in any cell layer, and often in vascular walls. Deposits can be secondary to retinal necrosis, atrophy, detachment, inflammation, tumors, fibrosis, and subretinal extracellular matrix deposits (drusen-like) in nonhuman primates. Mineralized sites usually contain calcium and phosphorus and are positive with von Kossa or Alizarin red staining.

Differential diagnosis: Retinal extracellular matrix deposits.

Synonym(s): **Retinal calcification**.

Retinal myelin hypertrophy, see the preferred term **Retinal increased myelin**.

Retinal neovascularization consists of an abnormal proliferation of small blood vessels that infiltrate the retina, usually related to ischemia or an imbalance in pro- versus antiangiogenic growth factors. New blood vessels can extend from the inner plexus and inner nuclear layer into the outer retina or from the inner plexus layer and ganglion cell layers into the inner limiting membrane, or as projections into the vitreous. Extension of vasculature into the retinal pigment epithelium and the subretinal space can only be differentiated from choroidal neovascularization by determining the integrity of Bruch's membrane, usually by ultrastructure examination (see Appendix 3 for additional information). Neovascularization in laboratory animals is most frequently an experimentally induced lesion by laser photocoagulation to model retinopathy of prematurity, but choroidal and retinal neovascularization is a spontaneous disease in JR5558 mice.

Differential diagnoses: **Choroidal neovascularization**; **Subretinal fibroplasia**.

Synonym(s): **Retinal vascular proliferation**; **retinal angiogenesis**.

Retinal peripheral cystoid degeneration is a common age-related change consisting of one or more large vacuoles in the peripheral retina near the junction with the ciliary body (ora serrata), particularly in dogs and nonhuman primates.

Synonym(s): **Retinal cysts**.



Retinal peripheral cystoid degeneration, cynomolgus monkey, H&E.

Retinal phospholipidosis, see the preferred term **Retinal pigment epithelium vacuolation**.

Retinal photoreceptor nuclei displacement (PND) consists of a small number of photoreceptor nuclei, normally separated from the inner and outer segments by the outer limiting membrane (refer to Appendix 3 for further information), that are displaced into the inner and outer segment layers. These nuclei have scant or no cytoplasm, and the nuclei resemble those of the outer nuclear layer, or may appear condensed and pyknotic. This may be a spontaneous or age-related change, and associated with retinal atrophy, inflammation, and intravitreal injections. Nuclei may also be artefactually displaced during microtomy. PNDs are eventually removed by the retinal pigmented epithelium or subretinal macrophages. See **Retinal rosette** for illustration.

Differential diagnosis: **Retina inflammatory cell infiltrate**.

Synonym(s): **Photoreceptor displaced nuclei (PDN)**; **subretinal photoreceptor "torpedo cells."**

Retinal phototoxicity, see the preferred term **Retina light-induced atrophy**.

Retinal pigment epithelium atrophy consists of swelling, nuclear loss, and irregular pigmentation causing RPE loss, often with attenuation and compensatory lateral spreading of the remaining cells. Atrophy may be accompanied by loss of pigment granules in the RPE, and retina increased pigment (lipofuscin). Atrophy occurs as part of aging, and RPE is a target for systemic toxicities as well as degenerative and inflammatory disease. Congenital abnormalities of RPE decreases are reported in rodents, dogs, and nonhuman primates. See **Retinal pigment epithelium hypertrophy** for illustration.

Synonym(s): **Decreased numbers of retinal pigment epithelium**; **retinal pigment epithelium cell loss**.

Retinal pigment epithelium cell loss, see the preferred term **Retinal pigment epithelium atrophy**.

Retinal pigment epithelium decreased pigmentation consists of a focal or segmental reduction in the number of pigment granules in the RPE, which may include abnormal cytoplasmic distribution of pigment granules or abnormally shaped or sized melanosomes in the RPE of pigmented strains

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of laboratory animals. Loss of melanin granules occurs spontaneously with aging, after photobleaching, in RPE atrophy or if melanin is diffused by fusion with lipofuscin (see **Retinal pigment epithelium hypertrophy** for further information), and in toxicities with melanin binding drugs (e.g., antipsychotics, antimalarials, sympathomimetics, antimuscarinics). Binding of these drugs, metals, and amines to melanin may be benign or associated with atrophy and other changes including loss of pigment, or changes in normal melanin distribution.

Synonym(s): **Retinal pigment epithelium hypopigmentation**; **retinal pigment epithelium depigmentation**; **retinal pigment epithelium pigmentary incontinence**.

Retinal pigment epithelium dedifferentiation, see the preferred term **Retinal pigment epithelium polarity loss**.

Retinal pigment epithelium degeneration, see the preferred term **Retinal pigment epithelium vacuolation**.

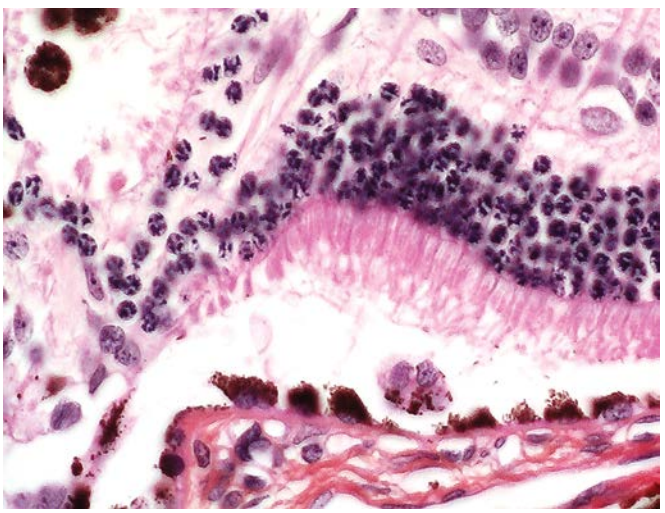
Retinal pigment epithelium depigmentation, see the preferred term **Retinal pigment epithelium decreased pigmentation**.

Retinal pigment epithelium detachment, see the preferred term **Retinal pigment epithelium polarity loss**.

Retinal pigment epithelium disorganization, see the preferred term **Retinal pigment epithelium polarity loss**.

Retinal pigment epithelium hyperpigmentation, see the preferred term **Retinal pigment epithelium increased pigmentation**.

Retinal pigment epithelium (RPE) hyperplasia is a focal increase in the number of retinal pigment epithelial cells, often associated with trauma, inflammation, and retinal degeneration and detachment. Refer to **Special Senses** in Appendix 2 for further information.



Retinal pigment epithelium (RPE) hypertrophy and RPE atrophy with RPE increased pigmentation, and retinal detachment and atrophy. Dutch belted rabbit, hematoxylin, phloxine saffron stain. See **Retinal detachment** for additional illustration.

Retinal pigment epithelium hypertrophy is enlargement of RPE cells, the enlarged cells sometimes containing abnormal or irregular melanin (melanolipofuscin) pigment granules. By transmission electron microscopy, enlarged smooth endoplasmic reticulum, increased numbers of lysosomes, and lipofuscin pigment may be noted. Enlarged RPE occasionally occur as an incidental or drug-induced (β-secretase inhibitors) finding, but most frequently hypertrophy occurs in association with inflammation, trauma, RPE hyperplasia**,** and neoplasms. Hypertrophy of RPE with rounded or "tombstone" profiles is a common finding following retinal detachment that allows differentiation of detachment from artifactual separation of the retina. Artifactual shearing may create RPE "tenting," with the cells having an angular peak and adherent fragments of photoreceptor outer segments.

Synonym(s): **Enlarged retinal pigment epithelium**; **increased size, retinal pigment epithelium**.

Retinal pigment epithelium hypopigmentation, see the preferred term **Retinal pigment epithelium decreased pigmentation**.

Retinal pigment epithelium inclusions, see the preferred term **Retinal pigment epithelium vacuolation**.

Retinal pigment epithelium increased numbers of pigment granules, see the preferred term **Retinal pigment epithelium increased pigmentation**.

Retinal pigment epithelium increased pigmentation consists of increases in light brown intracytoplasmic pigment granules, usually due to fusion of melanin with lipofuscin (see **Retinal pigment epithelium hypertrophy** for further information). This fusion may also cause dispersion of melanin (see **Retinal pigment epithelium decreased pigmentation** for further information). See **Retinal pigment epithelium hypertrophy** for illustration.

Synonym(s): **Retinal pigment epithelium hyperpigmentation**; **retinal pigment epithelium increased numbers of pigment granules**.

Retinal pigment epithelium lipofuscin, see the preferred term **Retinal pigment epithelium vacuolation**.

Retinal pigment epithelium lipofuscinosis, see the preferred term **Retinal pigment epithelium vacuolation**.

Retinal pigment epithelium lysosomes, see the preferred term **Retinal pigment epithelium vacuolation**.

Retinal pigment epithelium migration, see the preferred term **Subretinal fibroplasia**.

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Retinal pigment epithelium myeloid bodies, see the preferred term **Retinal pigment epithelium vacuolation**.

Retinal pigment epithelium pigmentary incontinence, see the preferred term **Retinal pigment epithelium decreased pigmentation**.

Retinal pigment epithelium polarity loss consists of conversion of RPE cells to a rounded or polygonal shape, with an altered apical-to-basolateral orientation of the cells and nuclei in conjunction with loss of apical microvilli and basal infoldings that typify the normal organization of RPE cells. RPE may be separated from Bruch's membrane and may be individualized or form aggregates in the subretinal space. These structural changes indicate cell injury and loss of integrity of the RPE that may be associated with subretinal fluid and retinal edema with progression to retinal atrophy. Polarity loss affects RPE function, including phagocytosis and cellular transport (refer to Appendix 3 for further information).

Differential diagnosis: **Retinal pigment epithelium vacuolation**.

Synonym(s): **Retinal pigment epithelium dedifferentiation**; **retinal pigment epithelium detachment**; **retinal pigment epithelium disorganization**.

Retinal pigment epithelium residual bodies, see the preferred term **Retinal pigment epithelium vacuolation**.

Retinal pigment epithelium vacuolation is a nonspecific term for usually well-delineated and round or polygonal cytoplasmic spaces that may be clear or contain granules, in RPE cells that are enlarged, have lost their polarity, or may be separated from Bruch's membrane. These vacuoles may appear with aging and genetic diseases of metabolism (accumulation of mucopolysaccharides and others) or represent organelles (lysosomes or endoplasmic reticulum) and abnormal cellular components (degraded photoreceptor outer segment or lipofuscin), crystals, or phospholipids following cationic amphiphilic drug administration. The immunomodulator tilorone induces mucopolysaccharidosis and phospholipidosis in the cornea, retina, and other tissues of the rat. These inclusions may be benign or interfere with RPE function. Vacuoles may also be present in other ocular compartments (see **Corneal vacuolation**; **Ciliary body epithelial cytoplasmic vacuolation**; **Lens vacuolation**; **Iris epithelial cytoplasmic vacuolation**; **Retinal cytoplasmic vacuolation**; **Retinal extracellular vacuolation**; **Retinal pigment epithelium vacuolation**). Vacuoles may also be an artifact from delays in fixation.

Synonym(s): **Retinal pigment epithelium degeneration**; **retinal pigment epithelium inclusions**; **retinal pigment epithelium lysosomes**; **retinal pigment epithelium lipofuscin**; **retinal pigment epithelium lipofuscinosis**; **retinal lipidosis**; **retinal phospholipidosis**; **retinal pigment epithelium myeloid bodies**; **retinal pigment epithelium residual bodies**.

Retinal preretinal arteriolar loop is a vascular anomaly (abnormal branching of the central retinal artery) that often extends as a convoluted vascular loop into the vitreous near the disc. These malformed loops may be associated with vascular occlusion and vitreal hemorrhage, and have been reported in rodents, dogs, and nonhuman primates.

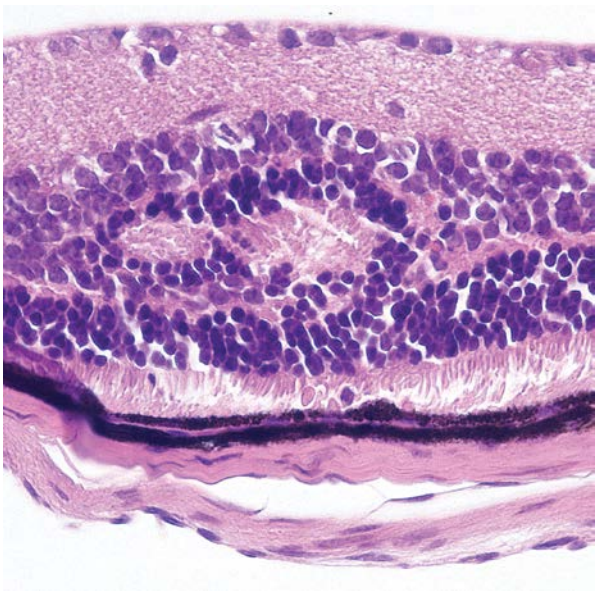
Differential diagnoses: **Vitreal persistent fetal vasculature**; **Retinal neovascularization**.

Synonym(s): **Retinal vascular anomaly**.

Retinal rosette is a focal to multifocal developmental malformation with cells of the outer nuclear layer radially distributed (polarized) around a lumen. Cells of the inner nuclear layer may also be incorporated into this circular structure with concurrent disorganization and loss of the photoreceptor cells and retinal atrophy and detachment. Rarely, rosette structures involve all layers of the retina. The lumen appears to be lined by an external limiting membrane, and the center may contain retinal pigment epithelium or macrophages that may be heavily pigmented (refer to Appendix 3 for further information). Rosettes are common in some strains of mice but may also be acquired secondary to injury such as at the injection tract in the retina after intravitreal injections. See **Retinal folds** for further information.

Differential diagnosis: **Retinal folds**.

Synonym(s): **Linear retinopathy**; **retinochoroidal degeneration**; **retinal dystrophy**; **retinal anomaly**.



Retinal rosette with retinal photoreceptor nuclei displacement, C57BL/6 mouse, H&E.

Retinal scar, see the preferred term **Retinal atrophy, global**.

Retinal single cell necrosis is irreversible cell injury which results in loss of cell detail, cell shrinkage, karyolysis and karyorrhexis, and sometimes pyknotic nuclei of individual cells within the retina, particularly the inner and outer nuclear cells, photoreceptor cells, and ganglion cells. This change may be associated with increased microglia and inflammation.

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Differential diagnoses: **Retinal apoptosis**; **Dark neuron artifact**.

Synonym(s): **Homogenizing cell change**; **ischemic cell change**; **metabolic arrest change**; **oncotic necrosis ("red dead" neurons)**.

Retinal vascular anomaly, see the preferred term **Retinal preretinal arteriolar loop**.

Retinal vascular proliferation, see the preferred term **Retinal neovascularization**.

Retinitis, see the preferred term **Retinal inflammation**.

Retinoblastoma is a malignant embryonic tumor originating from primitive neuroectodermal cells of the retina. It does not occur naturally in laboratory animals but is the most common malignant ocular tumor in children. Refer to **Special Senses** in Appendix 2 for further information.

Retinochoroidal degeneration, see the preferred term **Retinal rosette**.

Retinopathy of prematurity is disorganization of the developing retinal blood vessels that occurs in premature human infants that receive oxygen to support immature lung function. Abnormal blood vessels extending into the vitreous may bleed or form retraction bands leading to retinal detachment. Although not a disease of laboratory animals, hyperoxic conditions and laser-induced photocoagulation are frequently used in animals to model retinopathy of prematurity (see **Choroidal neovascularization** and **Retinal neovascularization**).

Retinoschisis, see preferred term **Retinal extracellular vacuolation**.

Retrocorneal membrane, see the preferred term **Cornea fibroplasia**.

Retrograde nephropathy, see the preferred term **Reflux nephropathy**.

Reverse mutation is a type of mutation that restores the ability of the gene to produce a functional protein.

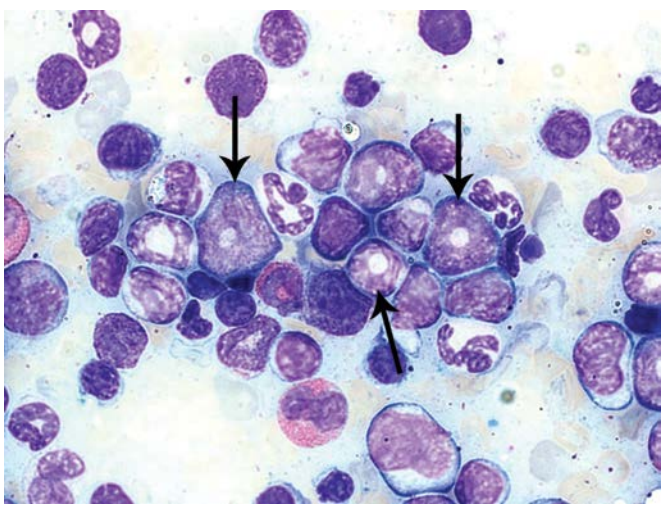
Reverse transcriptase is a viral enzyme that generates a complementary DNA (cDNA) using a single-stranded RNA template.

Reversible is a term used to describe a tissue injury that resolves, and the tissue returns to its normal morphological appearance after a specified dose/drug-free period. It is an assessment of whether a test article–related injury causes permanent alteration in morphology and reported in the context of a dose-free period, which means that the scientist must be familiar with the half-life of the drug and the recovery period of the specific injury in order to be certain that there was a sufficient dose-free interval for the specific injury to reverse. Assessment of reversibility may become complex for repair processes that are associated with regeneration of several cell stages/forms.

Rhabdomyoma is a benign neoplasm of striated muscle cells. This tumor is usually well-circumscribed, encapsulated masses composed of closely packed rhabdomyoblasts and a delicate stroma. As in rhabdomyosarcoma, rhabdomyoma cells contain glycogen granules that are removed during processing and leave cytoplasmic vacuoles. Cells containing substantial glycogen vacuoles with radiating cytoplasmic strands are often referred as "spiderweb cells." Mitotic figures are usually rare. Refer to **Bone, Muscle, and Tooth** in Appendix 2 for further information.

Rhabdomyosarcoma is a malignant neoplasm arising from striated muscle cells. Skeletal muscle rhabdomyosarcomas are characterized by a high mitotic index with numerous abnormal mitoses and a high degree of polymorphism. The classical neoplastic cell is the rhabdomyoblast-fusiform, strap-like, polygonal, or round cells with deeply eosinophilic fibrillary cytoplasm usually exhibiting cross-striations and glycogen granules that are often removed during processing leaving fine vacuoles. Refer to **Bone, Muscle, and Tooth** in Appendix 2 for further information.

Ring form neutrophil is characterized by ring formation of the nucleus in neutrophils. It is abnormal in dogs and nonhuman primates, but a normal finding in mice, rats, hamsters, and gerbils. In rodents, neutrophil precursors from the promyelocyte stage may develop into "ring" or "donut" forms with a small hole in the center of the nucleus. As the cell matures, the size of the hole increases and the nucleus becomes thinner and more peripheral. Ring forms are seen in neutrophil and eosinophil precursors but have not been observed in basophil precursors. In dogs and nonhuman primates, ring formation may be seen with severe inflammation, myeloproliferative disorders, or drug toxicity, and is often accompanied by other neutrophil cytoplasmic changes (i.e., Döhle bodies, basophilia, and vacuolation).



Ring-form neutrophils (arrows), normal bone marrow, rat.

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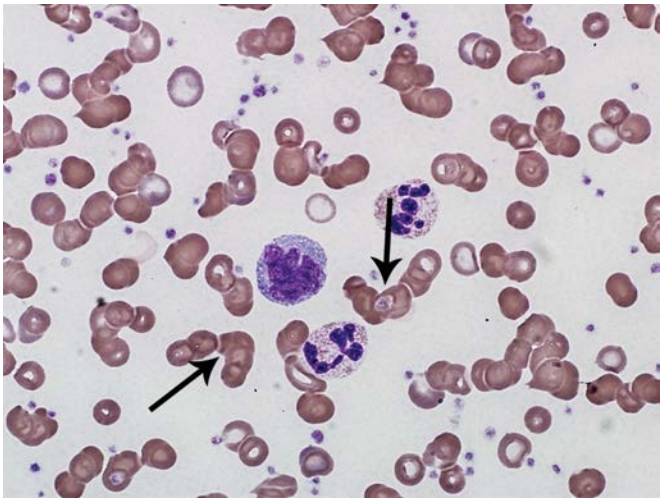
RNAi is an acronym for RNA interference. It is a sequence-specific gene silencing mechanism. RNAi technology can be used to block gene expression.

Rod cell, see the preferred term **Microglia**.

Rodent progressive cardiomyopathy, see the preferred term **Myocardial mononuclear cell infiltrate/fibrosis**.

Rosenthal fibers are prominent hyaline, brightly eosinophilic with hematoxylin and eosin (H&E) staining, wavy to worm-like intracytoplasmic inclusions that form within astrocyte processes in some situations of chronic robust gliosis and in some astrocytic neoplasms. The inclusions are composed of a mixture of intermediate filaments (specifically glial fibrillary acidic protein [GFAP]), ubiquitin, and heat shock proteins. Development of Rosenthal fiber inclusions involves an overproduction of aberrant GFAP within glial cells, but the inclusions do not occur in most common situations of reactive astrocytosis with GFAP upregulation. Overexpression of GFAP in transgenic mice results in an encephalopathy with astrocytic inclusions similar to those that occur in Alexander's disease, a rare genetic disorder in children. It is thought that the occurrence of Rosenthal fiber inclusions in some neoplasms and occasionally in lesions of chronic gliosis may be associated with the production of aberrant forms of the protein.

Rouleaux appears as lines of red blood cells stacked together as plates when viewed in blood smears. Rouleaux are commonly observed in horses under normal conditions. In other species, rouleaux is a nonspecific finding associated with a variety of pathological conditions ranging from dehydration and anemia to inflammation and neoplasia. Rouleaux formation is a reversible process that occurs in the circulation when plasma proteins are high and/or in the microcirculation with decreased blood flow or stasis leading to low shear force conditions. The rate and extent of rouleaux formation is based on the interaction between acute phase proteins present in plasma. The main acute phase protein responsible for rouleaux formation is fibrinogen; others are red blood cell membrane components, mostly sialic acid. Red blood cells in rouleaux are held together via weak force interaction and, unlike true agglutination, rouleaux disappear when resuspended in saline or the blood sample is diluted with saline. Rouleaux formation is sometimes referred to as pseudo-agglutination. Rouleaux are nonspecific indicators of underlying pathological conditions but may also be the cause of a disease, as they affect blood viscosity at low shear rate as well as blood flow in the microvasculature. In diabetes, rouleaux formation is considered responsible for microvascular occlusions and the development of diabetic retinopathy.



Rouleaux (arrows), peripheral blood smear, monkey.

Round spermatids form multiple layers in early-stage tubules (I–VIII, rat; I–V, dog) and overlay a single layer of pachytene spermatocytes within the adluminal compartment. Round spermatids are pale-staining, regular-appearing cells with an acrosomic cap that covers half of the nucleus. The acrosome cap is visible only following periodic-acid Schiff (PAS) staining. Round spermatids are about fourfold more numerous than spermatocytes, and therefore easier to assess when attempting to identify germ cell loss. In cases of testicular toxicity, one of the most obvious and common manifestations of round spermatid degeneration is the presence of multinucleate giant cells. Early changes in androgen deficiency include degeneration of round spermatids (chromatin margination), and pachytene spermatocytes in stage VII/VIII tubules of rats. Round spermatids are also specifically targeted by ethylmethane sulfonate and methyl chloride. See **Pachytene spermatocytes** for further information.

RT-PCR is an acronym for reverse transcription-polymerase chain reaction. It is a variant of PCR when the starting material to be amplified is RNA instead of DNA. In this technique, RNA is initially transcribed into complementary DNA (cDNA) by a reverse transcriptase. The cDNA is then used as a template for the PCR reaction.

Rubriblast, see the preferred term **Prorubricyte**.

Rubricyte, see the preferred term **Polychromatophilic rubricyte**.

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SAD (single ascending dose study), see Phase I clinical trial for further information.

Safe starting dose for clinical trial is calculated using the no observed adverse effect level (NOAEL) of the available GLP-compliant toxicity studies to calculate the **human equivalent dose (HED)**, to which a safety factor is then applied. A safety factor of 100 is normally used (a factor of 10 for the animal to human extrapolation, and a factor of 10 for differences in individual susceptibility).

Safety pharmacology, previously termed general pharmacology, became the commonly used terminology after lethal cardiac events were observed in individuals taking marketed nasal decongestants. Safety pharmacology is defined as the study of the response of critical organ systems to administered chemical agents or other medical procedures. Critical organs are those which could be life threatening if there were any disruption in their function. The core battery in safety pharmacology studies (as described in the ICH S7A guidance) consists of assessment of the cardiovascular system, central nervous system, and respiratory system, as these were designated as the most critical for life. Other systems studied in safety pharmacology as supplemental are the renal/urinary system, autonomic nervous system, gastrointestinal tract, and others such as the potential to induce dependency, skeletal muscle, and immune and endocrine functions.

Salivary gland accumulation of adipocytes is an age-related multifocal to coalescing accumulation of adipocytes within the interstitium of the salivary glands that may be associated with replacement/loss of acini; coalescing accumulation of adipocytes may lead to compression of the adjacent acini, ducts, and lobes. Accumulation of adipocytes occurs predominantly in the parotid salivary gland, and less commonly in the submandibular and sublingual salivary glands.

Differential diagnoses: Vacuolation; **Salivary gland atrophy**.

Synonym(s): **Adipocyte accumulation**; **lipomatosis**.

Salivary gland acinar cell degranulation, see the preferred term **Salivary gland acinar cell secretory depletion**.

Salivary gland acinar cell secretory depletion can be a partial or complete loss of acinar cell mucin or zymogen granules resulting in the shrunken appearance of these cells. Secretary depletion can be focal, lobular, or diffuse. This change is characterized by reduced acinar diameter and increased basophilia without fibrosis, inflammation, or adipocyte infiltration. Secretory depletion in acinar cell and ductal cells may occur concurrently.

Differential diagnosis: **Salivary gland atrophy**.

Synonym(s): **Salivary gland acinar cell degranulation**.

Salivary gland amyloid is an extracellular deposit of insoluble polypeptide fragments. Amyloid and amyloid-like material have been observed in various tissues, including salivary glands of aged mice. Rats are more resistant than mice to the deposition of amyloid.

Differential diagnosis: **Salivary gland necrosis**.

Salivary gland amyloid deposition, see the preferred term **Salivary gland amyloid**.

Salivary gland amyloidosis, see the preferred term **Salivary gland amyloid**.

Salivary gland atrophy is characterized by degranulation in the parotid gland and mucin reduction in the submandibular and sublingual glands leading to focal, lobular, or diffuse reduction in the number and/or size to total loss of acini, often accompanied by an infiltrate of chronic inflammatory cells and an increase in interstitial connective tissue and/or in the number of glandular ducts. It can and often is an age-related finding in laboratory animals and humans. Size of the secretory glands is responsive to functional demand, and salivary gland atrophy is observed following decreased food consumption, feeding of powdered or liquid diets, and/or a low-protein diet. The size of the salivary acinar cells and the weight of the salivary glands can vary as much as fourfold between fasted and recently fed animals. It can be secondary to obstruction of excretory ducts by ligation, sialoliths, and foreign bodies or alteration of trophic factors such as testosterone, adrenocorticoids, and sympathetic stimulation. Experimental procedures that alter trophic factors may potentially induce diffuse salivary gland atrophy as noted after hypophysectomy, adrenalectomy, and denervation. Drug-induced salivary gland atrophy is often reversible, and is reported following administration of methotrexate, alloxan, sunitinib, furosemide, and treatment with phosphodiesterase inhibitors as well as α- and β-adrenergic antagonists. Active sialodacryoadenitis virus infection has been associated with atrophy, necrosis, and inflammation of the salivary glands. Mononuclear cell leukemia infiltration of the salivary gland or local invasion by a malignant schwannoma arising in branches of the facial nerve has been associated with atrophy. Mineralization of material (i.e., calculus) in the ductular lumen occurs infrequently and may be seen incidentally or with atrophy. In rodents, atrophy more

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commonly affects the submandibular and parotid glands than the sublingual gland.

Differential diagnoses: **Salivary gland acinar cell secretory depletion**; **Salivary gland accumulation of adipocytes**.

Salivary gland calculus, see the preferred term **Salivary gland ductular calculus**.

Salivary gland concretion, see the preferred term **Salivary gland ductular calculus**.

Salivary gland dilatation, see the preferred term **Salivary gland duct ectasia**.

Salivary gland duct ectasia is characterized by irregular luminal dilatation of one or more of the intralobular or interlobular ducts due to obstruction. Typically, duct ectasia consists of multiple tortuous, irregularly enlarged lumina lined by flat cuboidal epithelial cells, and is sometimes associated with squamous metaplasia. Enlarged ducts may contain secretory material accompanied by a mild interstitial infiltration of lymphocytes and plasma cells. Diagnosis of ectasia is used in the absence of primary causes including calculi, sialodacryoadenitis, tumors, or foreign bodies.

Differential diagnosis: **Salivary gland ductular calculus**.

Synonym(s): **Salivary gland dilatation**; **salivary gland luminal distension**.

Salivary gland ductular calculus is the presence of basophilic or eosinophilic-staining material, sometimes mineralized, within (inspissated) the ductular lumen and formed as a result of precipitation of the secretory components after reabsorption of the water component by the ductular cells. Ductular epithelium may be attenuated and accompanied by a mild periductular, mononuclear inflammatory cell infiltrate. Ductular calculus is a less common background lesion in young animals but occurs more commonly in older animals. Calculus can lead to duct dilation, inflammation, and fibrosis. Hyperplasia and squamous metaplasia of the salivary ducts are common lesions secondary to calculi in both laboratory animals and humans.

Differential diagnosis: **Salivary gland duct ectasia**.

Synonym(s): **Sialoliths**; **sialolithiasis**; **salivary gland concretion**; **salivary gland duct concretion**; **salivary gland calculus**; **salivary gland inspissated material**.

Salivary gland ectopic tissue is the presence of focal, circumscribed, normal parotid, submandibular, or sublingual gland acini within a heterotopic salivary gland that has potentially been formed from the remnant of embryonic cell rests.

Salivary gland inflammation is an inflammatory response within a salivary gland.

Salivary gland inspissated material, see the preferred term **Salivary gland ductular calculus**.

Salivary gland luminal distension, see the preferred term **Salivary gland duct ectasia**.

Salivary gland necrosis is death of the acinar and/or ductal cells. Death may be of a single cell, focal or multifocal areas, or locally extensive to coalescing in form and may be of a variety of types.

Salivary gland squamous cell carcinoma originates from ductular epithelial structures of the salivary glands characterized by well-differentiated islands and cords of neoplastic squamous cells with keratin formation. Some squamous cell carcinomas are markedly anaplastic and composed of fusiform cells with pleomorphic nuclei and numerous mitotic figures. Refer to **Gastrointestinal Tract** in Appendix 2 for further information.

Differential diagnoses: **Salivary gland adenocarcinoma**; Zymbal's gland squamous cell carcinoma; Mammary gland adenosquamous carcinoma; Salivary gland squamous cell metaplasia; **Myoepithelioma, malignant**.

Synonym(s): **Epidermoid carcinoma**.

Salivary glandular adenocarcinoma is a malignant neoplasm of the ductal or acinar epithelium belonging to the salivary glands. Neoplastic cells are large, pleomorphic, and polyhedral with amphophilic cytoplasm, large vesicular nuclei, and often multiple nucleoli with a high nucleus to cytoplasmic ratio. Neoplastic cells may form whorls or spindle patterns with many mitotic figures, areas of squamous differentiation, and necrosis. Refer to **Gastrointestinal Tract** in Appendix 2 for further information.

Differential diagnoses: **Salivary gland hyperplasia**; Salivary gland atypical hyperplasia; **Salivary gland adenoma**; **Mammary gland adenocarcinoma**.

Salivary glandular adenoma is a benign neoplasm arising from ductal or acinar epithelium belonging to the salivary glands. Its growth pattern may be acinar, tubular, papillary, solid, or mixed type. Refer to **Gastrointestinal Tract** in Appendix 2 for further information.

Differential diagnoses: **Salivary gland hyperplasia**; Salivary gland atypical hyperplasia; **Salivary gland adenocarcinoma**; **Mammary gland adenoma**.

Salpingitis, see the preferred term **Oviduct inflammation**.

Salpingitis isthmica nodosa is a focal or diffuse thickening of the muscular wall of the uterine oviduct, with increased oviductal epithelial surface folds and invaginations. This change can be observed in mice exposed to exogenous estrogens and may be accompanied by local inflammation.

Sarcoma is a malignant neoplasm of mesenchymal origin. Although all soft tissue tumors probably arise from pluripotent mesenchymal stem cells rather than mature cells, these neoplasms can be classified into either tumors that resemble

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a mature mesenchymal tissue (e.g., skeletal muscle), which can further be divided into benign and malignant forms, or tumors composed of mesenchymal cells whose original cell type cannot be determined due to loss of differentiation.

Sarcoma, mixed, see the preferred term **Mesenchymoma, malignant**.

Sarcoma, NOS (not otherwise specified) is a category of malignant neoplasms created to group mesenchymal tumors with unclear histomorphological differentiation. The neoplastic cells are fusiform or spindle-shaped cells. Less frequently, neoplastic cells with various other shapes can be observed. Refer to **Bone, Muscle, and Tooth** in Appendix 2 for further information.

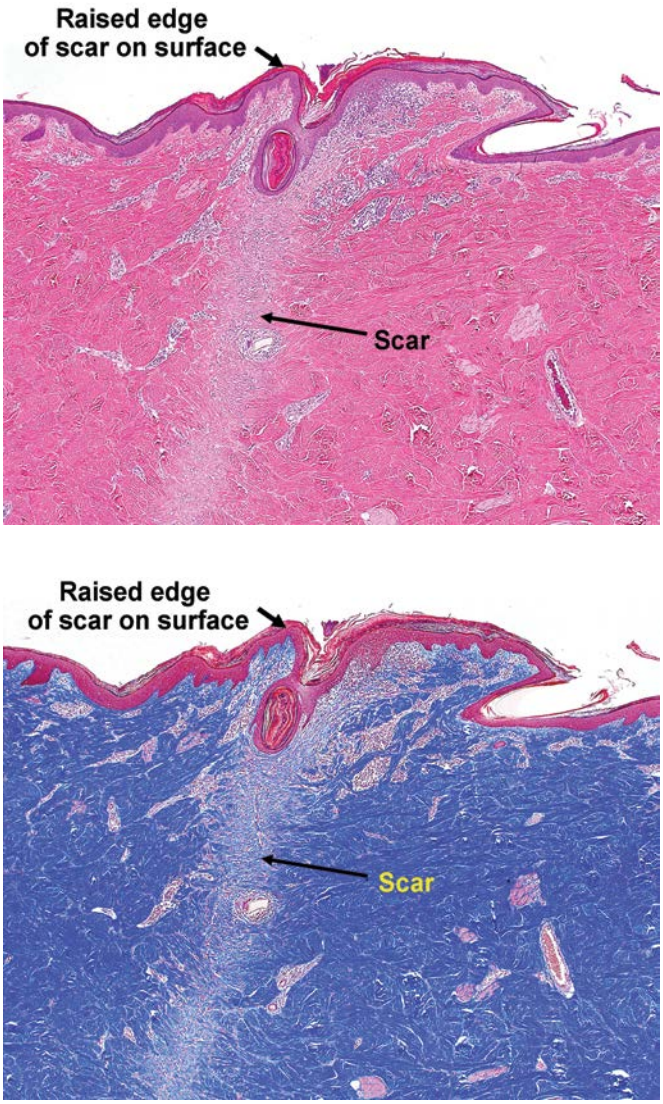
Sarcoma, pleomorphic undifferentiated, see the preferred term **Fibrosarcoma, pleomorphic**.

Sarcomatoid carcinoma, see the preferred term **Urinary bladder carcinosarcoma**.

Satellitosis represents rings or clusters of cells around a central degenerating cell. In the skin, these cells are normally lymphocytes surrounding a degenerating keratinocyte. In the central nervous system (CNS), satellitosis refers to oligodendroglia surrounding or proximal to a degenerating nerve cell body. Oligodendroglia are small cells with small round nuclei and a thin rim of pale cytoplasm that produce myelin in the CNS. Satellitosis will develop secondary to primary neuronal degeneration, and clustering of these cells near or around degenerating neurons may serve a support function for the neurons, as oligodendroglia are not generally a reactive cell population. Because one or two oligodendroglia immediately adjacent to neuronal cell bodies occurs as a normal feature in the CNS, the diagnosis of satellitosis should be made only after careful comparison to the same anatomic area in controls to verify a clear increase in numbers of these perineuronal cells.

Synonym(s): **Reactive oligodendroglia**; **oligodendrocyte satellitosis**.

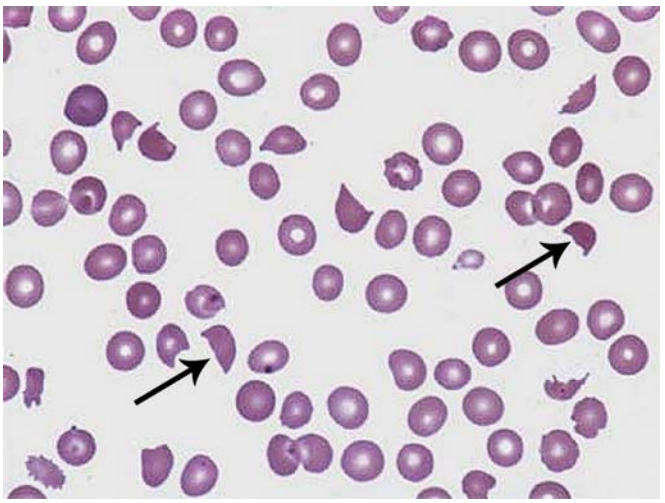
Scar tissue represents the later stages of wound healing that occur after re-epithelialization of the epidermis overlying a bed of granulation tissue (i.e., heavily vascularized loose connective tissue) that forms in the dermis, and subsequent remodeling. Scar tissue mainly consists of dense collagen bundles produced by fibroblasts, and various matrix components. Rather than being a static event, a scar is actually a process of continual remodeling toward eventual complete repair of the wound, which can take months or years. Certain genetic and/or immunomodulatory mechanisms may prevent normal scar remodeling, resulting in enlarged areas of scarring with increased numbers of fibroblasts/fibrocytes and/or larger collagen bundles, termed keloid or hypertrophic scar. In laboratory animal species, the red Duroc pig is often used as an animal model for the latter condition.



Linear scar in skin from red Duroc pig. Top, H&E stain; bottom, trichrome stain. Note raised edges of scar that would be palpable as firm skin.

Schistocyte is an abnormally shaped red blood cell that appears as a cellular fragment. Schistocytes can assume many irregular shapes, but often have pointed ends. Loss of erythrocyte membrane and cytoplasm contributes to the marked changes in morphology and may result as a consequence of physical trauma to the red cells. Production of large numbers of schistocytes is typically associated with hemolytic anemia. Trauma or mechanical injury in large vessels results in macroangiopathic hemolytic anemia, while injury in the microvascular results in microangiopathic hemolytic anemia. Several microangiopathic disease entities generate fibrin and form vascular thrombi. As red blood cells attempt to pass through the fibrin mesh, they can become entangled, causing them to be torn into schistocytes. Increased numbers of schistocytes are often seen in disseminated intravascular coagulation, prosthetic heart valves, in burn patients, and with march hemoglobinuria.

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Multiple schistocytes (arrows), blood smear, rat.

Schwann cell hyperplasia is a reactive proliferation of peripheral nerve glial cells subsequent to axonal injury. The axon distal to the injury degenerates and Schwann cells proliferate to form cell columns (bands of Bungner) that guide regenerating axon sprouts to sites of synapse reformation. Refer to **Nervous System** in Appendix 2 for further information.

Schwann cells produce myelin in the peripheral nervous system. Myelin represents multiple concentric layers of cell membranes derived from oligodendroglia in the central nervous system, and Schwann cells in the peripheral nervous system (PNS) that wrap around axons to insulate them and speed transmission of nerve impulses. Unmyelinated axons also are present and run in canals between Schwann cells.

Schwannoma, benign are encapsulated neoplasms derived from the myelin-producing glial cells of peripheral nerves. Benign schwannomas grow by expansion rather than infiltration. Tumor descriptions typically include references to Antoni A (palisades of thin nuclei) and/or Antoni B (regions of low cellularity with clear intercellular matrix and cyst-like spaces) patterns. Refer to **Nervous System** in Appendix 2 for further information.

Synonym(s): **Neurilemmoma**; **neurinoma**.

Schwannoma, malignant are unencapsulated and invasive neoplasms derived from the myelin-producing glial cells of peripheral nerves. Malignant features include high mitotic rate, cellular atypia, and locally invasive growth and/or metastases. Tumor descriptions typically include references to Antoni A (palisades of thin nuclei) and/or Antoni B (regions of low cellularity with clear intercellular matrix and cyst-like spaces) patterns. Refer to **Nervous System** in Appendix 2 for further information.

Synonym(s): **Neurilemmoma**; **neurinoma**.

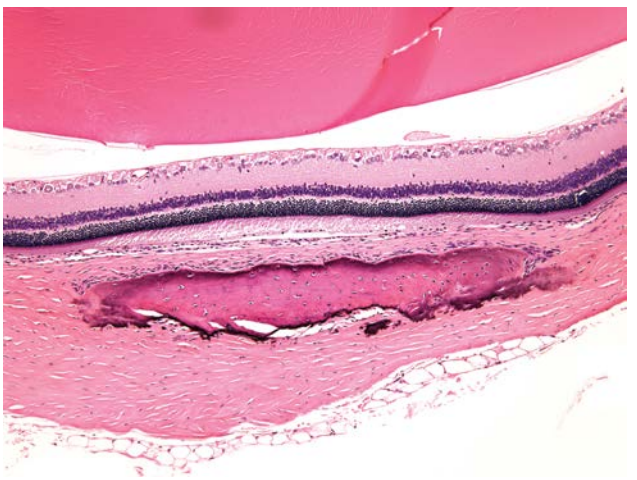
Scirrhous carcinoma is a tumor composed of malignant epithelial cells that are surrounded or infiltrated by abundant fibrous connective tissue.

Scleral atrophy is thinning due to loss of the episclera, scleral cells, and supporting connective tissue, with resultant stretching or breaking of the sclera. This change can be age-related but is usually secondary to chronic inflammation, tumors, glaucoma, or trauma.

Synonym(s): **Staphyloma**.

Scleral bone or cartilage metaplasia consists of single to multiple foci of well-differentiated mineralized bone, and less frequently, cartilage in the sclera. Bone metaplasia is an incidental aging change in rats, particularly in F344 rats, but is seldom found in mice. Bone and cartilage metaplasia may be a sequela of trauma such as following retroorbital bleeding. See **Metaplasia** for further information.

Differential diagnoses: **Osteoma**; **Chondroma**.



Scleral bone metaplasia, F344/N rat, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

Scleral inflammation consists of focal or diffuse accumulations of inflammatory cells (granulocytes or heterophils [rabbit], macrophages, lymphocytes, plasma cells, and multinucleated giant cells), often oriented on perivascular areas, in the episclera or sclera. The cell types are dependent on the chronicity and initiating agent. The majority of scleral inflammation occurs by extension from adjacent areas or is a manifestation of autoimmune uveitis and systemic connective tissue autoimmunity. Occasionally scleral inflammation can occur following exposure to topical irritants, chemical burns, and infections, and in conjunction with concurrent conjunctival inflammation. Xenobiotics are not known to induce primary scleral inflammation in laboratory animals, but bisphosphonates can do so in humans.

Synonym(s): **Episcleritis**; **scleritis**.

Scleral inflammatory cell infiltrate usually consists of focal, loose, or scattered lymphocytic cells in the scleral wall. Causality is seldom identified, but these may include sequelae to trauma, such as intraocular or periocular injections of xenobiotics, exposure to topical irritants, chemicals, and infections, and as an extension from the periocular tissues.

Differential diagnosis: **Scleral inflammation**.

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Scleritis, see the preferred term **Scleral inflammation**.

Sclerosis is the physical hardening of tissue, usually due to deposition of abnormal material components, such as collagen, bone, or cholesterol.

Sebaceous cell adenoma is a benign neoplasm of the sebaceous glands. These tumors are either exophytic (protruding) or endophytic (growing into the dermis) and well-demarcated. Cells comprising the tumor are arranged in lobules and can vary in morphology (basaloid/ precursor cells, well-differentiated sebocytes/gland cells, or squamous/ duct-forming cells), but are well-differentiated for the cell of origin. Refer to **Skin** in Appendix 2 for further information.

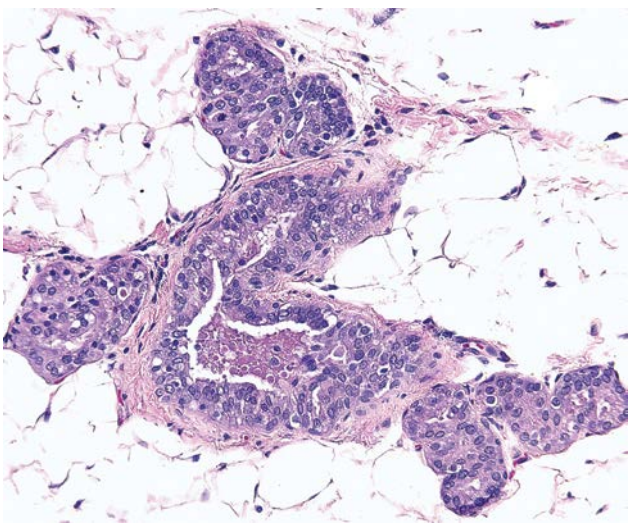
Sebaceous cell carcinoma is a malignant neoplasm of sebaceous cells. Derived from immature sebocytes, these tumors are invasive, unlike their benign counterpart. Cells are poorly differentiated/basaloid and often vary in size and morphology (pleomorphic). Refer to **Skin** in Appendix 2 for further information.

Sebaceous cell hyperplasia is a nonneoplastic proliferation of mature sebocytes/sebaceous cells. The cytoplasm of the cells may be expanded, as is overall size of the lobule/gland. Refer to **Skin** in Appendix 2 for further information.

Sebaceous gland adenoma, see the preferred term **Sebaceous cell adenoma**.

Sebaceous gland carcinoma, see the preferred term **Sebaceous cell carcinoma**.

Selective estrogen receptor modulators (SERM) are a class of xenobiotics that disrupt estrogen signaling via the estrogen receptor. These compounds modulate tumor growth for estrogen-receptor expression and estrogen-responsive neoplasms, but also have effects on other estrogen-sensitive tissues of the female reproductive tract and may disrupt normal cycle progression.



SERM-mediated hypertrophy/hyperplasia of ducts/alveoli of female mammary gland in rat, H&E. (Reproduced with permission of the Society of Toxicologic Pathology from Rudmann et al., 2012.)

Selective toxicity is any adverse change specific to a biochemical pathway, organelle, cell type, tissue, or organ system that is generally chemical/compound or class-specific, and typically represents the dose-limiting effects of a drug or chemical.

Sella turcica, see **Pituitary gland** for further information.

Semen is the liquid secreted by the sexual glands of the male that contains spermatozoa, also known as seminal fluid.

Seminal vesicle is an accessory male sex organ that produces secretions important for semen coagulation, sperm motility, stability of sperm chromatin, and suppression of immune activity in the female reproductive tract. The seminal vesicles are composed of tubular alveoli and join the ampulla of the deferens to form the beginning of ejaculatory ducts. Secretion of the seminal vesicles constitutes the main (50%), and last fraction of the ejaculate. Sex differentiation and the growth of seminal vesicles are highly dependent on androgen. In rats, an increase in serum testosterone or treatment with androgens is often associated with augmented secretory activity of the seminal vesicles and increased seminal vesicle weight. The seminal vesicles have 5 alpha-reductase activity, which converts testosterone to dihydrotestosterone, the active hormone. Seminal vesicles also contain luteinizing hormone/human chorionic gonadotropin (LH/hCG) receptors and are therefore a potential target of direct regulation by LH. The seminal vesicles and prostate share the same blood supply, with a comparable chance of exposure to carcinogens. Despite these similarities, adenocarcinomas of the seminal vesicles are considerably less common than those of the prostate.

Seminal vesicle epithelial stromal tumor is a benign tumor that has been reported exclusively in one rodent strain, the TRAMP transgenic mouse. It is composed of proliferating stromal and epithelial cells. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Seminiferous tubule atrophy, see the preferred term **Testicular tubular atrophy**.

Seminiferous tubules form the bulk of the testicular parenchyma and are the sites of spermatogenesis. They are long, highly convoluted tubules that consist of a basement membrane, a supporting cell (Sertoli cell) layer, and four concurrent overlapping generations of germ cells, regardless of species. They are ensheathed by contractile myoid cells and converge, through tubuli recti, on the rete testis, which is continuous with the efferent ductules and epididymis. Each germ cell generation develops in an orderly, precisely timed sequence, allowing for staging of different generations. The number of stages varies by species as follows: the rat has 14 stages, the mouse and monkey have 12 stages, the dog and

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rabbit have 8 stages, and the human has 6 stages. In the rat, mouse, dog, and most monkeys, tubular cross-sections depict only one stage, allowing for easy identification. In man and the marmoset, multiple stages can be present in one tubular cross-section, making assessment more challenging. Stage-aware evaluations of the testes enable the pathologist to detect subtle test article–related changes. Studies 1 month or less (with recovery periods) afford the highest degree of sensitivity for detecting cell-specific and/or stage-specific alterations in spermatogenesis. If seminiferous tubular degeneration occurs, anatomical differences across species produce different patterns of degeneration. In the rodent, seminiferous tubules are arranged in a transverse, circumferential pattern and when injured, tubules are scattered throughout the testis, while in the dog and monkey (and man), affected tubules may be confined to one lobule.

Seminoma, benign is the most common type of benign testicular tumor in man and these are relatively common in aged dogs, zebrafish (*Danio rerio*), and medaka (*Oryzias latipes*). They are rarely seen in rodents. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Seminoma, malignant is the most common type of malignant testicular tumor in man and are relatively common in aged dogs, zebrafish (*Danio rerio*), and medaka (*Oryzias latipes*). They are rarely seen in rodents. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

SEND is an acronym for Standard for Exchange of Nonclinical Data and is a part of the FDA's warehousing effort to require sponsors involved in generating/submitting nonclinical raw data in support of a drug approval submission to standardize formats to allow for further analysis by the FDA.

Sensitization is an immunologic (allergic) response induced by repeated exposures to an immunogenic substance over a short or long period of time. Preclinically, such effects are assessed in the Buehler test, Magnusson-Kligman maximization test, or the (murine) local lymph node assay. See **Buehler test, Magnusson-Kligman maximization test**, and **Local lymph node assay** for further information.

Sensory irritants are airborne substances that stimulate nasal trigeminal nerves and result in a decreased breathing rate by inducing a prolonged pause at the start of expiration (e.g., capsaicin, an active component in chili peppers).

Septal perforation refers to a discontinuity or "hole" in a tissue, such as the nasal septum. Clinical manifestations may include nasal obstruction, crusts, and epistaxis (i.e., hemorrhage from the nose).

Sequestrum refers to necrotic bone which is separated from living tissue and is enclosed by reactive bone (involucrum).

Serous atrophy of fat, see the preferred term **Gelatinous transformation**.

Sertoli cell (SC) imparts the supporting framework in which germ cells are embedded. The SC is irregularly columnar, and its basal aspect is attached to the basement membrane of the seminiferous tubule by hemi-desmosomes. The SC supports and moves the germ cells up and down within the seminiferous epithelium, utilizing a well-developed cytoskeleton of microtubules and intermediate filaments. The germ cells share a variety of specialized junctions with the SC, some of them unique to the testis, that hold the germ cells in place and are embedded within the SC cytoplasmic processes. Normal SC function is critical for the integrity of the seminiferous epithelium. SC functions include regulation of spermatogenesis, structural and metabolic support of the germ cells, sperm release, secretion of tubular fluid for sperm transport, and maintenance of a permeability barrier between the interstitial and tubular compartments. Disturbance of any of these functions is likely to impair spermatogenesis and in turn, sperm production.

Sertoli cell hyperplasia is an increased number of Sertoli cells in the ovary. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Sertoli cell–only seminiferous tubules, see the preferred term **Testicular tubular atrophy**.

Sertoli cell tubular adenoma, see the preferred term **Sertoli cell tumor, benign**.

Sertoli cell tubular carcinoma, see the preferred term **Sertoli cell tumor, malignant**.

Sertoli cell tumor, benign is a benign tumor of Sertoli cells, the multifunctional supporting cells within the testicular tubules. Spontaneous SC tumors are rare in rodents. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Sertoli cell tumor, malignant is a malignant tumor of the Sertoli cell, the multifunctional supporting cell within testicular tubules. Spontaneous malignant SC tumors are extremely rare in rodents. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Sertoli-Leydig cell mixed tumor, benign is rare and is composed of two different cell types reminiscent of Sertoli and Leydig cells, possibly indicating a common embryonic origin. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Severity is the assessment or grading of the magnitude and extent of a finding and is communicated through the use of a variety of modifiers in association with a diagnosis. Terms such as minimal, mild, slight, moderate, and severe are severity modifiers. These grading terms are an adjunct to distribution modifiers in communicating the relative importance of a finding.

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Sex cord mixed stromal hyperplasia is characterized by increased ovarian stromal and sex cord cells with minimal or no compression of the surrounding ovarian tissue. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Sex cord stromal tumor, see the preferred term **Sertoli cell tumor, benign**.

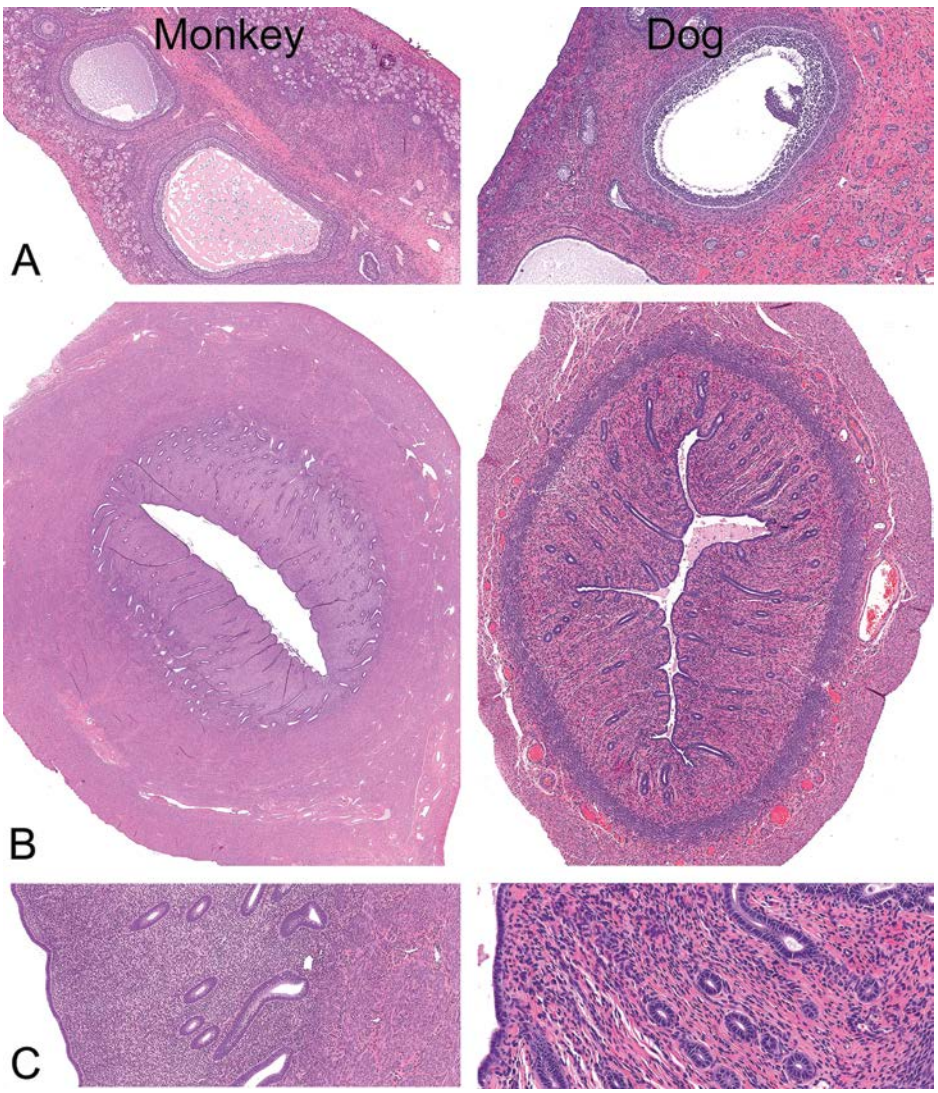
Sex cord stromal tumor, benign is a group of neoplasms that originate from the hormone-producing gonadal stromal cells. In the ovary, these can include estrogen-producing granulosa and Sertoli cells, androgen-producing theca and Leydig cells, progesterone-producing luteal cells, and/or fusiform thecal cells. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Sex cord stromal tumor, malignant is a group of neoplasms that originate from the hormone-producing gonadal stromal cells. In the ovary, these can include estrogen-producing granulosa and Sertoli cells, androgen-producing theca and Leydig cells, progesterone-producing luteal cells, and/or fusiform thecal cells. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Sex-cord stromal tumor, malignant, see the preferred term **Sertoli cell tumor, malignant**.

Sex ratio (%) is the ratio of male to female rat pups expressed as a percent or number of males/number of fetuses or pups × 100. This value is calculated per litter; since the litter is the reference unit, the group mean is the sum of the individual litter values divided by the number of litters.

Sexual immaturity, female is common in toxicology studies using nonhuman primates and less frequently dogs. In most cases prepubescent nonhuman primates are used in toxicology studies and as a result, the reproductive tissue histology will be immature (see figure below).



Histology of immature ovary (A) and uterus (B, C) in the dog and cynomolgus monkey, H&E. (Reproduced with permission of the Academic Press from Rudmann et al. in *Haschek and Rousseaux's Handbook of Toxicologic Pathology*, 3rd edition, 2013.)

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Sexual immaturity, male in nonclinical toxicity studies can be a significant confounding variable in the identification of reproductive toxicants. It is especially problematic in dog and nonhuman primate studies due to the common use of young animals in conjunction with study designs that contain small groups size. When reproductively immature animals are used in toxicity studies, testicular toxicity is difficult to identify due to the absence of developing germ cells and therefore the inability to evaluate spermatogenesis. When peripubertal animals are used, the testes can contain significant numbers of degenerating germ cells, which can be challenging or even impossible to distinguish from a response to a testicular toxicant. The best way to avoid these scenarios is to use animals that have reached sexual maturity by study termination. See **Sexual maturity** for further information.

Sexual maturity is the age or stage at which an organism can reproduce. Sexual maturity is different for all species, and for each species there is a special process whereby sexual maturity is reached. For male reproductive organs, sexual maturity is reached when hormone regulation is fully established, the production of sperm in the testes is complete, and the mature sperm is subsequently transported, stored, and released for fertilization. Ages of sexual maturity in the species most commonly used in toxicity studies are 10–12 months in the purpose-bred laboratory beagle, 4.5–5.5 years with a body weight greater than 5 kg in the cynomolgus monkey, 3–4 months with a body weight of 7–9 kg in the Gottingen minipig, 7–8 weeks in the mouse, and 9–10 weeks in the rat. In addition, it should be noted that reproductive maturity in the monkey is influenced by social hierarchy, which affects testosterone levels accordingly.

S-9 fraction is a postmitochondrial subcellular fraction, generally from liver, used to generate metabolites in many in vitro systems, particularly for toxicity testing. The name derives from the fact that it is the supernatant (S) from a 9000 g (9) centrifugation step.

Sialadenitis, see the preferred term **Salivary gland inflammation**.

Sialolith(s), see the preferred term **Salivary gland ductular calculus**.

Sialolithiasis, see the preferred term **Salivary gland ductular calculus**.

Siderocytes are red blood cells that contain iron aggregates in their cytoplasm. On routine blood smear examination, these aggregates normally appear as a cluster of 1–3 basophilic cytoplasmic granules adjacent to the cell membrane. They are also known as Pappenheimer bodies and are positive with Perls Prussian blue stain confirming the presence of iron in these granules. Pappenheimer bodies are ferritin aggregates in phagosomes or mitochondria. Siderocytes represent up to approximately 4% of human fetal red blood cells. Under physiological conditions, Pappenheimer bodies can be seen in reticulocytes, and more commonly in red blood cells after splenectomy. Under pathological conditions, siderocytes are seen in lead poisoning, alcohol excess, hemoglobinopathies, sideroblastic anemia, and megaloblastic anemia.

Silver impregnation technique, see the preferred term **Silver stain**.

Silver stain refers to several histochemical methods used to highlight structures that are normally indistinct or invisible using common staining methods such as hematoxylin and eosin, and cresyl violet that mainly highlight neuronal and glial cell bodies. Several silver staining methods are useful for highlighting axons (e.g., Holmes silver nitrate, which may be combined with the Luxol fast blue method to stain myelin), disintegrating axons and nerve cell bodies (e.g., de Olmos cupric silver stain), or to display abnormal structures such as amyloid plaques and neurofibrillary tangles (e.g., Bielschowsky stain). The "Golgi" methods (e.g., Cajal stain) highlight the entirety of random neurons (cell bodies, axons, and dendrites) and have been used for years in brain mapping studies. To some extent silver impregnation methods have been replaced by procedures such as the Fluoro-Jade stains for degenerating neurons, immunolabeling for amyloid plaque, and immunolabeling of various tau (protein) entities (e.g., for neurofibrillary tangles).

Synonym(s): **Silver impregnation technique**.

Single cell necrosis, see **Coagulative necrosis** and the preferred term **Necrosis**.

Single dose toxicity is (are) the toxicological effects of a drug or chemical after one dose, followed by an observation period of typically 14 days. Post-dose endpoints are generally limited to clinical signs, body weight/food consumption measurements, and optional necropsy after the observation period with gross pathological examination. "Extended" single dose toxicity studies in support of single dose human trials incorporate standard toxicology endpoints including clinical and anatomic (gross and microscopic) pathology at 24 or 48 hours post-dose and after 14 days of recovery. See **Acute Toxicity** for further information.

Single nucleotide polymorphism (SNP) is a type of genetic variation within a population resulting from single nucleotide variations at specific positions within the genome. They result in differential gene expression, or differences in the functionality of the gene product.

Sinus histiocytosis, see the preferred term **Lymph node, increased intrasinusoidal macrophages**.

Sinus/vessel dilation, see the preferred term **Angiectasis**.

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siRNA is an acronym for small interfering ribonucleic acid and consists of short, double stranded noncoding RNAs that are involved in genome regulation.

Sister chromatid exchange (SCE) is the reciprocal exchange of DNA between two sister chromatids during S phase. Tests have been developed to examine differences in the rate of SCE induced by chemicals as an indication of genotoxic activity. Such tests are not widely used today in drug development, mainly due to the unclear relevance of sister chromatid exchanges relative to permanent genetic damage.

Skeletal muscle age-related atrophy, see the preferred term **Myofiber atrophy**.

Skeletal muscle atrophy, see the preferred term **Myofiber atrophy**.

Skeletal muscle biomarkers are utilized routinely for assessing injury (e.g., degeneration/necrosis). Examples include creatine kinase (creatine kinase [CK]; specifically, the skeletal muscle isoform CK-MM), aspartate aminotransferase (AST), and lactate dehydrogenase (LDH). In addition to these enzymes and due to the short half-life of CK in rat, aldolase is sometimes associated with CK in this species. In rats, the European Medicines Agency and the U.S. FDA recommend the following exploratory biomarkers to supplement the above-listed classical biomarkers: myosin light chain 3, fatty acid binding protein 3, and skeletal muscle troponin I. Troponin I is a calcium-binding, cardiac and skeletal muscle cytoskeletal protein with three isoforms specific for cardiac and type I or type II skeletal muscle fibers. Skeletal muscle troponin I also has the potential to distinguish type I from type II myofiber injury (e.g., peroxisome proliferator activated receptor-alpha vs statins toxicity) and has immunologic assays commercially available for rat, mouse, and monkey. Myoglobin is a heme-containing protein that stores oxygen in the muscle. It is mainly expressed in the heart muscle and type I fibers of skeletal muscle and could be used to assess skeletal muscle injury not associated with heart lesions. Xin is an actin-binding protein that is expressed in the heart and skeletal muscle, has two isoforms (isoform A, specific for the heart, and isoform B, specific for the skeletal muscle) and could prove useful in skeletal muscle injury assessment in animal studies.

Skeletal muscle denervation atrophy, see the preferred term **Myofiber atrophy**.

Skeletal muscle disuse atrophy, see the preferred term **Myofiber atrophy**.

Skeletal muscle hyperplasia is a rarely observed phenotype in toxicology studies, probably limited to regenerative hyperplasia of skeletal myofibers after local (injection sites) or systemic drug administration (statins) or after prolonged decubitus in moribund conditions. Regenerating skeletal muscle hyperplasia is usually limited to specific regions of a muscle, and myofibers in these regions have reduced size and their sarcoplasm is basophilic with multiple centrally located nuclei arranged in a single row. Refer to **Bone, Muscle, and Tooth** in Appendix 2 for further information.

Skeletal muscle hypertrophy is the increase in size of individual skeletal muscle cells. Skeletal muscle hypertrophy may have physiological causes such as exercise, or pharmaceutical causes such as anabolic steroid treatment.

Skeletal muscle nutritional atrophy, see the preferred term **Myofiber atrophy**.

Skene's paraurethral gland is a vestigial, paired gland communicating with the urethra in females, developmentally analogous to the prostate gland in males. These glands can be found in most mammals but are not often included in standard sections collected for toxicologic pathology examination.

Skin is the largest organ of the body and provides important barrier function against external environmental, infectious, and chemical insults, as well as contributing to important homeostatic, endocrine, sensory, and immune system functions in the body, at its most basic level. The skin is comprised of the epidermis, dermis, and subcutis, known as the skin strata. For Anatomy and Histology, see Appendix 3 for further information.

Skin sensitization tests are assays conducted either in vitro, in vivo in animals, or in humans, to determine the potential of a chemical or experimental compound to induce an allergic reaction when applied to the skin. In vitro methods based on mechanisms of skin sensitization have gained popularity, and legacy in vivo guinea pig models (e.g., Buehler skin test and Magnusson-Kligman maximization test) have been largely replaced by the local lymph node assay. See **Magnusson-Kligman maximization test, Buehler skin test**, and **Local lymph node assay** for further information.

Skin toxicity tests include irritancy and local dermatotoxicity studies using in vitro models (e.g., cell cultures, artificial skin) as a replacement for rabbit skin irritancy testing, and standard laboratory animal models for repeat-dose safety evaluation studies. Species preference is for use of the minipig due to the similarity in structure and function of the minipig skin compared to human skin. See **Dermal irritation tests** and **Minipigs in dermal studies** for further information.

Skin wound healing occurs when there is a mechanical breach of the epidermis (erosion) or deeper breach beyond the epidermal basement membrane (ulcer). Re-epithelialization of the affected area occurs during healing and can lead to **Scar tissue formation** (see description of term).

Slow acetylators are persons with a deficiency of the hepatic *N*-acetyl transferases which results in a reduced capacity for

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acetylation of certain drugs containing aromatic amines, sulfonamides, or hydrazides. See **Acetylator phenotype, Rapid acetylators, *N*-acetyl transferases**, and **Acetylation** for further information.

Small lymphocytes are round, mononuclear white blood cells, ~7–10 μm in diameter (smaller than a neutrophil), with a scant rim of basophilic cytoplasm surrounding the nucleus. The nucleus itself is round or slightly reniform (kidney-shaped) with a condensed chromatin pattern. They are the main lymphoid population in blood and bone marrow smears, and on cytology from lymphoid tissue. They correspond to lymphocytes in a "resting state." They originate from bone marrow lymphoid precursors and then migrate to peripheral lymphoid tissues and circulate in the blood. They are highly represented in rodent bone marrow and can be easily confused with rubricytes of the erythroid series. Most lymphocytes in the circulation are T lymphocytes, but based on morphology alone, one cannot differentiate between T and B lymphocytes. Lymphocyte concentrations in the blood are affected by production (stem cell proliferation, differentiation and blastogenesis following antigenic stimulation), lymphocyte distribution between the marginating and circulating pool, and lymphocyte migration to and from lymphoid and other tissues. In rodents, small lymphocytes are the main leukocyte population in circulating blood. Lymphocyte lifespan is highly variable and can be from hours to years.

Smooth muscle hyperplasia is a nonneoplastic proliferation of smooth muscle cells. Smooth muscle cells have cytological features comparable to normal cells (well-differentiated elongated fusiform cells with eosinophilic cytoplasm and nuclei with tapered ends) within muscle bundles that have conserved normal architecture (intersecting fasciculi with parallel myofibers within each fasciculus). Refer to **Bone, Muscle, and Tooth** in Appendix 2 for further information.

Smooth muscle hypertrophy is the increase in size of individual smooth muscle cells, arranged into bundles and whorls that may be encountered in the smooth muscle layers of the uterus, gastrointestinal tract, and pulmonary arteries. Smooth muscle hypertrophy may be a test article–related finding in the mesovarium in studies with beta stimulants.

snRNA are small nuclear ribonucleic acids that are confined to the nucleus and involved in RNA processing such as splicing.

Solitary bone cyst, see the preferred term **Bone cyst**.

Solute carrier transporters (SLCs) facilitate cellular uptake of a drug by coupling the uptake with cotransport of a secondary substrate, usually an ion, which moves with the cellular gradient, thereby driving the uptake of the drug. This co-transport can be in the same direction (symport) or opposite direction (antiport) as the drug. Such transporters occur in both extracellular and intracellular membranes. There are a large number of solute carrier transporters comprised of products from several gene families.

In general, the study of drugs as substrates or inhibitors of transporters is limited to those which are known to be associated with drug-drug interactions. A typical panel of such transporters is shown in the table below.

A Typical Transporter Panel Used during Drug Discovery and Development

Transporter	Location	Substrate	Type
OATP1A2	Liver, kidney, choroid plexus	Sulfobromophthalein, cholic acid statins	SLC
OATP1B1	Liver	Bilirubin, bosentan, statins	SLC
OATP1B3	Liver	Bilirubin conjugates, statins, valsartan	SLC
OATP2B1	Liver	Steroid conjugates, thyroxin, statins	SLC
OAT1	Kidney	Acyclovir, methotrexate, furosemide, prostaglandin E	SLC
OAT2	Kidney	Steroid conjugates, acetylsalicylate, cGMP, cAMP	SLC
OAT3	Kidney	Antivirals, steroid conjugates, benzylpenicillin	SLC
OAT4	Placenta	p-aminohippurate, steroid conjugates, uric acid	SLC
OATN2	Kidney	verapamil, cephaloridine and oxaliplatin	SLC
OCT1	Liver, kidney, intestine	Acyclovir, metformin, quinine, serotonin, cimetidine	SLC
OCT3	Heart, lung, trachea, testis, ovary	Atropine, dopamine, epinephrine, histamine	SLC
MATE1	Kidney	Acyclovir, cimetidine, creatinine, metformin	SLC
MATE2-K	Kidney	Metformin, cimetidine, triethylammonium	SLC
PEPT1	Intestine, kidney	в-lactam antibiotics, 5-aminolevulinic acid	SLC
PEPT2	Kidney, CNS, lung	5-aminolevulinic acid, peptide-like drugs, dipeptides	SLC
NTCP	Liver	Bile salts, steroid conjugates, sulfobromophthalein	SLC
P-gp (MDR1)	Intestine choroid plexus, liver, kidney	Actinomycin D, cyclosporine A, daunorubicin	ATP
BCRP (MXR)	Intestine choroid plexus, liver, testis	Abacavir, ciprofloxacin, erlotinib, imatinib Prazosin	ATP
BSEP	Liver	Bile salts	ATP

The different transporter families, such as organic anion–transporting peptides (OATP), organic anion transporters (OAT), multidrug and toxin extrusion transporters (MATE), peptide transporters (PEPT), and concentrative nucleotide transporters (CNT), are classified according to function and gene family.

Somatofugal atrophy, see the preferred term **Axonal atrophy**.

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Somatofugal transport is a synonym for anterograde axonal transport. See preferred term **Axonal transport**.

Somatopetal transport is a synonym for retrograde axonal transport. See the preferred term **Axonal transport**.

Somatostatin, see the preferred term **Growth hormone inhibitory hormone**.

Somatotroph cell is a subset of acidophil cells that produce somatotropin. See **Pituitary acidophil cell** for further information.

Somatotropin, see the preferred term **Growth hormone**.

SOT is an acronym for the Society of Toxicology.

Space of Disse refers to the thin space that separates the sinusoidal surface of the hepatocytes from the sinusoidal endothelial cells. The space of Disse contains plasma that directly contacts the sinusoidal microvilli on the hepatocyte membrane. It is an area where solutes are freely exchanged between hepatocytes and the blood that is circulating through the hepatic parenchyma.

Synonym(s): **Perisinusoidal space**.

Special senses, Anatomy and Histology, see Appendix 3 for further information.

Species extrapolation, see **Allometric scaling** for further information.

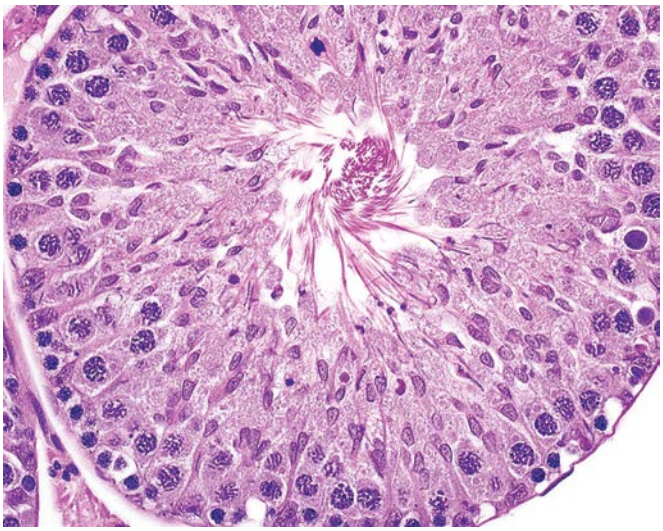
Spermatic granuloma, see the preferred term **Testis, efferent ducts and epididymis sperm granuloma**.

Spermatid is one of the germ cell types that represents the haploid product of meiotic division rather late in the process of sperm development. Spermatids have not left the seminiferous tubules and have a dense nucleus and an acrosome. They have a round or elongated appearance, depending on their stage of development. Spermatids heavily depend on the Sertoli cells for successful terminal differentiation and release.

Spermatid elongation is the haploid product of meiotic germ cell division in the spermatogenic cycle. The appearance is due to an elongated nucleus coated with acrosomes. The elongating spermatids are embedded in the luminal cytoplasm of the Sertoli cell, with their tails projecting into the luminal compartment of the seminiferous tubule. The standard nomenclature adopted by pathologists divides spermatid maturation into "steps" based on morphology. The step numbers for elongating spermatids vary by species, due to species-specific variations in spermatogenesis: rat, steps 9–19; mouse, steps 9–16; dog, steps 6–12; and monkey, steps 7–14. Degenerative changes in elongating spermatids appear as clubbing and misshapen heads and/or retention and phagocytosis by Sertoli cells. Xenobiotics such as boric acid, methyl chloride, and dibromoacetic acid are toxic to elongating spermatids.

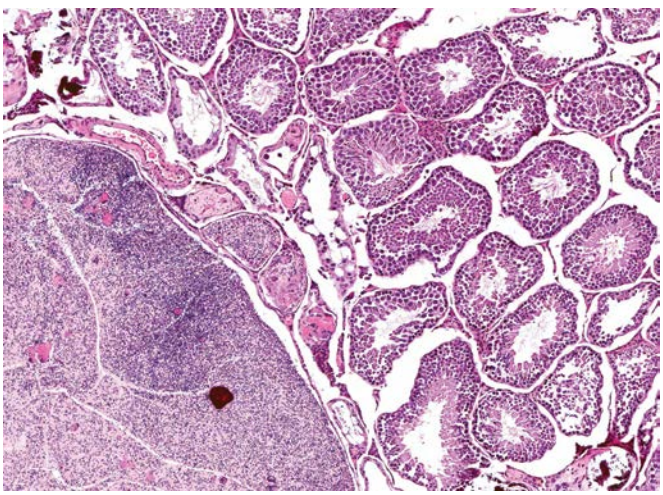
Spermatid retention is the persistence of mature, elongated spermatids (in mouse step 16, in rat step 19) in the lumen of seminiferous tubules stages IX–XII. In rodents, the release of spermatids normally occurs at the morphological stage VIII. Retained spermatids are present at the luminal surface or in the basal Sertoli cell (SC) cytoplasm parallel to the basement membrane. A functional disturbance in the release of spermatids may result from abnormal SC, reduced testosterone levels, or abnormal spermatid development. Spermatid retention is frequently associated with abnormalities in sperm parameters and infertility.

Synonym(s): **Spermiation delayed**.



Retained spermatids adjacent to spermatocytes, testis, rat, H&E. (Reproduced with permission of Society of Toxicologic Pathology from Creasy et al., 2012.)

Spermatocele is a sperm-filled tubule or duct that is greater than two times the normal tubular diameter in the testis, and more than three times the normal ductal size in the efferent duct/epididymis. Spermatocele pathogenesis is as described for sperm stasis: disturbances in fluid dynamics and smooth muscle contractions or sperm obstruction or propulsion.



Duct filled with sperm, testis, B6C3F1 mouse, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

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A spermatocele can result in proximal tubular dilation and sperm granulomas and although it is often a spontaneous change, it can be induced by compounds that effect intratubular secretion.

Synonym(s): **Testicular sperm cyst**; **testicular efferent ductal cyst**; **testicular epididymal cyst**; **testicular efferent ductal sperm retention cyst**; **epididymal sperm retention cyst**.

Spermatocyte is the largest germ cell and represents the meiotic phase of germ cell differentiation. The first spermatocyte type (preleptotene) is formed by mitotic division of the B-type spermatogonia (see **Spermatogonia**). The preleptotene cell is the start of a continuing process of DNA exchange, first entering the 3-week long meiotic phase of prophase, passing through the leptotene, zygotene, pachytene, and diplotene stages, diakinesis, and the first meiotic division to produce secondary spermatocytes. The second meiotic division will produce the haploid spermatid. Similar to other germ cell types, spermatocytes are susceptible to apoptosis because of androgen deficiency or the cytotoxic effects of agents interfering with cell division. See **Spermatid** for further information.

Spermatocytic seminoma, see the preferred term **Seminoma, benign** or **Seminoma, malignant**.

Spermatocytoma, see the preferred term **Seminoma, benign** or **Seminoma, malignant**.

Spermatogenesis is the process in which the initial germ cells (i.e., spermatogonia) will develop into mature, elongated spermatids. Spermatogenesis is divided into three phases based on function as follows: (1) the proliferative phase, in which germ cells (i.e., spermatogonia) undergo divisions; (2) the meiotic phase, in which genetic material of the germ cells (i.e., spermatocytes) is recombined and segregated; and (3) the differentiation or spermiogenic phase, in which the germ cells (i.e., spermatids) transform into the mature sperm that will be able to fertilize the egg. See **Spermatid** for further information.

Spermatogenic epididymitis, see the preferred term **Testis, efferent ducts and epididymis sperm granuloma**.

Spermatogonia represent the stem cell population of the germ cells. They are located on the basement membrane without being attached to it. Spermatogonia are unique since they are the only proliferative cell population in the seminiferous epithelium, and they reside outside the protection of the blood-testes barrier. For this reason, spermatogonia are vulnerable to cytotoxic agents. After division by mitosis, the primary spermatocytes are formed. There are three types of spermatogonia: stem cell spermatogonia, proliferating spermatogonia, and differentiating spermatogonia. The stem cell and proliferative spermatogonia are responsible for their own cell number, and a pool of cells will be produced that are ready to differentiate. The differentiating spermatogonia consist of four successive generations each derived by meiotic division (type A1–A4). After another division of type A4, the intermediate type is formed which gives rise to the type B spermatogonia. The morphologic variation of the different cell types is mainly based on differences in the distribution of the chromatin in the nucleus (pale-staining nucleus in type A, and densely clumped in type B, the intermediate type somewhere in between). See **Spermatocyte** for further information.

Spermatozoan (sperm, spermatozoa) is the male gamete. See **Spermatogenesis** for further information.

Spermiation is the process by which mature spermatids are released from Sertoli cells into the seminiferous tubule lumen prior to their passage to the epididymis. It takes place over several days at the apical edge of the seminiferous epithelium, and involves several discrete steps, including remodeling of the spermatid head and cytoplasm, removal of specialized adhesion structures, and the final disengagement of the spermatid from the Sertoli cell.

Spermiation delayed, see the preferred term **Spermatid retention**.

Sperm impaction, see the preferred term **Testis, efferent ducts and epididymis sperm stasis**.

Sperm morphology describes the structure or form of spermatozoa (i.e., mature sperm cells). It is one of the sperm parameters evaluated when sperm assessment is required for regulatory submissions for environmental xenobiotic exposure and may be required by regulatory agencies for pharmaceutical development if there is a reproductive toxicity issue. Sperm morphology is performed on material sampled from the epididymis (preferably caudal) and although different methods have been described, the evaluation is focused on the distinction of normal sperm and abnormal sperm. The abnormal sperm is classified in different categories based on the structure of the head and the flagellum of the sperm and is analyzed manually by using a light microscope. See **Sperm parameters** for further information.

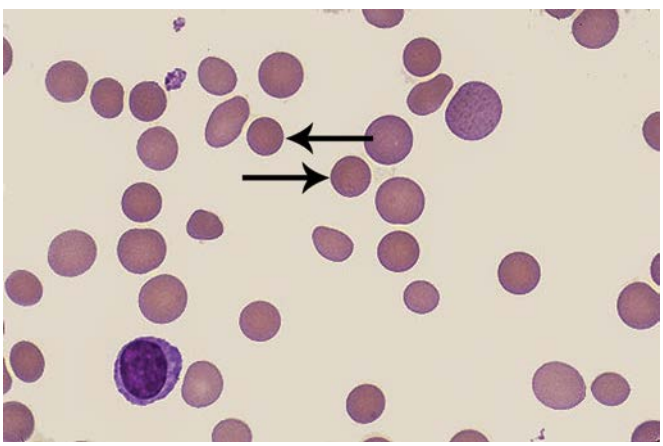
Sperm motility describes the ability of spermatozoa (i.e., mature sperm cells) to move from one site to another (i.e., sperm cell motion). It is one of the sperm parameters evaluated when sperm assessment is required for regulatory submissions for environmental xenobiotic exposure and may be required by regulatory agencies for pharmaceutical development if there is a reproductive toxicity issue. Sperm motility is performed on material sampled from the vas deferens or from the epididymis. The evaluation of motility mainly involves the assessment of the percentage of motile sperm and the percentage of progressive motile sperm, which is a measure of the nature of the movement of the spermatozoon. Data can be obtained automatically by a specialized analyzer or manually counted using a light microscope. See **Sperm parameters** for further information.

Sperm parameters are variables or characteristics of sperm that are indicative of the quality of the spermatozoa

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(i.e., mature sperm cells). In general, sperm parameters include sperm count, sperm motility, morphology of epididymal sperm, and testicular spermatid heads counts. Analyzing sperm parameters is considered a valuable tool for obtaining information on reproductive health in the clinic or in epidemiologic studies of environmental exposure. In addition, it is important in predicting potential toxicity of pharmaceutical and/or xenobiotic compounds. The analysis of sperm parameters is common practice in many species, including the human.

Spherocyte is an abnormally shaped red blood cell in which the erythrocyte has a decreased surface area-to-volume ratio. This is typically due to the loss of cell membrane and results in cells that also have a reduced diameter, called microspherocytes. Spherocytes are more densely hemoglobinated due to their decreased area. Morphologically they appear perfectly round and lack a central pallor. Numerous spherocytes are observed in the inherited conditions of hereditary spherocytosis and hereditary infantile pyropoikilocytosis. Spherocytes can also be observed in a broad variety of acquired conditions including hemolytic disease of the newborn, burns, snakebite, ABO hemolytic transfusion reaction, autoimmune hemolytic anemia, Heinz body hemolytic anemia, *Clostridium* bacterial infection, and hypophosphatemia. Hereditary spherocytosis is caused by a molecular defect in the proteins of the cytoskeleton. Whether the spherocytosis observed is hereditary or acquired, the cell is less flexible than the normal disk shape. Therefore spherocytes are more prone to hemolysis, and typically demonstrate a high osmotic fragility. The presence of spherocytes and a decreased red blood cell count is consistent with hemolytic anemia.



Spherocytes (arrows), blood smear, dog.

Spheroids are large, eosinophilic, fusiform structures within axons (axonal spheroids), that represent intra-axonal accumulations of cytoskeletal constituents. These can be seen with axonal degeneration or axonal dystrophy. See **Axonal degeneration** and **Axonal dystrophy** for further information.

Spiral ganglion decreased cellularity is reduced density or loss of the ganglion cells in the spiral ganglion of the cochlea in the inner ear compared with concurrent controls that are age-, sex-, and section matched. Due to variability in ganglion cell density along the cochlea from the apex to the base, other indicators of injury (necrosis of ganglion cells or concurrent cochlear nerve axonal changes) should also be considered prior to making a determination of decreased spiral ganglion cells. See **Inner ear neuronal necrosis** for illustration.

Differential diagnosis: **Inner ear neuronal necrosis**.

Spiral ligament decreased cellularity consists of a histologic decrease in the density of fibrocytes of the spiral ligament of the cochlea in the inner ear (refer to Appendix 3 for further information) when compared to concurrent controls. Toxicities or injury to the overlying stria vascularis may cause the cell loss. See **Spiral limbus decreased cellularity** and **Stria vascularis decreased cellularity** for further information.

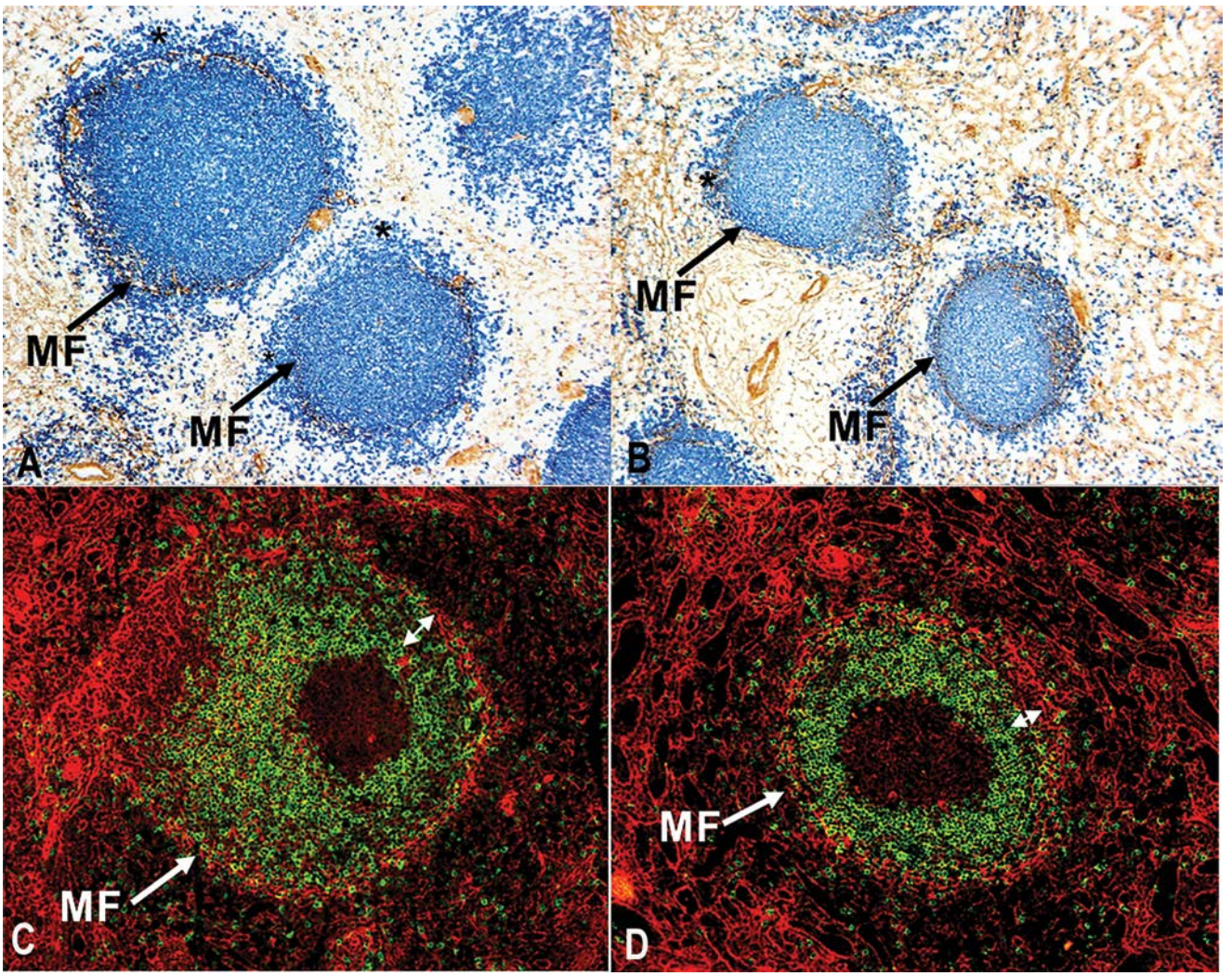
Differential diagnosis: **Vestibulocochlear axonal degeneration**.

Spiral limbus decreased cellularity consists of a histologic decrease in the density of fibrocytes of the spiral limbus of the cochlea in the inner ear (refer to Appendix 3 for further information) when compared to concurrent controls. Loss of cellularity of the spiral limbus will often follow hair cell loss by an unknown process, but possibly by a feedback mechanism. See **Spiral ligament decreased cellularity** and **Stria vascularis decreased cellularity** for further information.

Differential diagnosis: **Vestibulocochlear axonal degeneration**.

Spleen is both the largest secondary lymphoid tissue and a component of the mononuclear phagocyte system (MPS). It is located in the left anterior quadrant of the abdominal cavity in nearly all vertebrates. Although the spleen has the same blood supply, the celiac artery, as the anterior portion of the gastrointestinal (GI) tract, it is embryologically derived from dorsal mesenteric mesenchyme rather than from foregut endoderm, which gives rise to the anterior GI tract, including the liver and pancreas. The lymphoid tissue compartment is referred to as the white pulp, while the other compartment, termed the red pulp, consists of vascular sinuses lined by discontinuous endothelium and separated by cords comprised of macrophages that are a part of the MPS. The splenic white pulp consists of lymphoid follicles containing B and T lymphocytes surrounded by a marginal zone containing dendritic cells, macrophages, and recirculating B lymphocytes. Outside the lymphoid follicles and marginal zones lies the red pulp, consisting of venous sinuses delineated by splenic cords comprised of macrophages and other phagocytic cells, divided by a trabecular fibrovascular stromal network that extends into the red pulp parenchyma from the splenic capsule. The white pulp functions as part of the secondary lymphoid system, while the red pulp phagocytizes pathogens and removes senescent red blood cells from the circulation. The red pulp is also often the site of extramedullary hematopoiesis (EMH), particularly in murine rodents. See Appendix 3, **Splenic Red Pulp and Splenic White Pulp** for further information.

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Splenic lymphoid follicles from cynomolgus monkey that demonstrate a decrease in marginal zone cellularity. Panels A and B are stained for the B-cell marker CD20 (blue) and smooth muscle actin SMA–brown) illustrating how the band of SMA+ myofibroblasts (MF) divides the follicle and the inner marginal zone from the outer marginal zone. Panel B illustrates a decrease in both total follicle size but particularly in the outer marginal zone area (CD20+ lymphocytes outside the SMA+ band identified by asterisks) induced by BR3-Fc, an immunoglobulin fusion protein that blocks the B-cell growth factor BAFF. Bars = 200 μm. Panels C and D are dual labeled for IgD (green) and F-actin (red). As demonstrated in panel B, panel D illustrates a decrease in the follicular area expressing IgD, particularly in the lymphocytes that are strongly IgD+ (the mantle zone) induced by BR3-Fc. In addition, panel D also illustrates a decrease in the IgD+ lymphocytes in the weakly to moderately strongly IgD+ lymphocytes in the inner marginal zone (illustrated by double-headed arrows as the area between the strongly IgD+ mantle zone and the red band of myofibroblasts). (Reproduced in modified form with permission from the American Society for Investigative Pathology from Vugmeyster et al. *Am J Pathol* 2006.168: 476–489.)

Splenic decreased cellularity of the lymphoid follicle marginal zone is a decrease in the size and cellularity of the follicular marginal zone that lies between the follicular mantle zone and the splenic red pulp. This anatomic region can best be demonstrated by IHC staining for a B-cell marker such as CD20 and a myofibroblast marker, such as smooth muscle actin (see figure above).

Differential diagnoses: **Lymphoid atrophy** (preferred term) and its synonym **Lymphoid depletion**. (Both of these terms refer to a more generalized and widespread decrease in lymphoid tissue and lymphoid follicles.)

Splenic extramedullary hematopoiesis is a normal morphological presentation in many animal species used in toxicological pathology, depending on species and age of the animal. It is normally present in the rodent. See **Extramedullary hematopoiesis** for further information.

Splenic marginal zone is a distinct anatomic region that surrounds the central lymphoid follicle and contains mature B lymphocytes. In mouse, the marginal zone B cells are delineated from the lymphoid follicles by a marginal sinus containing marginal metallophilic macrophages that delineate the follicular B cells from the marginal zone. In contrast, splenic white pulp in the primate lacks marginal zone sinuses and has large B-cell lymphoid follicles with a prominent smooth muscle, actin-positive band of myofibroblasts that divides the outer marginal zone from the rest of the follicle. In addition, mouse

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marginal zone B cells do not recirculate, are naïve B cells, and are found only in the spleen, while in the human, and very likely all primates, marginal zone B cells recirculate, consist primarily of memory B cells, and are found in other anatomic sites. There are data to suggest that marginal zone B lymphocytes are important in the T lymphocyte–independent immune response as well as in the development of autoimmunity; hence their depletion has ramifications for both the therapy of autoimmune conditions as well as for potentially increased susceptibility to T lymphocyte–independent pathogens, such as *Streptococcus pneumoniae*. See Appendix 3 for further information.

Splenic red pulp lies outside and between the splenic lymphoid follicles and marginal zones (arrows) and consists of venous sinuses delineated by splenic cords comprised of macrophages and other phagocytic cells that are part of the mononuclear phagocyte system. The red pulp parenchyma is supported by a trabecular fibrovascular stromal network that extends into the red pulp from the splenic capsule. The red pulp functions to phagocytize pathogens as well as to remove senescent red blood cells from the circulation. It is also often the site of extramedullary hematopoiesis, particularly in murine rodents. See Appendix 3 for further information.

Splenic red pulp angiectasis is the dilatation of splenic red pulp sinuses and is frequently associated with red pulp fibrosis and accompanied by congestion.

Splenic red pulp atrophy is a decrease in red pulp size due to a decrease in all red pulp components, including hematopoietic cells. It is often associated with hemosiderin accumulation and sometimes with fibrosis. It can occur as a spontaneous incidental finding, particularly in old rats and mice. It can also be secondary to weight loss or possibly a treatment-related effect. An example is the marked reduction in splenic weight with corresponding red pulp atrophy induced by acute oral diazinon administration in dogs. It is unclear whether this splenic effect is a direct treatment-related effect or secondary to marked weight loss and emaciation.

Splenic red pulp congestion is a common finding, particularly in the dog and rat. It is frequently seen following euthanasia using barbiturates. It is characterized by increased numbers of red blood cells filling the splenic red pulp sinuses. Chronic congestion is often accompanied by hemosiderin pigment deposition. Erythrophagocytosis is sometimes evident.

Splenic red pulp contraction is a decrease in the size of the splenic red pulp, generally due to the contraction of myofibroblasts residing in the splenic red pulp stromal cords.

Splenic red pulp erythrophagocytosis is the engulfment of red blood cells by splenic red pulp macrophages. It may occur as the result of autoimmune hemolytic anemia, either spontaneously or as the result of an immune-mediated toxicologic reaction.

Splenic red pulp extramedullary hematopoiesis is the presence of hematopoietic precursors, erythroid, myeloid, and megakaryocytic, that are normally found in the bone marrow, within the splenic red pulp. Red pulp extramedullary hematopoiesis can occur as the result of increased demand for bone marrow hematopoietic production, such as profound anemia. It can also occur as the result of decreased bone marrow hematopoietic production, such as secondary to a leukemic process or other neoplastic infiltration into the bone marrow. Finally, it is considered a very common incidental finding in murine rodents, particularly in mice.

Splenic red pulp fat accumulation is a rare spontaneous incidental finding in the rat. It also occurs following exposure to aromatic amines such as aniline and represents adipocyte metaplasia of stromal cells. It is generally focal in nature, and is often associated with red pulp fibrosis.

Splenic red pulp fibrosis is the presence of collagenous fibrous connective tissue in the red pulp and may also involve the splenic capsule. It can occur secondary to leukemic infiltration of the splenic red pulp (e.g., large granular leukemia in F344 rats) or to chronic inflammation. It may also occur as the result of toxicity, such as following exposure to aromatic amines.

Splenic red pulp macrophage vacuolation can occur spontaneously, as in the various lipid storage diseases, or may be acquired, such as following administration of high molecular weight, poorly soluble compounds, such as polyethylene glycols (PEGs) that are used to augment exposure of biologic therapeutics. Macrophage vacuolation has also been reported as the result of toxicity, such as in mice treated with pentosan polysulfate (Elmiron), a semisynthetic polysulfated xylan indicated for the relief of various medical conditions including thrombi and interstitial cystitis in humans and osteoarthritis in dogs and horses. In the latter case, the vacuoles contain neutral and acidic mucins, which are identified as lysosomal structures by transmission electron microscopy. Vacuolation of splenic macrophages may be a component of phospholipidosis occurring in macrophages within other tissues.

Splenic red pulp nodular hyperplasia is generally found in older rats, particularly the Fisher 344 strain, and usually presents as a solitary nodular mass composed of relatively normal-appearing red pulp that lacks normal white pulp/lymphoid structures. It is considered most likely to be a hamartoma or congenital malformation. Refer to **Lymphoid System** in Appendix 2 for further information.

Splenic red pulp stromal hyperplasia is a rare finding in rodents and is characterized by an increase in the number of splenic red pulp stromal cells, usually with a corresponding contraction and loss of the red pulp venous sinuses. Stromal hyperplasia is not considered to be preneoplastic. Refer to **Lymphoid System** in Appendix 2 for further information.

Splenic white pulp consists of the splenic lymphoid follicle and the periarteriolar lymphoid sheath (PALS). The lymphoid follicle contains primarily B lymphocytes with a central region

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termed the germinal center (GC) that contains proliferating and differentiating B lymphocytes, surrounded by concentric zones of more mature B lymphocytes starting with (from innermost to outermost) the mantle zone, the inner marginal zone (IMZ), and the outer marginal zone (OMZ) that lies at the junction of the lymphoid follicle and surrounding splenic red pulp. Immediately outside the central lymphoid follicle is the central splenic arteriole (CA) which is surrounded by the PALS, consisting primarily of T cells. See Appendix 3 for further information.

Spongiosis is the presence of edema fluid between cells of the epidermis, causing clear visualization of intercellular bridges (desmosomes) within the stratum spinosum. It indicates inflammation. The edema can mechanically disrupt the intercellular bridges, causing a vesicle to form.

Spontaneously hypertensive rat (SHR) is a rat model with essential (primary) hypertension used to study cardiovascular diseases and treatments. SHR rats begin to develop hypertension at 5–6 weeks of age and develop many features of human hypertensive cardiovascular disease as they age, including thickening of the walls of blood vessels, enlargement of the heart, stroke, and kidney dysfunction.



Spontaneously hypertensive rat. (Image courtesy of Charles River Preclinical Services, Reno, NV.)

Squamous cell carcinoma is an invasive, malignant neoplasm of the skin originating within the epidermis, breaching the epidermal basement membrane, extending into the dermis or underlying tissue. It is comprised of neoplastic epidermal keratinocytes with variable atypical features such as nuclear pleomorphism, anisocytosis, and increased mitoses. Refer to **Skin** in Appendix 2 for further information.

Squamous cell hyperplasia, see the preferred term **Epidermal hyperplasia**.

Squamous cell hyperplasia of nonglandular stomach, focal/diffuse is a proliferation and thickening of the squamous layer of the nonglandular stomach in a local or extensive fashion. Refer to **Gastrointestinal Tract** in Appendix 2 for further information.

Differential diagnoses: Nonglandular stomach squamous cell papilloma; Nonglandular stomach basal cell hyperplasia; **Nonglandular stomach squamous cell carcinoma**.

Synonym(s): **Nonglandular stomach squamous hyperplasia**; **nonglandular stomach squamous cell hyperplasia**.

Squamous cell metaplasia occurs when squamous cells form in noncornified tissues. Metaplasia itself is normal tissue in an abnormal location. When squamous metaplasia is present, it is usually found in non-squamous epithelial (mucosal) surfaces such as in the respiratory or gastrointestinal tract. The presence of squamous metaplasia generally indicates an adaptive change to chronic irritation. Since multilayered squamous epithelium is tougher and less permeable than the typical mucosal epithelium in an affected area, this adaptation often results in reduction of inflammation and irritation. As long as the source of irritation persists, the squamous metaplasia will persist, but if the irritation is removed the mucosa will eventually return to the native epithelial type. Squamous metaplasia is not a preneoplastic change.

Squamous cell papilloma is the benign counterpart of malignant squamous cell carcinoma, as they also arise from epidermal keratinocytes. These masses may feature atypical cells and frequent mitotic figures. Typically, they are associated with extensive keratinization, but this is not always present. Refer to **Skin** in Appendix 2 for further information.

Squamous cell papilloma (gastrointestinal) is a benign epithelial tumor growing as an exophytic (outwardly projecting) mass, often with fingerlike fronds. Refer to **Gastrointestinal Tract** in Appendix 2 for further information.

Squamous cyst(s) are intradermal cystic structures lined by stratified squamous epithelium and filled by concentric, lamellar, orthokeratotic keratin. They are not associated with a pilosebaceous unit (see **Adnexa** for further information.). Squamous cysts are primarily distinguished from adnexal/follicular hyperkeratosis by not being associated with a pilosebaceous unit. Keratoacanthomas are distinguished from adnexal/follicular hyperkeratosis by having a large central cavity containing central keratinization, often with cholesterol clefts, lined by hyperplastic squamous epithelium. Refer to **Skin** in Appendix 2 for further information.

Differential diagnoses: **Adnexal hyperkeratosis**; **Keratoacanthoma**.

Synonym(s): **Horn cyst**; **keratin cyst**.

Squamous hyperplasia, see the preferred term **Epidermal hyperplasia**.

Squamous metaplasia is a transition from any normal epithelial type to a squamous phenotype. Squamous metaplasia is a reaction that most commonly occurs following persistent toxic or mechanical irritation of a mucosal surface. Squamous metaplasia is also seen in cases of hypovitaminosis A where the ductular epithelium becomes squamous and in the healing stages of infections of glands (coronaviral infections in rats).

Squamous polyp is a polyp that originates from and is mainly composed of and covered by squamous epithelium. Refer to **Gastrointestinal Tract** in Appendix 2 for further information.

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Staphyloma, see the preferred term **Scleral atrophy**.

STD10 is the abbreviation for severely toxic dose 10 and refers to the dose that produces severe toxicity in 10% of the animals dosed with the test substance. The STD10 is referenced in ICH S9 guidance (ICH Tripartite Guideline) as an optional approach to determining a starting dose in human cancer trials (1/10th of the STD10 in rodents). The STD is not defined in ICH S9, but the HNSTD (highest non-severely toxic dose) is defined as the highest dose level that does not produce mortality, life-threatening toxicities, or irreversible findings. By comparison, the STD would be defined as any dose that produces mortality, life-threatening toxicities, or irreversible findings.

Reference

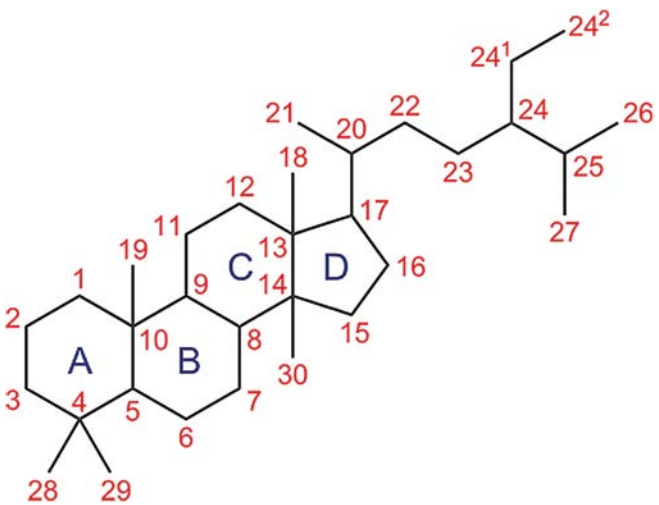
ICH Tripartite Guideline. Nonclinical Evaluation for Anticancer Pharmaceuticals S9, Current Step 4 version, October 29, 2009.

Steatitis, see the preferred term **Lipogranulomatous inflammation**.

Steatosis, see the preferred terms **Lipid accumulation, Fatty change, and Hepatocellular lipidosis**.

Sternal cartilage degeneration, see the preferred term **Chondromucinous degeneration**.

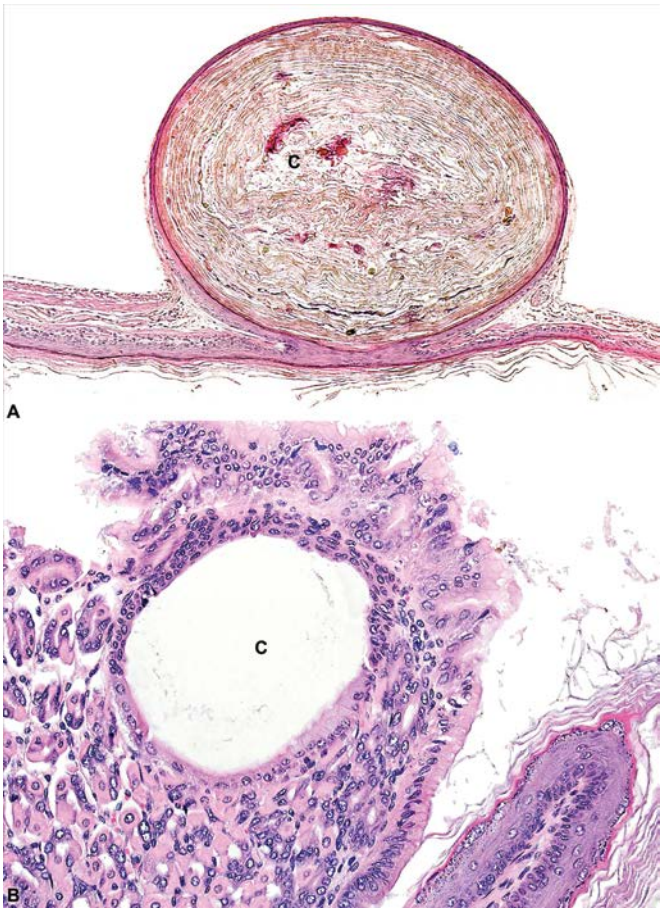
Steroids are organic compounds with a core structure of seventeen carbon atoms within four fused cyclic (ring) structures made up of three six-member cyclohexane rings (A, B, C) and one five-member cyclopentane ring (D) as depicted below.



Steroids include naturally occurring compounds such as cholesterol, cortisol, testosterone, estrogen, and progesterone.

Stomach glandular cysts are congenital or age-related lesions in rodents where markedly dilated glands lined by well-differentiated cuboidal to flattened chief, parietal, or mucous epithelial cells without cellular atypia are observed. The lumen may contain mucus or mixed inflammatory exudate with mineralization in aged rodents. Lining epithelium of the glandular cysts may show occasional areas of squamous metaplasia often surrounded by chronic inflammation.

Differential diagnoses: Glandular stomach cystic or atypical diverticulum; Glandular stomach atypical focal mucosal hyperplasia; **Glandular stomach adenocarcinoma**; **Glandular stomach mucosal atrophy**.



Stomach, male B6C3F1 mouse. H&E. (A) C = Cyst, nonglandular (keratin). (B) C = Cyst, glandular stomach. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Stomach inflammation mucosal lining is most commonly defined according to the nature and severity of the infiltrating cell types or other morphologic criteria. Inflammation may be acute or chronic, with a variety of infiltrating inflammatory cells reflecting the etiology, severity, and duration of the inciting stimulus. Such inflammation may occur with concurrent alterations to the overlying gastric epithelium, ranging from loss (acute erosion and ulceration) to atrophy or hyperplasia (typically a subacute to chronic reaction with less severe inflammation) and/or dysplasia. Such epithelial alterations may also occur in the absence of an inflammatory stimulus by a variety of other mechanisms. Sequelae to inflammation may range from complete resolution to mucosal and submucosal fibrosis with loss of the normal architecture depending on the severity and duration of insult. Chronic inflammation may predispose to epithelial dysplasia, metaplasia, and/or neoplastic transformation, and has been most investigated in the context of *Helicobacter* species infection.

Synonym(s): Gastritis.

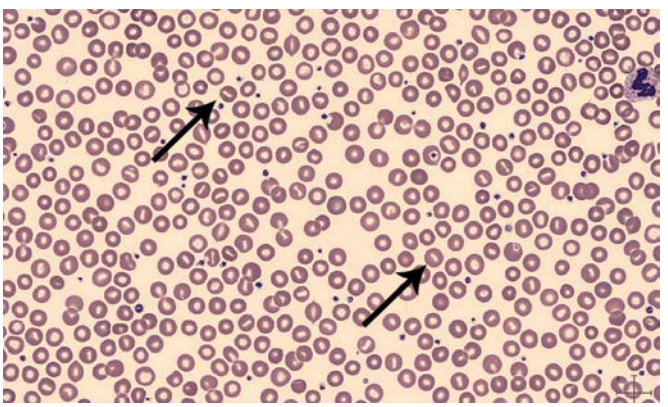
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Stomach neuroendocrine cell tumor, benign is comprised of discrete, well-demarcated aggregates of neuroendocrine cells, which may arise from hyperplastic areas in the oxyntic mucosa (i.e., corpus region). Refer to **Gastrointestinal Tract** in Appendix 2 for further information.

Stomach neuroendocrine cell tumor, malignant is characterized by infiltration through muscularis mucosae by neoplastic, often less differentiated cells arranged in cords or nodules or serosal deposits or distant metastases. Refer to **Gastrointestinal Tract** in Appendix 2 for further information.

Stomatitis, see preferred term **Oral cavity inflammation**.

Stomatocytes are red blood cells, which on blood smear examination and have an elongated rather than circular central pallor, which gives them a mouth-like appearance. Ultrastructurally, stomatocytes appear as bowls. They can be associated with excess membrane surface such as with polychromatophil erythrocytes that often appear as stomatocytes on blood smear examination. Stomatocytes are associated with hemolytic anemia when more than 10% of the red blood cells present are stomatocytes. Stomatocyte formation is associated with increased cell permeability to water and increased osmotic fragility as compared to normal red blood cells. They can form in the blood with acidosis, chronic liver disease, decreased high density lipoprotein (HDL) plasma levels such as in Tangier disease, or hereditary defects in the erythrocyte membrane.



Stomatocytes (arrows), blood smear, dog.

STP is an acronym for the Society of Toxicologic Pathology.

Strain differences are typically mentioned in reference to laboratory animal strains used in research and toxicity testing. Examples include Sprague Dawley versus Wistar rats, New Zealand White versus Dutch-Belted rabbits, and CD-1 (outbred) versus C57BL/6 (inbred) strains of mice. Strain differences in toxic responses can vary markedly, often as a consequence of strain differences in metabolism. For example, the rate of *N*-oxidation reactions in the Fischer 344 rat is much higher than that of the Sprague Dawley rat such that the former strain is more susceptible to the toxicity of aromatic amines.

Streptozotocin (STZ) is a glucosamine-nitrosourea compound that is particularly toxic to the insulin-producing beta cells of the pancreas in mammals. It is a naturally occurring alkylating agent in the nitrosourea class that damages DNA by inducing activation of poly ADP-ribosylation. Streptozotocin is similar enough to glucose to be transported into the cell by the glucose transport protein GLUT2 but is not recognized by the other glucose transporters. As such, the chemical is more toxic to beta cells, since these cells have relatively high levels of GLUT2. It is used in medicine for treating certain cancers of the islets of Langerhans and is commonly used in research to produce animal models of hyperglycemia, as well as type 1 or type 2 diabetes. High doses of STZ induces rapid islet necrosis and hyperglycemia, while low multiple doses induce type 1 or type 2 diabetes.

Stress effect is an expression used in toxicology studies to refer to change(s) in behavior, clinical observations, vital signs, clinical or anatomic pathology, or data generated under experimental conditions, related to external influences producing stress. Stress responses are associated with acute release of neurochemical mediators from sympathetic nervous system pathways, including epinephrine (adrenaline) and norepinephrine, followed by corticosteroid release from the adrenal cortex. Chronic stress results in a multitude of physiologic changes, including immunosuppression that may adversely impact tolerability in long-term studies and confound data interpretation. Examples include increased neutrophils (acute response) and histopathologic thymolytic changes (chronic response). See **Stress response** for further information.

Stress-induced leukocytosis is a condition where acute or chronic stress primarily affects circulating leukocyte counts, leading to increased mature neutrophil counts and decreased lymphocyte and eosinophil counts, and in some species (i.e., dogs), increased monocyte counts. A stress leukogram can be endogenous, and mediated by glucocorticoid release from the adrenal gland, or exogenous following administration of glucocorticoids.

Stress response is the physiological means whereby the body manages a challenge, real or perceived, causing up-regulation of the hypothalamic-pituitary-adrenal (HPA) axis, elevated serum glucocorticoid (cortisol), and hyperarousal with increased catecholamine production. Elevated cortisol and catecholamines induce cardiovascular, gastrointestinal, and respiratory changes (the "fight-or-flight" response). Chronic stress may reduce the feedback inhibition of elevated serum cortisol. Chronically elevated hormones, especially cortisol, disrupt multiple biological functions, including the sleep cycle, energy balance, and immunity. In mammals, the stress response may result in physical changes in endocrine organs, such as adrenal gland hypertrophy or hyperplasia, and alterations of clinical pathology, such as decreased lymphocyte counts.

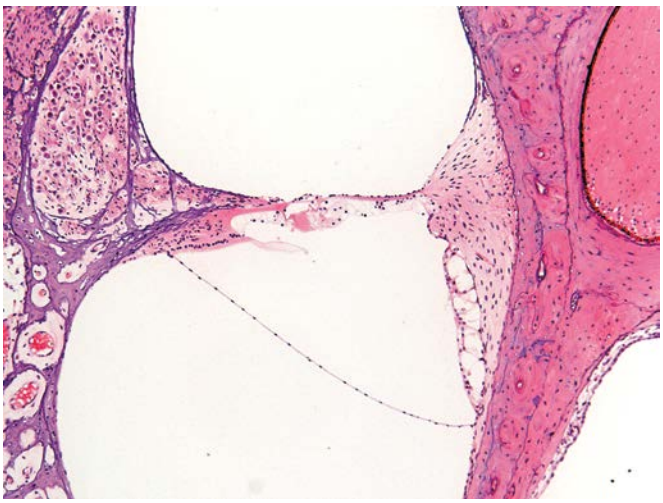
Stria vascularis decreased cellularity consists of a decrease in the density of cells of the stria vascularis in the cochlea of the inner ear (refer to Appendix 3 for further information)

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when compared to concurrent controls. Epithelial cells overlying stria vascularis cells may also be abnormal. The stria vascularis may be injured by various toxicants and have loss of cells of the inner, intermediate, or outer layers. See **Spiral limbus decreased cellularity** and **Spiral ligament decreased cellularity** for further information.

Differential diagnosis: **Vestibulocochlear axonal degeneration**.

Stria vascularis vacuolation involves swelling and vacuolation of epithelial cells of the stria vascularis of the cochlear duct in the inner ear. The stria vascularis produces endolymph for the scala media (refer to Appendix 3 for further information). Injury to the stria vascularis may be intracellular swelling (hydropic change) or extracellular swelling (edema).



Stria vascularis vacuolation, cochlea, chinchilla, H&E. (Image courtesy of K. Schafer, Vet Path Services, Mason, Ohio.)

Stromal hyperplasia can involve a variety of cell types of connective tissue origin. Some of the more common examples include stromal hyperplasia of the endometrium, prostate, bone marrow, mammary gland, and ovary. Stromal hyperplasia must be differentiated from tumors arising from stromal cells.

Stromal nephroma, see the preferred term **Renal mesenchymal tumor**.

Study Director is the individual who represents the single point of control in conducting a nonclinical study needed to support nonclinical safety in applications for an Investigational New Drug (IND) and submission of a New Drug Application (NDA). The Study Director has the overall responsibility for the technical conduct of a preclinical laboratory study. Responsibilities include interpretation, analysis, documentation, and reporting of results. The Study Director is responsible for overseeing all phases and aspects of a drug or medical device investigation to ensure that all Good Laboratory Practice (GLP) regulations are met and that the outcome of the study is valid and reliable.

Subacute generally refers to a timeframe spanning between the acute and chronic phases of a condition or disease state. It may also refer to the onset of a disease state that is less rapid than an acute onset but of shorter duration than a chronic condition. See **Acute** and **Chronic** for further information.

Subacute exposure is a term traditionally used in toxicology to characterize durations of exposure to a test substance or chemical over a time-course of up to approximately 1 month. The term "subacute" is an early or legacy toxicology term used in more recent times interchangeably with "subchronic," referring to study durations of less than 3 months (e.g., 2 or 4 weeks). Because of the confusion and ambiguity concerning the meaning of "subacute" versus "subchronic," the use of the term "subacute" is finding less favor in deference to simply describing the exposure duration or using the term "subchronic."

Synonym(s): **Subacute toxicity testing**.

Subacute inflammation is characterized by the movement of lymphocytes and mononuclear phagocytic cells to the site of injury during resolution and may be followed by a period of tissue repair. Damaged tissues are regenerated or replaced with fibroblasts, collagen, and/or endothelial cells. If pro-resolving lipid mediators are not produced or are defective, or the initiating stimulus for inflammation continues, the acute inflammatory process remains unresolved and progresses to chronic inflammation that encourages fibrosis and is associated with the pathogenesis of multiple diseases.

Subacute toxicity testing, see **Subacute exposure** and **Subchronic exposure** for further information and context.

Subcapsular cell adenoma see the preferred term **Adrenal gland subcapsular cell tumor, benign**.

Subcapsular cell carcinoma see the preferred term **Adrenal gland subcapsular cell tumor, malignant**.

Subcapsular cell hyperplasia see preferred term **Adrenal gland subcapsular hyperplasia**.

Subcapsular nephrons are characterized by short loops of Henle that extend only into the outer medulla. They are most prominent in rodents and occur in the outer zone of the renal cortex.

Subchronic exposure is a term used to describe durations of exposure to a test substance or chemical over a time-course of up to roughly 3 months (at least 90 days) and has recently replaced the term "subacute." Subchronic studies are generally used in drug development to enable IND filing They usually employ three dose groups with ten rodents and three non-rodents per gender per dose group; extra animals may be included in control and high dose groups to

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assess reversibility of any findings observed at necropsy or during treatment. Observations include, but are not limited to clinical signs, body weight changes, food consumption, clinical and anatomic pathology (including histopathology), organ weights, ophthalmic examinations, electrocardiograms (ECGs) (non-rodents), and toxicokinetics.

Subchronic toxicity testing describes toxicity studies of up to 3 months' (at least 90 days') duration. See **Subacute exposure** and **Subchronic exposure** for further information.

Subcutaneous administration is the injection or delivery of an experimental compound or chemical into the subcutis (the layer of skin directly below the dermis and epidermis). This mode of administration is often used as an alternative to intravenous dosing to achieve target systemic concentrations while avoiding potential liver first-pass effects. It is also used in rodents when intravenous administration is indicated but the chemical or test substance is a local (injection site) or vascular irritant.

Subcutis is the deepest layer of the skin, underlying the dermis. It attaches the skin to underlying tissues and contributes to energy storage and thermoregulation with its adipose-rich composition. In addition to fat, this skin layer is comprised of dense connective tissue, vessels, and nerves that provide strength and shock absorption and aid in movement. Refer to **Skin** in Appendix 3 for further information.

Synonym(s): **Hypodermis**; **panniculus adiposis**.

Subendocardial hemorrhage is known to occur after cardiac injury. It can also occur secondary to noncardiac injuries such as head injury, infectious disease, trauma, and shock. It is localized in the upper part of the interventricular septum, contralateral side of the papillary muscles, and adjacent columnae carneae of the free wall of the left ventricle. It develops as a consequence of massive sympathetic neural discharge and catecholamine secretion occurring in shock and certain types of head injury. Excessive sympathetic activity aggravates the ischemia in the subendocardial zone, causing conduction disturbances, myocardial necrosis, and in severe hemorrhage. Subendocardial hemorrhage also occasionally occurs just prior to death as an agonal change.

Subendocardial hyperplasia, see the preferred term **Endocardial Schwann cell hyperplasia**.

Subendocardial Schwann cell hyperplasia is characterized by proliferation of spindle cells immediately below the endocardium with no or minimal invasion of the myocardium. The lesion is most commonly seen in the left ventricle wall, but the atria and/or valve leaflets may rarely be affected. Refer to **Cardiovascular System** in Appendix 2 for further information.

Submandibular gland increased granules of the granular duct occur in humans and rodents whereby saliva produced by acinar secretory cells in the salivary gland body flows sequentially through intercalated, striated, excretory ducts. In the rodent, but not human, submandibular gland, the granular duct lies between the intercalated and striated ducts. Columnar cells of this duct contain secretory granules containing cell growth factors and hormones and are exocytosed in response to neural and hormonal stimuli. In humans, other ductular regions function similarly. Granular duct cells are maintained by male sex hormones, such as testosterone, are lost by castration or hypophysectomy, and are less prominent in female rodents (especially mice). Conversely, prominence of these cells in females suggests a masculinizing effect of certain chemicals or hormones.

Subretinal extracellular matrix deposits include extracellular accumulation of irregular, amorphous material between the retinal pigment epithelium (RPE) and Bruch's membrane. Deposits containing apolipoprotein, clinically called drusen, are thought to be derived from the RPE metabolizing the outer segments of the photoreceptor layer in the presence of plasma-derived complement. The RPE cells lose their polarity, or they may be enlarged or degenerating and contain numerous pigment granules. The retina may be detached and edema present in the retina and subretina. Instead of being filtered across Bruch's membrane into choroidal circulation, cellular debris accumulates as subretinal deposits (refer to Appendix 3 for further information). "Soft drusen" are large, irregular, and yellow, and are associated with age-related macular degeneration in humans and nonhuman primates. "Hard drusen" are small, well-demarcated and sometimes mineralized subretinal foci of matrix that can be found in the eye of young animals, including rodents, dogs, and rabbits.

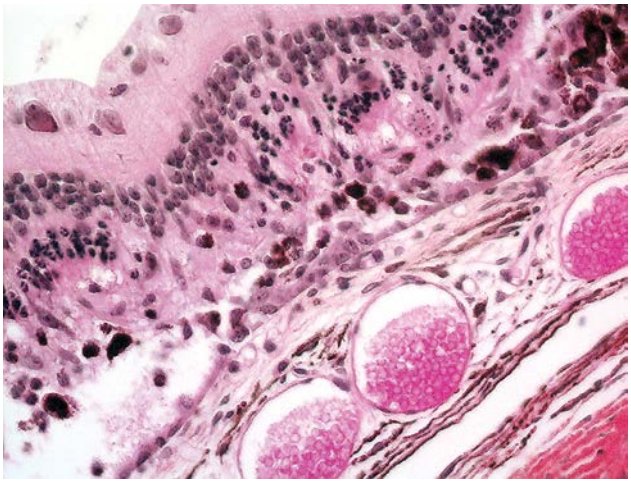
Synonym(s): **Drusen**; **drusen-like deposits**; **retinal hyaline deposits**.

Subretinal fibroplasia consists of linear arrays of spindle cells that form mats of fusiform or fibroblast-like cells and new blood vessels between the retina and Bruch's membrane. Fibroblasts, vitreal hyalocytes, retinal Müller cells, and retinal pigmented epithelium (RPE) may proliferate, migrate, and transdifferentiate to contribute to fibroplasia. Buckling (retinal folds) and retinal detachment may occur secondary to contracture caused by the fibroplasia. This finding is associated with age-related macular degeneration in humans and, rarely in nonhuman primates, inflammation and hemorrhage, intraocular surgery, and choroidal inflammation. Fibroplasia also occurs following experimental laser photocoagulation in rodents and rabbits.

Differential diagnoses: **Retinal neovascularization**; **Choroidal neovascularization**.

Synonym(s): **Subretinal membranes**; **subretinal fibrosis**; **fibrous metaplasia**; **retinal pigment epithelium migration**.

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Subretinal fibroplasia with outer retinal atrophy and retinal detachment, Dutch belted rabbit, hematoxylin phloxine saffron stain. See **Vitreal inflammation** for an additional illustration.

Subretinal fibrosis, see the preferred term **Subretinal fibroplasia**.

Subretinal membranes, see the preferred term **Subretinal fibroplasia**.

Subretinal photoreceptor torpedo cells, see the preferred term **Retinal photoreceptor nuclei displacement**.

Subretinal vascular proliferation, see the preferred term **Choroidal neovascularization**.

Sulfotransferases (EC 2.8.2.-) are a class of enzymes which transfer a sulfo group from a donor molecule (3′-phosphoadenosine-5′-phosphosulfate) to drugs with alcohol or amine groups. This sulfate conjugation is an important Phase 2 reaction. See **Phase 2 reaction** for further information.

Sunburn cells are single cells that undergo apoptosis in the epidermis due to ultraviolet light exposure. These represent one of many patterns of epidermal necrosis. See **Epidermal necrosis** for further information.

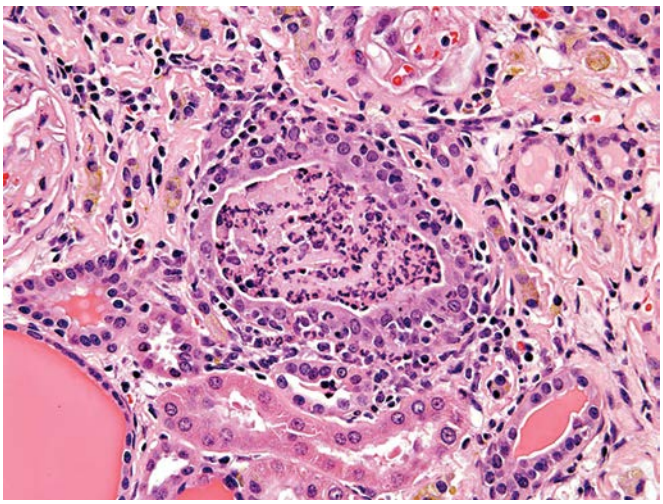
Superoxide is a reduced form of oxygen which is converted to hydrogen peroxide by the enzyme superoxide dismutase. See **Reactive oxygen species** for further information.

Suppressor T cell, see the preferred term **T lymphocytes**.

Suppurative inflammation is characterized by large amounts of exudate consisting of neutrophils, necrotic debris, and edema fluid. Certain organisms (e.g., Staphylococci) are more likely to induce such responses and are thus referred to as pyogenic bacteria.

Synonym(s): **Purulent inflammation**.

Suppurative nephritis is infiltration of the renal parenchyma by neutrophils. See **Renal parenchymal inflammation with neutrophils** and **Pyelonephritis** for further information.



Suppurative nephritis, tubule, rat kidney, H&E.

Suppurative pleuritis, see the preferred term **Pyothorax**.

Suprarenal gland, see the preferred term **Adrenal glands**.

Surrogate endpoint is a biomarker expected to substitute for a clinical marker to predict clinical benefit or toxicity; for example, measurement of plasma transaminase activity as an indication of liver toxicity, or behavioral scores for psychotic drugs.

Suspected adverse drug reaction is any adverse event for which there is a reasonable possibility that the drug caused the effect (Federal Register 21CFR part 312).

Sustentacular cell tumor, see the preferred term **Sertoli cell tumor, benign**.

Sustentacular cell tumor, testis, malignant, see the preferred term **Sertoli cell tumor, malignant**.

Sweat glands are apocrine and eccrine glands. Refer to **Skin** in Appendix 3 and **Adnexa** for further information.

Sweat gland tumor is a synonym for eccrine gland carcinoma in most species. In rodents, it is synonymous with primary adenoid cystic carcinoma. See the preferred term **Eccrine gland carcinoma**.

Sympathetic ophthalmia is bilateral granulomatous inflammation that may occur after trauma in one eye inadvertently releases ocular proteins into systemic circulation, with initiation of an autoimmune reaction in the originally affected and the unaffected eye. The onset of inflammation may be delayed as long as years after the initiating event, even with

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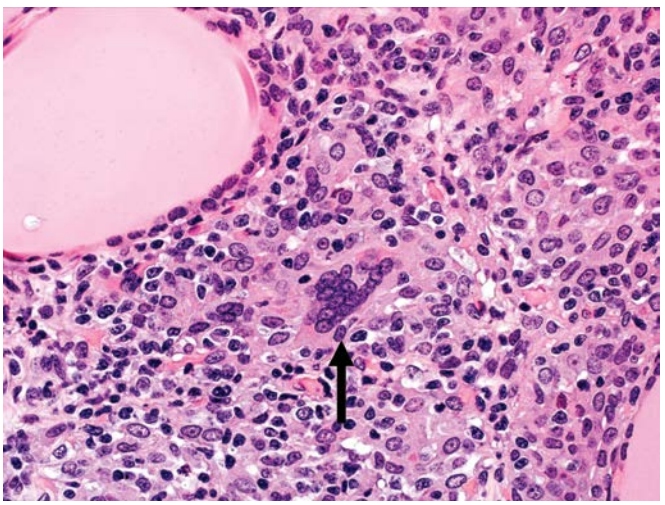
enucleation. This autoimmune inflammation usually involves the iris, ciliary body, and sclera, but seldom the retina.

Synaptophysin is a glycoprotein that is localized to the presynaptic vesicle membrane of neurons within the central nervous system and is expressed by neuroendocrine cells as well. Though still under investigation, synaptophysin appears to have a role in endocytosis and the recycling of synaptic vesicles. Synaptophysin is a useful immunohistochemical marker for a variety of neural and neuroendocrine tumors.

Synaptopodin is an actin-associated protein that has been identified in postsynaptic densities and associated dendritic spines as well as in renal glomerular podocytes. In the rat brain, synaptopodin expression appears to be restricted to areas of high synaptic plasticity and is thought to be involved in actin-related remodeling of dendritic spines.

Syncytial cell is a multinucleated cell that results from the fusion of multiple single-nucleated cells. In pathological conditions, epithelial cells may fuse to form a syncytium, which is characteristic for some viral infections such as human immunodeficiency virus (HIV) or morbillivirus (measles, distemper). Macrophages may fuse to form a syncytial cell known as the multinucleated giant cell and is characteristic of many fungal and some bacterial (*Mycobacteria* sp.) infections. Spermatocytes develop as syncytia before full cytoplasmic separation to form spermatids.

Differential diagnosis: **Multinucleated giant cell**.



Syncytial cell within the thyroid of a nonhuman primate with measles, H&E. The large multinucleated cell in the center of the image (arrow) resulted from fusion of multiple cells.

Synovial cell hyperplasia is an increase in the number of cells lining the joint space (synovium). Grossly, this may appear as firm, pale nodules in the synovium. This nonneoplastic lesion manifests typically as larger cells (hypertrophy) composing multiple cell layers, with or without formation of folds and villi. These villi can have variable size and shape. Refer to **Bone, Muscle, and Tooth** in Appendix 2 for further information.

Synovial cell hyperplasia/hypertrophy, see the preferred term **Synovial cell hyperplasia**.

Synovial sarcoma is a malignant neoplasm of the synovium. It is observed in association with the joint to include the capsule, bursae, and tendon sheath. This tumor is characterized by a biphasic or monophasic morphologic appearance; however, the cell of origin is unknown. Biphasic tumors contain a mix of neoplastic cells, some having an epithelioid appearance while others have mesenchymal characteristics (spindle-shaped). Synovial sarcomas are rarely reported in rats and mice. Refer to **Bone, Muscle, and Tooth** in Appendix 2 for further information.

Synovitis is inflammation of the synovial membrane and can result from an autoimmune reaction, infection, or as a response to joint degeneration. The synovium is very responsive to cytokines, and the ensuing inflammatory reaction can be very destructive to joint tissues.

Syringomyelia is dissection and cavitation (referred to as syrinx formation) of the spinal cord parenchyma by fluid, typically cerebrospinal fluid (CSF) and/or edema fluid. Syrinx formation occurs most often in the cervical cord; however, thoracic and lumbar segments may also be affected. Syringomyelia may occur as a primary lesion due to a developmental defect wherein edema formation results in accumulation of fluid within the parenchyma. In such instances, disruption of the central canal is not necessarily an a priori assumption. More typically, Syrinx formation occurs as a consequence of hydromyelia, whereby expansion of the central canal by CSF results in rupture and leakage into the parenchyma. The edges of dissected parenchyma may be lined by astrocytes, but there is little other evidence of inflammation or glial reaction. In animals, there are a number of reports relating hydromyelia and/or syringomyelia to congenital malformations, as well as to acquired conditions resulting in disruption of CSF flow such as spinal cord cyst formation or neoplasia. A model of syringo/hydromyelia has also been evaluated in rabbits and rats. See **Hydromyelia** for further information.

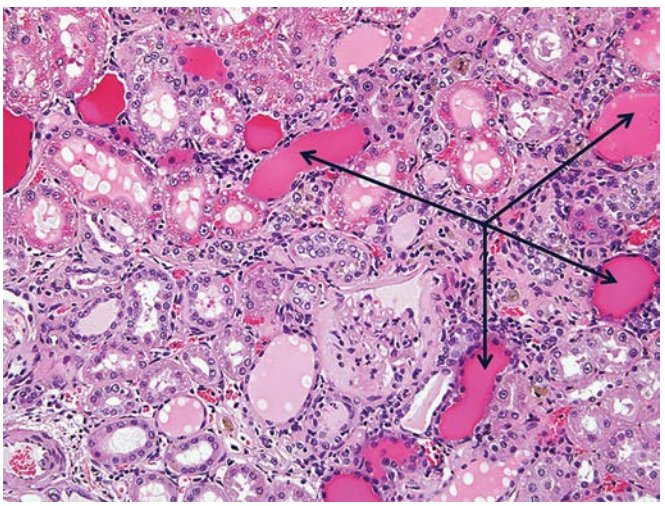
Systemic exposure to a drug given by a nonsystemic route (e.g., oral, transdermal, inhalation, etc.) is assessed by measuring parent drug levels in either blood or plasma. See **AUC** for further information.

Systemic necrotizing vasculitis, see the preferred term **Polyarteritis nodosa**.

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T

Tamm-Horsfall protein is a glycoprotein exclusive to the kidney and the most abundant protein in human urine and other mammals. It is specifically localized to epithelial cells of the thick ascending limb of Henle where it is produced. Increased viscosity in the tubule lumen is believed to lead potentially to gel formation by the protein, and ultimately, hyaline casts. In urine, the Tamm-Horsfall protein exists as a highly aggregated, filamentous molecule, which can disintegrate into monomers under certain conditions. It forms part of the matrix of urinary calculi, but its role in inhibiting stone formation is still unknown. Recent work suggests that it may function as a defense system against renal crystal formation and/or infection.

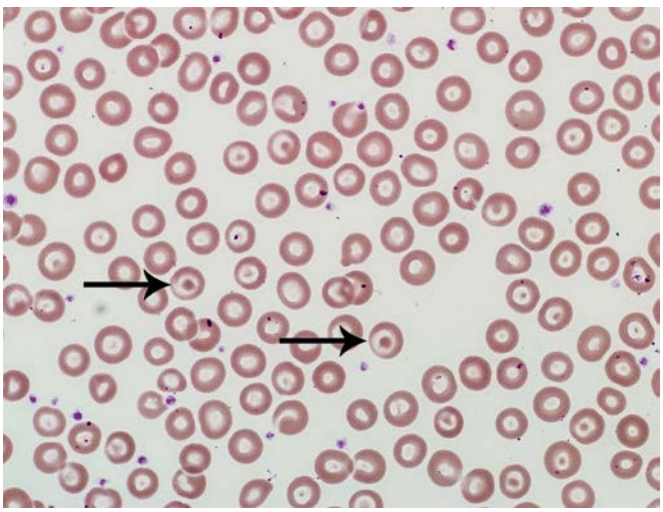


Hyaline casts, CPN, rat kidney, H&E.

Tanycytes are specialized ependymal cells within the ventricles of the brain. See **Ependymal barrier** for further information.

Target cell is also known as a codocyte or "Mexican hat cell." These cells are red blood cells with a dark, hemoglobinized center surrounded by a clear non-hemoglobinized halo and a dark hemoglobinized outer ring. They assume the target appearance when spread on blood smears. Ultrastructurally they have a bell-shaped appearance. These cells are associated with an increased surface-to-volume ratio due to either increased membrane surface area or decreased hemoglobin content. They can be seen with liver disease affecting cholesterol metabolism, iron deficiency anemia, hemoglinopathy, and with increased frequency on splenectomy or with decreased splenic function.

Synonym(s): **Codocyte**; **Mexican hat cell**.



Target cells (arrows), peripheral blood smear, dog.

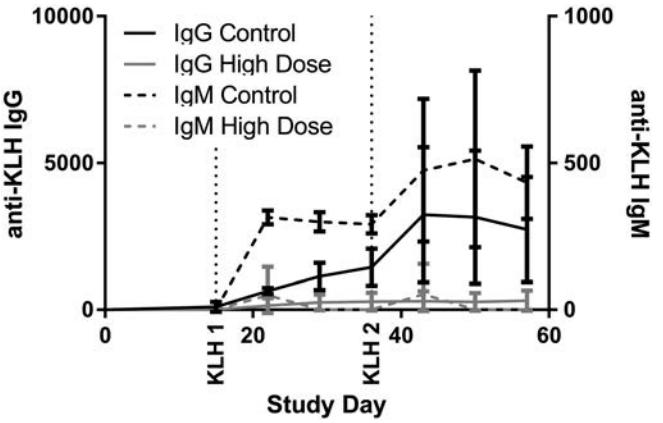
Target dose is the dose intended to be administered in total, or to be delivered to a certain compartment within the body. The target dose is highly dependent upon several factors including dose volume, concentration of the drug or chemical to be delivered, body weight/body surface area, size of the compartment, and physical barriers to entry. An example would be a target dose of an inhaled product to be delivered to the lung in an animal toxicity study (expressed as mg/g lung tissue). Such a scenario requires consideration of the aerosolized concentration, the respirable fraction of the aerosol, the percentage likely to penetrate into the lung, and the rate at which the animal will inhale the material (respiratory minute volume) as well as the average lung weight for the species, given the age and weight of the animal.

Taurine conjugation is a metabolic route (Phase 2 reaction) for certain carboxylic acids. See **Amino acid conjugation** and **Phase 2 reaction** for further information.

T-cell–dependent antibody response (TDAR) is a functional in vivo immunotoxicology test used in regulatory and research environments to characterize the effect of a dosed compound on the host's ability to mount antibody responses to a T-dependent antigen. A T-dependent antigen requires $CD4^+$ helper T cells for generation of antibody response. The TDAR assay presumes the necessity for function and coordinated interaction of multiple effector cells such as antigen-presenting cells, T and B lymphocytes to produce an antigen-specific antibody response. By following the dynamics of the response, immune regulatory systems are also evaluated. TDAR assays are used for safety and risk assessment of pharmaceuticals and environmental chemicals. Commonly used antigens include sheep

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red blood cells (sRBC), keyhole limpet hemocyanin (KLH), and tetanus toxoid (TT). Environmental chemical assessment requires the SRBC plaque-forming assay, while pharmaceutical development favors use of ELISA with KLH or TT for quantification of antigen-specific antibody responses. The TDAR assay is not standardized, and considerable variation occurs among different testing protocols. Appropriate study design is needed to generate data that can be interpreted to achieve conclusions that have meaningful biological significance.



TDAR assay: Primary and secondary anti-KLH IgM and IgG responses in cynomolgus monkeys. Animals were immunized on days 15 and 36 (KLH1 and 2). Blood samples were drawn on days 1, 15, 22, 29, 36, 43, 50, and 57. Control cynomolgus demonstrate expected anti-KLH responses. IgG titer is much higher than IgM. High dose–treated animals demonstrate severe suppression of both primary and secondary IgG and IgM responses.

Telangiectasis, see the preferred term **Angiectasis**.

Telemetry (or radiotelemetry) is the term applied to the use of devices that can be attached or implanted into the subject and transmit signals to a remote site so they can be used to monitor the subject without the subject being aware of the monitoring. This is especially useful when behavioral or external stimuli might alter the results. It is commonly used for cardiovascular monitoring in animals and humans.

Tendonitis is an inflammation of the dense fibrous connective tissue of a tendon, caused by acute trauma or chronic degeneration.

Tension lipidosis represents a focal area of hepatocellular lipidosis immediately subjacent to the hepatic capsule, and in the proximity of a capsular attachment or adhesion.

Teratogenesis is the process involved in the abnormal development (i.e., malformation) of an embryo or fetus during gestation.

Teratogenesis, critical periods are the specific stages of fetal development and organogenesis that are considered to be the most important when risk of malformations (teratogenicity) can occur.

Teratogenic effects are anatomical alterations of fetal external morphology (dysmorphogenesis), skeleton, or internal organs (viscera).

Teratogenic mechanisms are a means by which an agent can be a teratogen or agent that causes an abnormal development (morphological or functional) of an embryo or a fetus during gestation. For example, a teratogenic mechanism can cause effects via induction of cell death, alteration of apoptosis, metabolic inhibition, or vascular disruption.

Teratogens are agents that cause an abnormal development (morphological or functional) of an embryo or a fetus during gestation.

Teratology is the study of the causes, mechanisms, and manifestations of abnormal development. The latter can be either structural or functional nature.

Teratology studies, see **Embryo-fetal developmental toxicity studies** for further information.

Teratoma, malignant, testis is a rare malignant tumor in the testis of many species which arises from pluripotent germ cells and is characterized by poorly differentiated tissues from more than one germ layer. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Terminal ductal lobular unit (TDLU) is the secretory unit of the mammary gland, arising from a single terminal end bud during development. Each TDLU is composed of a short segment of the intralobular duct and the mammary gland alveoli that connect to it.

Terminal end bud (TEB) is the pre-lobular unit of mammary gland development that reflects the epithelial transition from ductular to lobuloalveolar structure. During puberty in females, the TEB is highly sensitive to hormonal effects of prolactin, progesterone, and estrogen, noting that there are some species differences in relative sensitivity.

Tertiary lymphoid organs, see the preferred term **Tertiary lymphoid structure**.

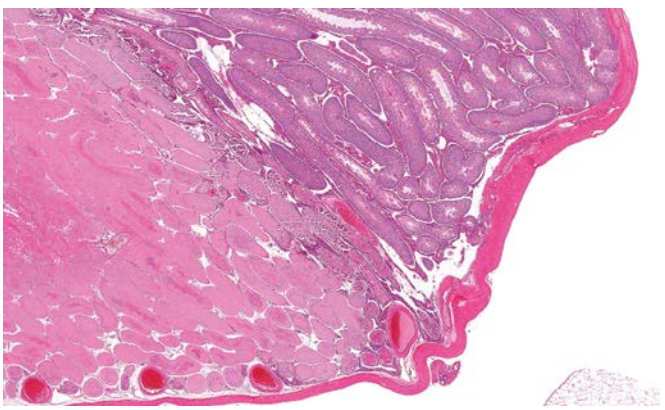
Tertiary lymphoid structure refers to the development of an unencapsulated but fully formed lymph node–like lymphoid follicle with germinal centers in nonlymphoid tissues or in lymphoid tissues where follicles typically do not form. These microstructures appear to be immunologically functional and are a frequent sequela to chronic immune responses in autoimmunity, transplantation, neoplasms, and other diseases. These structures contain typical B-, T-, and dendritic cells, high endothelial venules (HEV), and lymphatics. Tertiary lymphoid structures can be an incidental finding in the thymus and thyroid of dogs, in epididymal granulomas in rats, in bone marrow in monkeys with immunodeficiency virus, in liver of mice with *Helicobacter* infections, around tumors, and associated

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with environmental irritants and medical implants. These structures should not be mistaken for normal lymphoid tissue.

Synonym(s): **Tertiary lymphoid organs**; **ectopic lymphoid follicle**; **ectopic lymph node**; **lymphoid neogenesis**; **lymphoneogenesis**.

Testes, efferent ducts and epididymis tubular necrosis is characterized by coagulative necrosis of germ cells, and generally involves disruption and necrosis of Sertoli cells (SC) lining the tubule. If there is significant disruption of SC, the blood-testis barrier will be breached, resulting in inflammation around and within affected tubules. Tubular necrosis most often occurs in response to ischemic injury. Vasoactive agents, such as serotonin, histamine, and epinephrine, the endothelial toxicant, cadmium, and torsion or infarction due to vascular thrombosis cause necrosis of focal areas, or of the entire testis (testicular necrosis). A characteristically focal necrosis at the frontal lower part of the rat testis has been described following a single administration of human chorionic gonadotropin. Necrosis was deemed the result of local ischemia caused by prostaglandin release from LC. Extensive necrosis of the testis can also be caused by accidental intraperitoneal injection directly into the testis of rodents because of their ability to retract the testes into the abdominal cavity. Testicular necrosis is not reversible and results in fibrosis due to SC loss and tubular basement membrane disruption.



Extensive coagulative necrosis, testis, rat, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

Testes fixatives include three recommended fixatives for the preservation of the testis in laboratory animals. Modified Davidson's fixative is an acetic acid-alcohol-formalin-based fixative which is advocated as the best fixative for the preservation of testis. It provides excellent preservation of cellular details and does not cause shrinkage. The testis is fixed for 48 hours, then transferred to 10% neutral buffered formalin for storage prior to trimming and processing. Bouin's and Davidson's fixatives are good for tissue preservation of testis but cause excessive shrinkage. Bouin's also contains picric acid, which is a human safety hazard.

Test Facility Management includes individuals who have the authority and formal responsibility for the organization and functioning of the nonclinical test facility according to Good Laboratory Practices (GLPs).

Testicular agenesis is a rare developmental anomaly of the embryonic germ cells or somatic gonadal primordia in the gonadal (i.e., urogenital) ridge resulting in one or both testes being absent. Agenesis has been reported in development toxicology studies with lower molecular weight phthalates and arsenic, and in the unilateral urogenital anomalies (UUA) mutant rat strain and steroidogenic factor 1 (SF-1) knockout mouse.

Differential diagnosis: **Testicular hypoplasia**.

Synonym(s): **Testicular aplasia**.

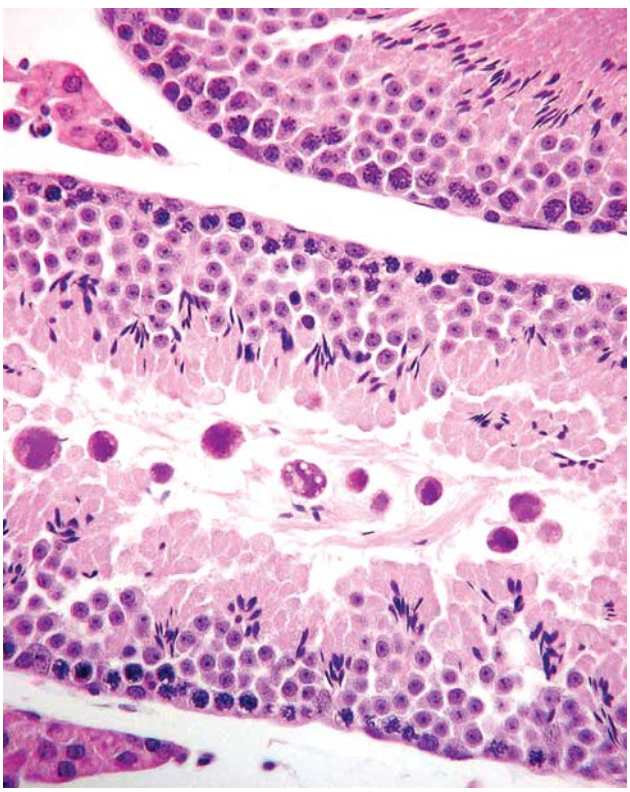
Testicular angiectasis is a rare spontaneous lesion in aging rats and mice, characterized by focal dilation of blood vessels that often compress adjacent tissue and are filled with erythrocytes and lined by normal endothelial cells.

Differential diagnosis: **Testicular hemangioma**.

Testicular aplasia, see the preferred term **Testicular agenesis**.

Testicular artery is the long, slender, paired, highly convoluted branch of the abdominal aorta that supplies oxygenated blood to the testis and epididymis. It has been proposed that the numerous coils in the mammalian testicular artery have a functional role in reducing the pulse pressure reaching the testis.

Testicular atypical residual bodies represent abnormal residual bodies that result from impaired maturation of elongating



Atypical residual bodies, mouse testis, H&E.

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spermatids and/or impaired processing of residual bodies by the Sertoli cell. Affected residual bodies are generally large, misshapen, or clumped, and appear as apoptotic bodies in the epididymal lumen or stage XI or later tubule in the rat and stage IX or later tubule in the mouse. They are a frequent background finding in mice but can also be a treatment-related finding in rats and mice and have been described following administration of the water-disinfecting xenobiotic, dibromoacetic acid.

Differential diagnoses: **Testicular germ cell exfoliation**; **Testicular germ cell degeneration**.

Testicular choriocarcinoma is a rare tumor in rats and mice arising from pluripotent cells originating from a displaced visceral yolk sac. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Testicular descent is the movement of the testis from the roof of the abdomen through the inguinal canal into the scrotum. The descent occurs at postnatal day 22 in rats, at 5–6 weeks in dogs, at 3 years in cynomolgus monkeys, and at the 7th or 8th month of fetal life in humans. The descent is guided by the gubernaculum ligament and driven by Müllerian-inhibiting substance and testosterone. An undescended testis stays in the abdominal cavity and undergoes tubular degeneration/atrophy, most likely due to the exposure of the relative high temperature in the abdominal cavity compared with the scrotum. See **Cryptorchidism** for further information.

Testicular edema is characterized by the accumulation of eosinophilic fluid in the testicular interstitial space and is usually a result of increased vascular permeability. Testicular edema is generally accompanied by severe tubular atrophy or inflammation and must be differentiated from fixation artifact, which occurs after testes fixation in hyperosmotic fixatives such as Bouin's and modified Davidson's. In cases of fixation artifact, the eosinophilic fluid is generally present surrounding normal-appearing but contracted tubules, and is most commonly noted in the center of the testis.

Testicular efferent ductal cyst, see the preferred term **Spermatocele**.

Testicular efferent ductal sperm retention cyst, see the preferred term **Spermatocele**.

Testicular epididymal cyst, see the preferred term **Spermatocele**.

Testicular fibrosis typically occurs secondary to inflammation, necrosis, and/or hemorrhage and is characterized by interstitial, perivascular, and/or peritubular tissue collagen deposition. The overall shape and size of the testis may be reduced and/or distorted. In addition, seminiferous tubular diameter may be reduced. Causes include ischemia, inflammatory or degenerative processes, or iatrogenic administration of cocaine or cadmium. A variation in testicular fibrosis occurs in the cynomolgus monkey as a background finding. It is characterized by dense collagen tissue replacement of large areas of parenchyma without any accompanying inflammatory or degenerative processes. It can be observed in both immature and mature monkeys.

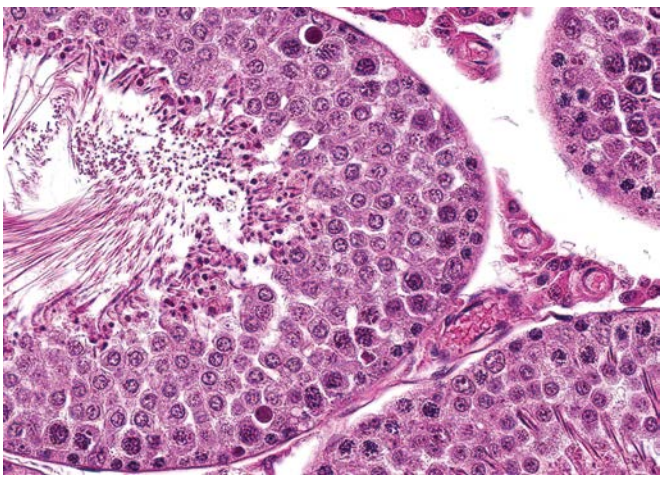
Testicular function may be assessed by examination of sperm morphology and motility, or by assessment of male fertility. Such studies are generally performed in rodents, most often in the rat.

Testicular germ cell apoptosis, see the preferred term **Testicular germ cell degeneration**.

Testicular germ cell degeneration is a spontaneous or treatment-related change in laboratory animals where germ cells have cytoplasmic eosinophilia, hyalinization, and/or contraction with nuclear changes that include apoptotic bodies (i.e., spermatogonia), chromatin condensation (i.e., spermatocytes), chromatin margination (round spermatids), and clubbed and misshapen heads (i.e., elongating spermatids). Treatment-related changes are best evaluated in shorter-term toxicology studies (<90 days). They are generally bilateral, multifocal to diffuse, and affect specific cell types and stages of spermatogenesis based on the inciting cause. Germ cell degeneration may be transient and inconspicuous, due to the rapid phagocytosis of degenerating cells by Sertoli cells resulting in germ cell depletion. Testicular germ cell degeneration increases in incidence with age as a background change in rats, mice, monkeys, and dogs. The term germ cell degeneration/depletion is appropriate in toxicity studies when both findings are evident concurrently. See **Testicular tubular degeneration** and **Testicular germ cell degeneration/depletion** for further information.

Differential diagnosis: **Testicular tubular degeneration/atrophy**.

Synonym(s): **Testicular germ cell apoptosis**; **testicular germ cell single cell necrosis**.

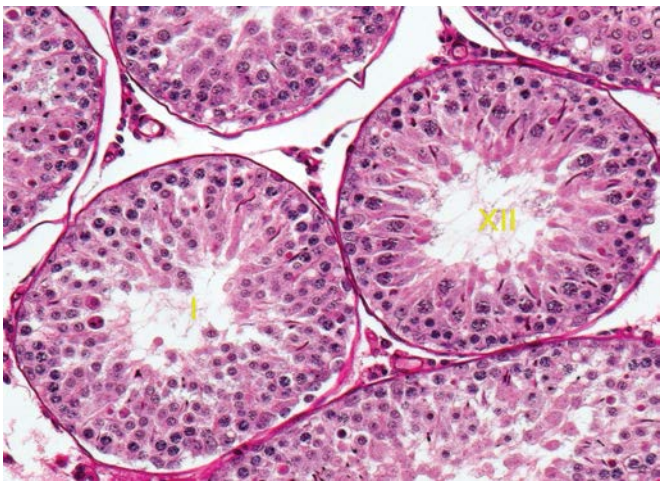


Degeneration, spermatocytes, Stage XIII, rat, H&E. (Reproduced with permission of Society of Toxicologic Pathology from Creasy et al., 2012.)

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Testicular germ cell degeneration/depletion is a combined term used testicular germ cell degeneration and depletion are both observed concurrently.

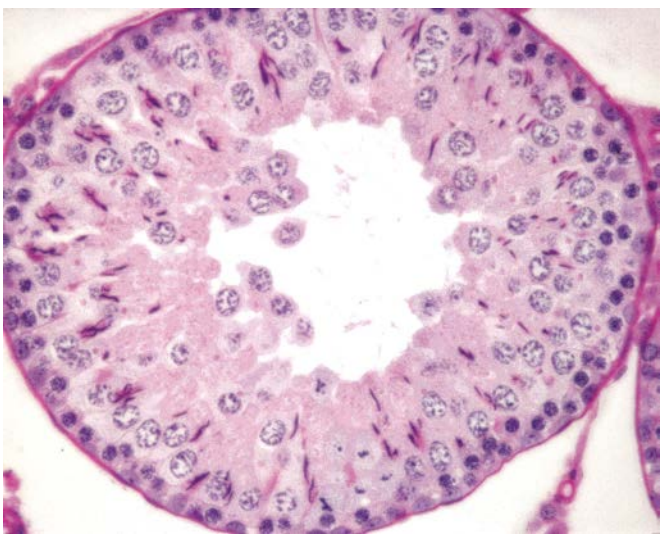
Testicular germ cell depletion is a spontaneous or treatment-related change characterized by the loss of one or more germ cell types within the seminiferous tubule. The term is used when there is an absence due to overt germ cell degeneration. The change is generally bilateral, multifocal to diffuse, and affects specific cell types and stages of spermatogenesis based on the inciting cause. The term germ cell degeneration/depletion is appropriate in toxicity studies when both findings are evident concurrently.



Depletion, elongated spermatids, rat, H&E.

Testicular germ cells exfoliation is due to Sertoli cell disturbances. Morphologic characteristics include the presence of nondegenerative germ cells in the seminiferous tubular lumen, rete testis, and/or epididymal lumen. In addition, the seminiferous tubular epithelium may appear depleted. Specific mechanisms involve abnormalities in the Sertoli cell microtubular cytoskeleton or retraction of the Sertoli cell cytoplasmic processes, which result in loss of germ cell adherence. Sertoli cell toxicants known to induce germ cell exfoliation include colchicine, vinblastine, carbendazim, and phthalate esters.

Differential diagnoses: **Sexual immaturity**; **Testicular atypical residual bodies**.


Luminal exfoliation of germ cells, rat, H&E.

Testicular germ cell single cell necrosis, see the preferred term **Testicular germ cell degeneration**.

Testicular granulosa cell tumor, benign is a tumor that occurs primarily in the mouse, and rarely in the rat. The cell of origin is unknown. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

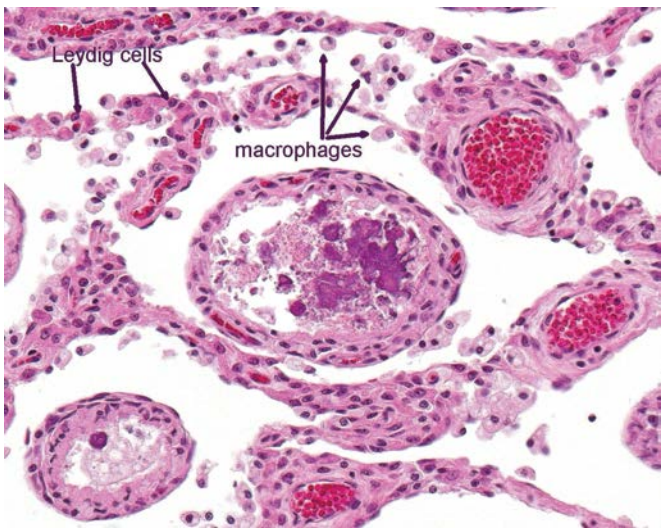
Testicular hemosiderosis, see the preferred term **Testicular pigment**.

Testicular hypoplasia is a developmental abnormality consisting of reduced numbers of seminiferous tubules. It may be unilateral or bilateral and appears macroscopically as a small testis or testes. Organ weight is reduced due to the reduced numbers of tubular profiles. Testicular hypoplasia does not commonly occur in rodents and may stem from in utero test article administration.

Differential diagnoses: **Seminiferous tubule atrophy**; **Testicular fibrosis**; **sexual immaturity**.

Testicular lipofuscinosis, see the preferred term **Testicular pigment**.

Testicular macrophage vacuolation due to phospholipidosis is characterized by interstitial macrophages with foamy cytoplasm. These macrophages can be distinguished from Leydig cells (LC) using the periodic acid-Schiff (PAS) method, which will stain macrophages. Interstitial macrophages form approximately 25% of the interstitial cells and are generally difficult to distinguish from LC in normal testes. See **Leydig cell vacuolation** for further information.



Macrophage vacuolation (arrows) and tubular mineralization, testis, rat, H&E.

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Testicular membrane–bound residual bodies represent the redundant cytoplasm and organelles (lysosomes, mitochondria, and endoplasmic reticulum) discarded during maturation of elongating spermatids into spermatozoa at the time of spermiation (stage VIII in rats and X in mice). These residual bodies are phagocytosed by Sertoli cells cytoplasm during stages IX–XII.

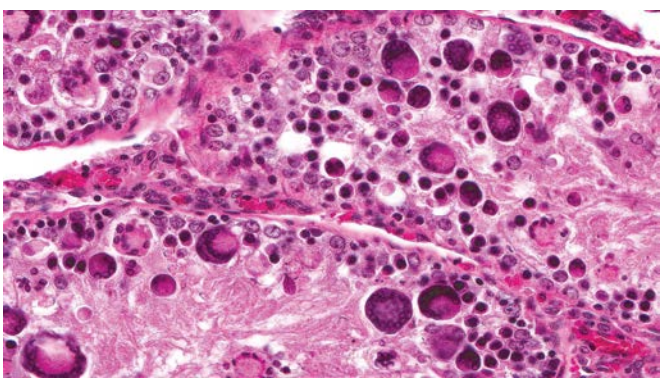
Testicular mesothelial hyperplasia is a proliferative lesion localized to the serosa of the tunica vaginalis of the testis in the rat. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Testicular mesothelioma, malignant is a malignant neoplasm that preferentially develops on the tunica vaginalis of the rat testis arising from the region of the rete/pampiniform plexus. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Testicular mineralization may occur within degenerate tissue (i.e., dystrophic calcification). Microscopically, there are basophilic, amorphous, or lamellar deposits, most commonly within seminiferous tubular basement membranes, tubular epithelium, or the tunica albuginea. Calcium salts are frequently deposited in areas of sperm stasis (impacted sperm). If Bouin's fixative is used, the mineral may dissolve prior to microscopic examination.

Testicular multinucleated giant cells reflect germ cell degeneration or impaired Sertoli cell maintenance of cytoskeletal bridge closure among cohorts of spermatids and, less frequently, spermatocytes. These cells are large with multiple germ cell nuclei of the same maturity. They may be present within the seminiferous epithelium or tubular and epididymal lumens. Multinucleated giant cells are found in association with age-related focal testicular atrophy, following efferent duct ligation, or because of exposure to gamma irradiation or administration of xenobiotics, most classically di(n-butyl) phthalate.

Synonym(s): **Testicular syncytial cells**.



Multinucleated giant cells, testis, F344/N rat, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

Testicular peritubular myoid cells surround the seminiferous tubules, provide structural integrity to the tubule, and partake in the regulation of spermatogenesis and testicular function. They have androgen receptors, are contractile, and are involved in retinol processing and the transport of spermatozoa and testicular fluid in the tubule.

Testicular pigment is usually age-related, yellow-brown, and finely granular ceroid pigment (i.e., early stage of lipofuscin), and can accumulate within the Sertoli cells (SC), Leydig cells (LC), or macrophages within the testis. Lipofuscin pigment is the remnant of breakdown products of lipid oxidation. It may be observed in association with degenerative changes and is positive for periodic-acid Schiff (PAS) and Schmorl reactions. Darker brown hemosiderin may be observed in the same cells after hemorrhage in animals of any age. Hemosiderin is positive following the application of Perl's stain. Lipofuscin and hemosiderin are challenging to differentiate from one another without special histochemical-staining methods; thus the term "pigment" is recommended when only viewed following hematoxylin and eosin (H&E) staining.

Synonym(s): **Testicular hemosiderosis**; **testicular lipofuscinosis**.

Testicular sperm cyst, see the preferred term **Spermatocele**.

Testicular syncytial cells, see the preferred term **Testicular multinucleated giant cells**.

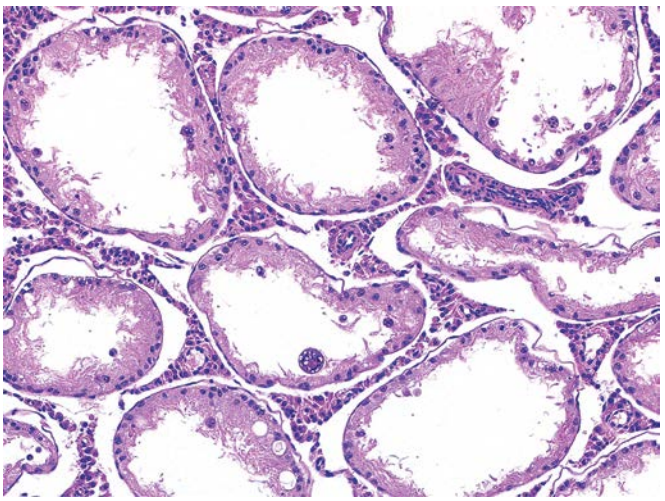
Testicular teratoma, benign is a rare, spontaneous benign tumor in the testis of many species (including human) which arises from pluripotent germ cells. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Testicular toxicity is an adverse event caused by a substance (e.g., chemical, drug), a pathogen (e.g., microorganism, virus), or any other agent (e.g., radiation) that could affect the male testes. Effects on the testis may be assessed functionally in fertility studies, or via cytological/histopathological assessment in general toxicity studies.

Testicular tubular atrophy is the end-stage lesion where no or sparse germ cells remain within a testicular tubule, due to prolonged or severe germ cell degeneration or cumulative depletion of germ cells (e.g., prolonged maturation depletion). Histologically, tubules have a decreased diameter and are lined only by Sertoli cells. The atrophy may be focal, segmental or diffuse, and interstitial cells may be increased in size and/or number. Tubular atrophy is a nonspecific change, and if there is a mixture of atrophic and degenerating tubules, the term "degeneration/atrophy, tubular" is more suitable. See **Testicular tubular degeneration/atrophy** and **Testicular tubular degeneration** for further information.

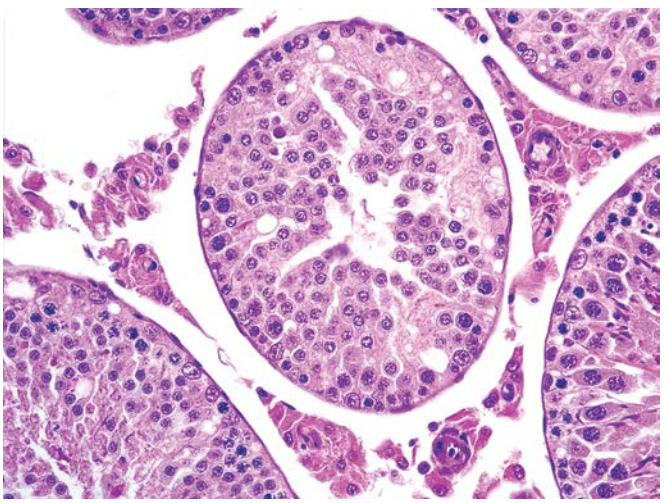
Synonym(s): **Seminiferous tubule atrophy**; **Sertoli cell–only seminiferous tubules**.

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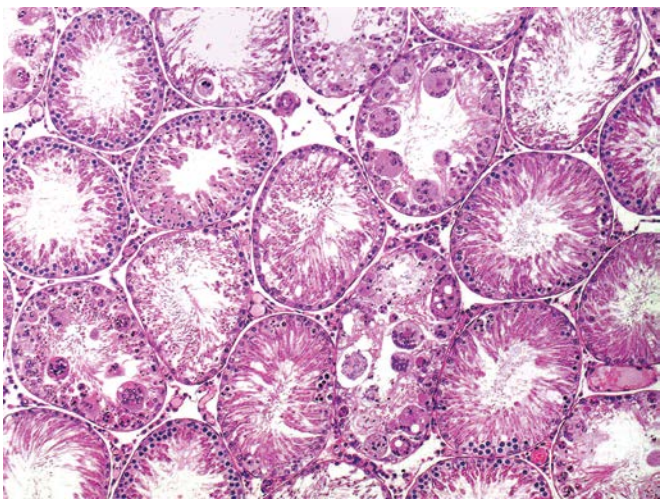
Tubular atrophy, rat, H&E. (Reproduced with permission of Society of Toxicologic Pathology from Creasy et al., 2012.)

Testicular tubular degeneration is a lesion of the seminiferous tubule that is a consequence of germ cell degeneration. Potential causes include Sertoli cell injury, primary cytotoxicity, hypoxia, inflammation, hormonal disruption, or vascular effects. While it is possible to identify changes specific to a single cell type (Sertoli cell or specific germ cell types) in shorter-term studies (<3 months), when dosing for a longer period, a more generalized, nonspecific tubular degeneration or tubular atrophy is often observed. Features of tubular degeneration include (1) diffuse or segmental germ cell degeneration (individual germ cells with eosinophilic cytoplasm and nuclear condensation) which is not restricted to a specific germ cell type or stage; (2) the presence of multinucleated germ cells; (3) spermatid retention; (4) Sertoli cell cytoplasmic vacuolation; (5) disorganization of germ cells; and (6) exfoliation of germ cells. Tubular degeneration is associated with epididymal germ cell debris and reduced organ weight. Although it may occur spontaneously, often affecting only a small number of tubules and/or germ cells, tubular degeneration and its sequel, tubular atrophy, are common manifestations of toxicologic injury to the testis.



Tubular degeneration, testis, rat, H&E. (Reproduced with permission of Society of Toxicologic Pathology from Creasy et al., 2012.)

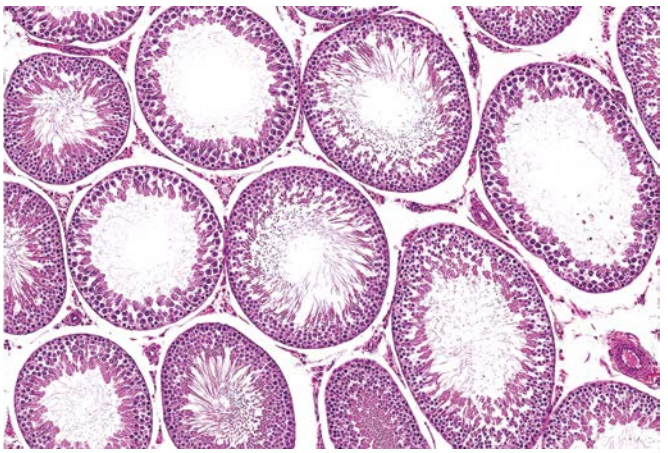
Testicular tubular degeneration/atrophy is a diagnostic term used when both tubular degeneration (see **Testicular tubular degeneration** for further information) and seminiferous tubule atrophy (see **Testicular tubular atrophy** for further information) are present microscopically. Diagnostic features include germ cell degeneration and disorganization, multinucleated giant cells, spermatid retention, Sertoli cell cytoplasmic vacuolation, exfoliation of germ cells into the tubular lumen, and tubular atrophy. Individual use of the terms "tubular degeneration" and "tubular atrophy" may be justified for more specific, test article–related changes if there is a clear separation of the two processes. Unilateral and bilateral tubular degeneration/atrophy may be a low incidence, background finding in rats and mice, but occur more frequently in other species such as dogs and minipigs. In the latter species, the preferred diagnostic term for this spontaneous change is hypospermatogenesis, which reflects the pathogenesis of the intermittent failure of spermatogonia to divide rather than active degeneration of germ cells.



Testicular degeneration/atrophy, testis, rat, H&E.

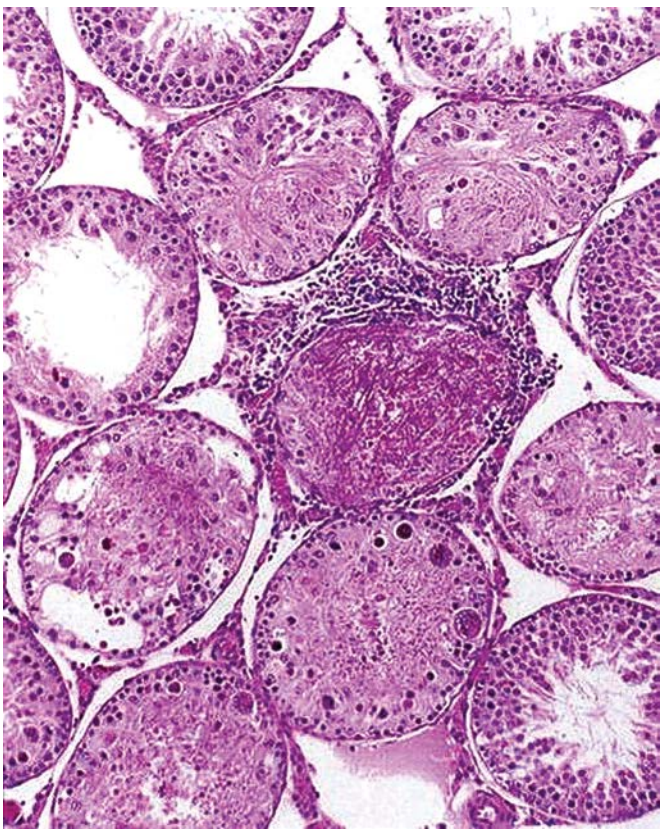
Testicular tubular dilation is an increase in the diameter of the seminiferous tubules accompanied by thinning of the epithelium, though the number of germ cell layers usually remains normal. Tubular dilation is often associated with increased testis weight and may be accompanied by dilated rete testis, dilated efferent ducts, or sperm stasis/sperm granulomas in the efferent ducts. Due to progressive increased pressure, dilated tubules can result in germ cell degeneration. Tubular dilation can be unilateral or bilateral, and a background or treatment-related lesion. Compounds cause tubular dilation by multiple mechanisms, including (1) excessive resorption resulting in sperm stasis and blockage; (2) inadequate resorption resulting in fluid back pressure; (3) interruption of the active transport mechanism via estrogens; or (4) vasoconstriction of the blood vessels overlying the rete testis (e.g., exposure to endothelin, carbendazim, 5HT). Other causes for tubular dilation include increased secretion of seminiferous tubule fluid by Sertoli cells or inhibition of peritubular contractions.

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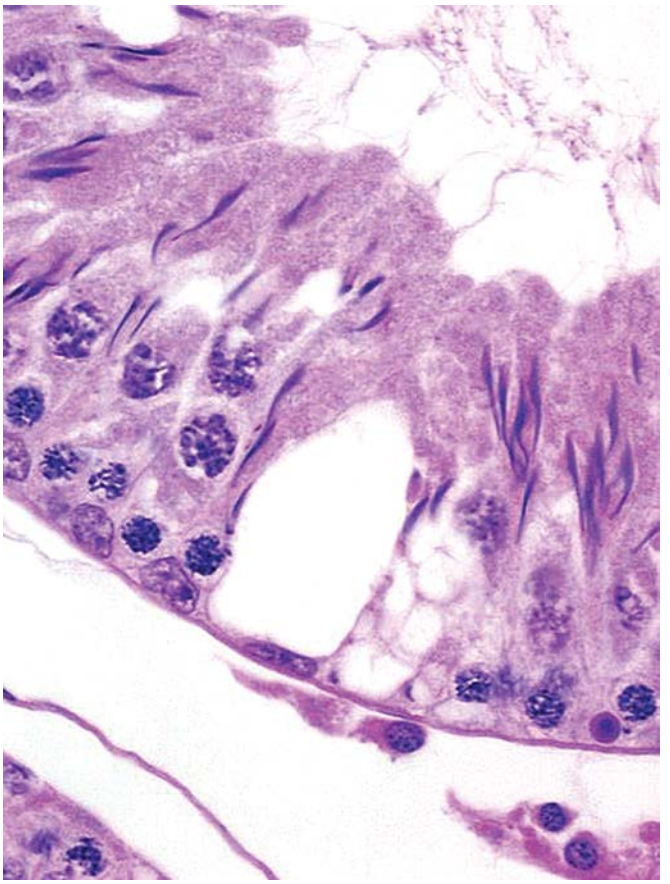
Tubular dilation, testis, rat, H&E. (Reproduced with permission of Society of Toxicologic Pathology from Creasy et al., 2012.)

Testicular tubular necrosis is caused by intermittent ischemia or hypoxia (e.g., caused by disturbances in blood flow) impacting germ cells and Sertoli cells. Microscopically there is coagulative necrosis of germ cells and Sertoli cells, which is generally focal or multifocal (segmental), disrupting the normal tubular architecture. This type of necrosis is frequently associated with inflammation, since ischemia damages the Sertoli cell tight-junctions, and consequently the blood-tubular barrier. When the tubular basement membrane is damaged, the necrosis is irreversible resulting in fibrosis. Tubular necrosis can be induced by endothelial cell toxicants (e.g., cadmium) or vasoactive compounds.



Tubular necrosis, testis, rat, H&E.

Testicular tubular vacuolation represents a seminiferous tubule epithelial degenerative change. Vacuoles may contain fluid, lipids, or phospholipids, but may represent an empty space formerly occupied by germ cells that are degenerated and exfoliated. Vacuoles can be single and large (i.e., macrovacuolation) or multiple and small (i.e., microvacuolation), the latter within the Sertoli cell (SC). Single vacuoles are commonly observed as an incidental finding. Vacuolation is usually an early morphological indicator of dysfunction in fluid balance within the SC. Microvacuolation of the basal SC cytoplasm occurs with some SC toxicants, and with some phospholipidosis-inducing xenobiotics.



Sertoli cell vacuolation, testis, rat, H&E.

Testicular tunica vaginalis is a serous membrane pouch that covers the testis and epididymis. It forms prior to the descent of the testis from the vaginal process (outpouching) of the peritoneum and consists of an outer parietal and inner visceral serous layer.

Testicular yolk sac carcinoma is a rare malignant tumor arising from the extraembryonic portion of the egg cylinder or visceral yolk sac. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Testis is the main organ of the male reproductive system in which spermatogenesis takes place. Testicular development and function are highly controlled by endocrine hormones

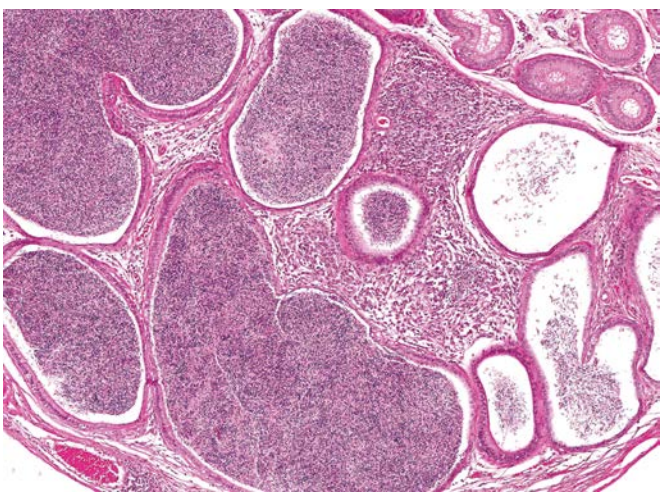
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such as luteinizing hormone (LH)/testosterone and follicle-stimulating hormone (FSH). Morphologically, the testis consists of compactly arrayed, convoluted loops of seminiferous tubules containing different germ cell types and Sertoli cells. The testicular interstitium contains Leydig cells, vasculature, macrophages, a protein- and testosterone-rich ultrafiltrate, and supporting stroma.

Testis, efferent duct and epididymis inflammatory cell infiltrate consists of small focal accumulations of inflammatory cells, most commonly composed of lymphocytes, which may reside in the interstitium, perivascularly, and may also be intraluminal. Microabscesses composed of mixed inflammatory cells may be noted as a background finding in the adipose tissue adjacent to the epididymis. The pathogenesis is often unknown but may represent an early stage of inflammation, and could indicate sperm stasis. Inflammatory cell infiltration is the preferred diagnostic term when other inflammatory changes (degeneration/necrosis, edema/congestion/hemorrhage, fibrosis, regeneration) are not observed.

Testis, efferent ducts and epididymis inflammation is an uncommon finding due to the immunologically privileged environment of the sperm transport system. When present, the type of inflammatory cells can be suggestive of the inciting agent. A neutrophilic response typically indicates a response to early tubular or ductal necrosis. A granulomatous response suggests a foreign body reaction, most likely to extratubular or -ductal sperm. A lymphocytic response may be indicative of an autoimmune condition. Edema and/or hemorrhage may accompany the inflammatory response. Testicular inflammation usually results from a compromise in seminiferous tubular integrity, specifically the Sertoli cell tight junctions which form the blood-testis barrier. One exception is when the drug di-n-pentyl phthalate is given to rats, transient neutrophilic infiltrates occur early on and then disappear.

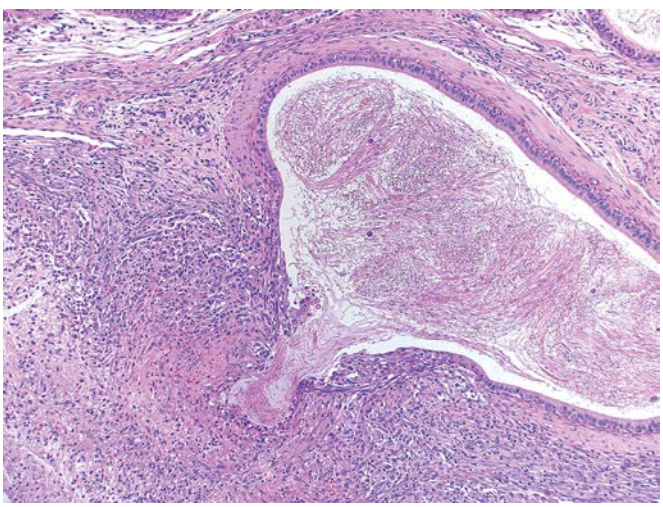
Differential diagnoses: **Testis, efferent duct and epididymis inflammatory cell infiltrate**; Sperm granuloma.



Neutrophilic inflammation, epididymis, B6C3F1 mouse, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

Testis, efferent ducts and epididymis sperm granuloma is a specific form of inflammation characterized by central accumulation of degenerating sperm surrounded by a granulomatous (e.g., foreign body) inflammatory response consisting of a layer of epithelioid (i.e., spermiophagic) macrophages within loose vascular connective tissue containing abundant lymphocytes and plasma cells. Sometimes the granuloma has a fibrous capsule. Sperm granuloma formation is mostly initiated by damage of the lining epithelium and/or loss of integrity of the tubular structures with subsequent leakage of sperm through the epithelium into the interstitium, resulting in a foreign body inflammatory response. Underlying causes may be rupture, obstruction of the vas deferens, or sperm stasis. Although sperm granulomas may be found in the rete testis and efferent ducts, they are more common in the epididymis (mainly in the corpus or cauda). Sperm granulomas are described in many species, including the human. It is a well-known incidental background lesion in rodents but can also be induced by ligation or by xenobiotics. Examples of xenobiotic-induced spermatogenic epididymitis are methyl chloride, dibromochloropropane, α-chlorohydrin, 2-methylimidazole, L-cysteine, guanethidine, testosterone given by implantation, in rats and/or mice and some aminopyrimidine inhibitors in dogs.

Synonym(s): **Spermatic granuloma**; **spermatogenic epididymitis**.



Sperm granuloma, epididymis, rat, H&E. (Reproduced with permission of Society of Toxicologic Pathology from Creasy et al., 2012.)

Testis, efferent ducts and epididymis sperm stasis is luminal aggregation of released sperm in the testis or increased density of luminal sperm in a segment of the epididymal or efferent ducts. In the testis, stasis is seen within atrophic tubules, and most commonly near or within the rete testis. In efferent ducts/epididymis, the ducts distal to the site of impaction are usually empty, and with time, an inflammatory response will be induced. Both in the testis and efferent duct/epididymis, sperm stasis is frequently associated with mineralization. Sperm stasis is the result of either decreased sperm

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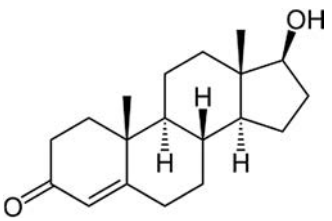
motility, sperm propulsion, obstruction, impaction, disturbed fluid reabsorption, or impaired intratubular fluid secretion by the supporting Sertoli cells. Sperm stasis is occasionally observed as an incidental finding in rats and mice, and when causing obstruction of the fluid can lead to tubular dilation and atrophy.

Synonym(s): **Sperm impaction**.



Sperm stasis adjacent to empty ducts, epididymis, B6C3F1 mouse, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

Testosterone is an anabolic steroid and the principal male sex hormone produced in the Leydig cells of the testes, and key in the development of male reproductive tissues. Testosterone is also critical to the growth of bone/muscle mass and body hair. See **Male sex hormones** and **Androgens** for further information.



Testosterone.

Theca cell is the perifollicular androgen-producing cell in the ovary. The theca cells differentiate from ovarian stromal cells around ovarian follicles at the secondary follicle stage of development and form two distinct layers: the theca externa and theca interna. The theca externa has a stromal, fibroblast-like appearance and includes smooth muscle differentiation, which is important for ovulation. Theca interna cells produce the androgen precursors for conversion to estrogen by the granulosa cells of the follicle. After ovulation, the theca cells help form the corpus luteum and produce androgens and progesterone following luteinization. Balanced theca cell hormone production is critical, as both excess and insufficient ovarian androgen production can lead to infertility.

Synonym(s): **Theca folliculi**.

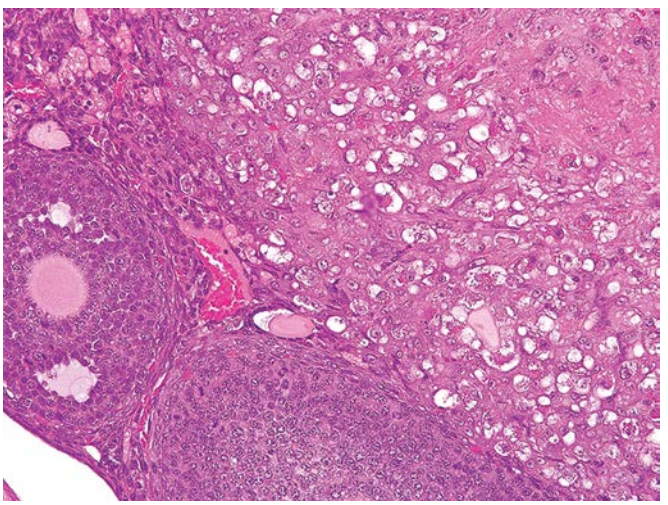
Theca cell hyperplasia is an increase in the number of thecal cells in the ovary. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Theca cell tumor, benign is a sex cord stromal tumor in which the predominant cell type is the theca cell. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Theca cell tumor, malignant is a sex cord stromal tumor in which the predominant cell type is the theca cell. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Theca cell vacuolation consists of a fine vacuolation of theca cells surrounding developing follicles in the ovary and is related to their steroid hormone biosynthesis. Relatively increased or decreased vacuolation of theca cells may reflect increased or decreased steroidogenesis. Phospholipidosis is another potential cause of increased cytoplasmic vacuolation and can be diagnosed based on overall tissue distribution and/or characteristic lamellar cytoplasmic figures (myeloid bodies) evident upon transmission electron microscopy.

Differential diagnosis: **Interstitial cell vacuolation**.



Theca cell vacuolation, ovary, mouse, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Dixon et al., 2014.)

Theca folliculi, see the preferred term **Theca cell**.

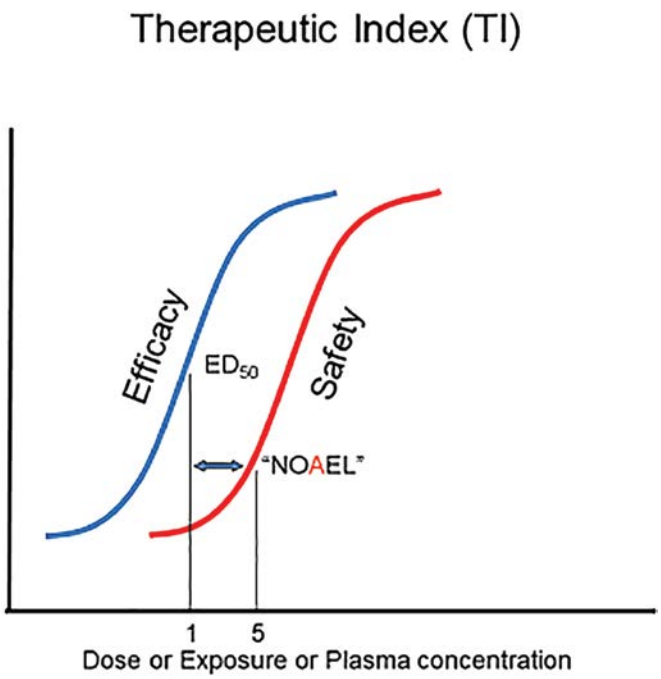
Thecoma, see the preferred term **Theca cell tumor, benign**.

Thecoma, malignant, see the preferred term **Theca cell tumor, malignant**.

Therapeutic index is the difference between the dose of a pharmacological agent causing the desired effect (efficacy) and the dose causing undesired effects (toxicity). It is also sometimes known as the therapeutic window, safety

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window, or therapeutic ratio. In preclinical safety studies, it may be calculated by dividing the no observed adverse effect level (NOAEL) from toxicity studies by the median effective dose (ED_{50}) from pharmacology studies in the same species. Such calculations may be based on the given dose in mg/kg or the systemic exposure to the compound based on levels measured in blood or plasma. In the past, the LD_{50} value from acute toxicity studies was often used to calculate the therapeutic ratio, but it is currently more common to use the NOAEL. In human therapy the term therapeutic window is used to describe the ratio between a dose of a drug causing side effects and the normally used therapeutic dose.



A visualization of the therapeutic index as the difference between the dose dependence of efficacy and that of safety (toxicity).

Threshold dose is the lowest dose level at which effects related to an administered experimental compound or chemical can be observed or measured.

Thrombocytes, see the preferred term **Platelets**.

Thrombocytopenia is defined as a low platelet blood count for the species as determined by automated analyzers. Similar to humans, dog and monkey platelet counts range from 150 to 450 $\times$ 10^9/L. When a platelet count falls below 50 $\times$ 10^9/L, it is associated with an increased risk of spontaneous bruising, petechia, and bleeding after injury, including venipuncture. False thrombocytopenia, or pseudothrombocytopenia, should be ruled out first. This consists primarily of platelet clumping, and high numbers of large platelets that are not counted as such by the hematology analyzers. Causes of thrombocytopenia include abnormal platelet distribution due to splenic or lung sequestration, decreased production as in myelosuppression, neoplasia and genetic defects, and decreased platelet survival due to increased destruction and consumption associated with immune mediated destruction, acute and severe blood loss, vasculitis, and/or intravascular coagulation.

Thrombocytosis consists of a high platelet count for the species. It can be due to increased platelet production related either to a myeloproliferative disorder affecting the megakaryocytic lineage or secondary to other conditions such as iron deficiency anemia, inflammation, neoplasia, or recovery/rebound to thrombocytopenia. Thrombocytosis can also be due to redistribution of platelets secondary to exercise or epinephrine release. Severe thrombocytosis (platelet counts above 750 $\times$ 10^9/L) is associated in humans with an increased risk of stroke and thrombosis.

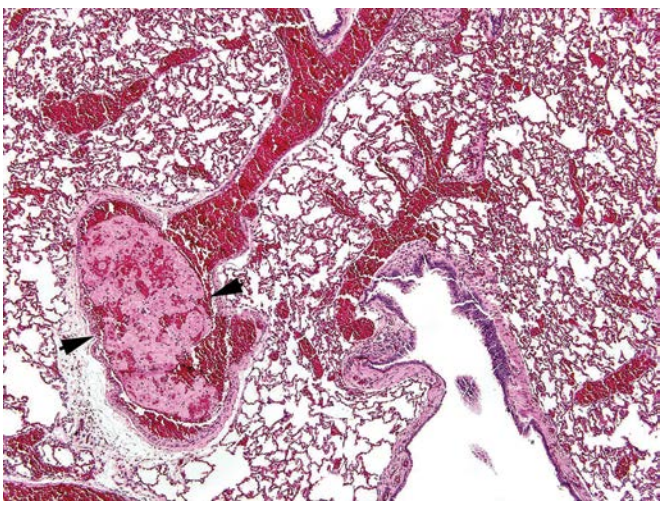
Thrombodysplasia, see the preferred term **Hematopoietic megakaryocytic dysplasia**.

Thrombopoietin (TPO) is a cytokine that acts via its receptor c-Mpl on megakaryocyte differentiation, maturation, and proliferation as well as platelet production. It is primarily produced constitutively by the liver and is released into the circulation as a glycoprotein with EPO-like and carbohydrate-rich domains. Despite their structural similarity, TPO does not bind to the EPO receptor and vice versa. The TPO receptor appears to be a preformed inactive dimer on the surface of many hematopoietic cells (i.e., stem cells, megakaryocyte progenitors, megakaryocytes, erythroid and myeloid progenitors, and platelets). Upon TPO binding to its receptor, there is activation of multiple signal transduction pathways such as the JAK and STAT pathways that promote cell growth, the MAP kinase pathways that drive maturation, and antiapoptotic pathways for cell survival. Binding of TPO to its receptor on platelets, and potentially megakaryocytes, appears to be a way to remove TPO from circulation, and to regulate its circulating concentration under physiological conditions. Clearance of TPO is the main way to control its concentration rather than increased production. TPO functions include stem cell survival, division of megakaryocyte precursors, promotion of megakaryocyte endomitosis and ploidy, and megakaryocyte maturation. Although TPO is the main regulator of platelet production, it seems to have a limited role in platelet release from megakaryocytes. TPO is also involved in the early maturation of all hematopoietic lineages.

Thrombosis is the process of thrombus formation within a blood or lymphatic vessel. A thrombus is a blood clot formed in situ within the vascular system of the body that impedes blood flow. Thrombosis is the result of calcium-dependent activation of the clotting cascade, leading to formation of fibrin, which adheres to both platelets and

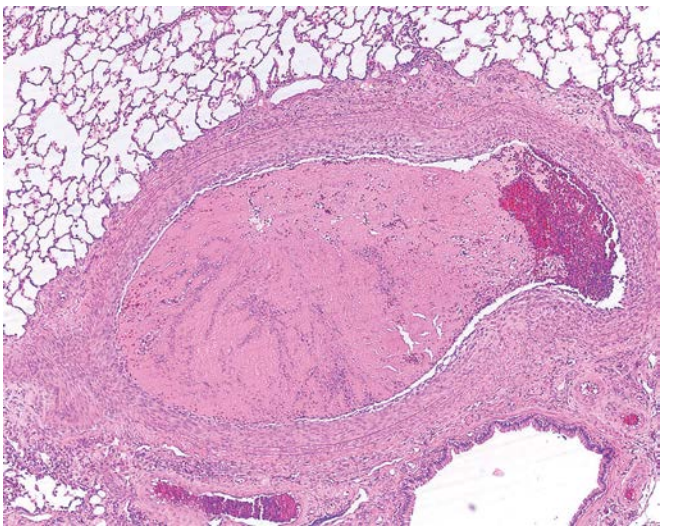
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vascular endothelial cells. Thrombosis can be physiologic as an appropriate hemostatic response to a small wound, or pathologic as associated with atherosclerosis or blood stasis in deep vein thrombosis. Thrombosis may be initiated by damage to endothelial cells, static or turbulent blood flow, and/or hypercoagulability of the blood; these three conditions together are referred to as Virchow's triad. Thrombi can be large or small and may completely or only partially occlude a vessel. They can also break off from a larger thrombus, forming an embolus likely to lodge in a vessel of smaller caliber. Therefore the effects of thrombosis are difficult to predict, and are highly dependent on thrombus size and the caliber and number of vessels affected as well as the tissue in which they occur. In tissues with a large collateral circulation (e.g., liver, lungs, or gastrointestinal tract), the effect of thrombosis can be inapparent, but in tissues with little collateral circulation (e.g., kidney, heart, or brain), the effects can range from local infarction to death. Thrombi have several possible fates: they can increase in size and extent, undergo lysis and dissolution, organize and resolve in situ, or embolize. Pulmonary thromboembolism is a potentially fatal consequence of deep vein thrombosis. Thrombi are physiologically removed by the fibrinolytic system. Increased activity of the thrombotic and fibrinolytic systems (uncontrolled thrombosis and thrombolysis) can deplete the elements of the fibrinolytic system, leading to disseminated intravascular coagulopathy (DIC), which can lead to death.



Thrombosis of a pulmonary vessel in a rat, H&E. Arrows note the organized fibrin thrombus that largely occludes the vessel. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

Thrombus is a partial or complete occlusion of a vessel, by an aggregation of platelets, red blood cells, and fibrin with varying admixtures of white blood cells. By definition, a thrombus is attached to the vessel wall, though this is not always obvious in the section being examined microscopically. Over time they become organized by fibrosis and can exhibit recanalization by endothelial cells. See **Thrombosis** for further information.



Thrombus, lung, rat, H&E.

Thymic agenesis is a congenital condition that is associated with complete developmental failure of the third and fourth pharyngeal pouches and is histologically defined by the complete absence of thymus tissue. There is a lack of primordial tissue and failure to develop in the embryo. Nude mice and rats are common immunodeficient models with a mutation in the FOXN1 gene, causing thymic agenesis with a lack of T cells as well as hairlessness when homozygous. B2-NC::noggin transgenic mice inhibit BMP signaling that causes a block of either the production or migration of neural crest cells, and results in thymic aplasia or hypoplasia. The lack of thymic tissue that results from agenesis is present in young animals and should not be confused with severe thymic involution or thymus atrophy from any cause that occurs after development.

Synonym(s): **Thymic aplasia**.

Thymic aplasia, see the preferred term **Thymic agenesis**.

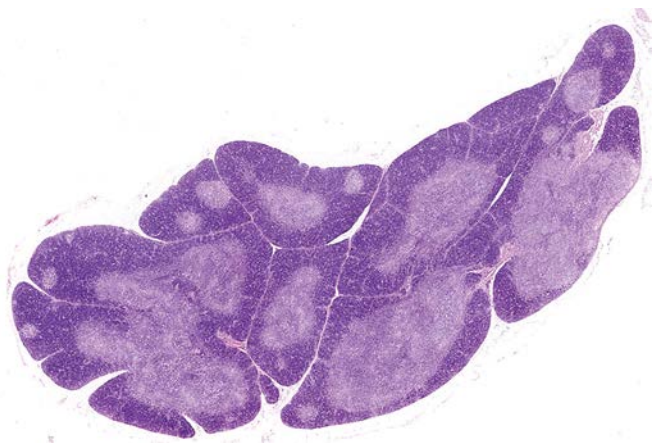
Thymic cortex is a densely cellular region in the thymus containing mostly T lymphocytes. Double negative ($CD4^-CD8^-$) precursor cells travel from the bone marrow to the thymus during fetal development. At this stage, these early T lineage precursors do not express CD4, CD8, or the T-cell receptor. They cross the blood-thymus barrier via vessels at the corticomedullary junction, and with the help of the reticular endothelial cells travel away from the medulla toward the outer cortex and enter the subcapsular zone. Here they rearrange their TCR genes, which promotes alpha beta or gamma delta selection. Cells without functional receptors die by apoptosis. Cells that are able to receive signals proliferate and develop into the double positive phenotype ($CD4^+CD8^+$) as they move from the outer cortex toward the medulla. These cells are small and deeply basophilic, comprising most of the cells in the thymic cortex. See Appendix 3 for further information.

Thymic corticomedullary junction is the interface between the cortex and medulla of the thymus and contains postcapillary venules. These venules contain specialized cuboidal endothelium similar to that of the high endothelial venules

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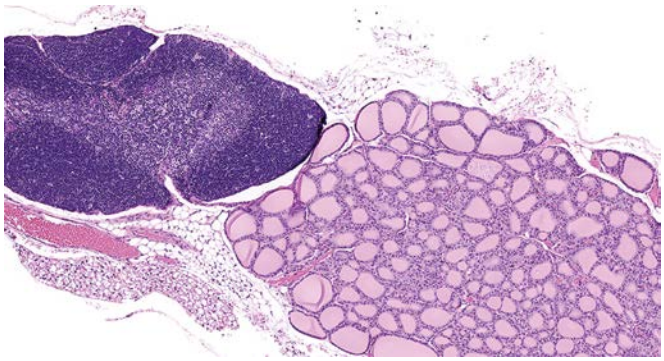
(HEV) of the lymph node and mucosa-associated lymphoid tissue (MALT). This endothelium expresses specialized ligands that selectively allow passage of specific T lymphocytes into and out of the thymus. These cells also express adhesion molecules that interact with the L-selectins on lymphocytes and anchor the T cells in preparation for passing through the endothelium via diapedesis. Importantly, only the single positive T cells will leave the thymus to enter the peripheral blood. See Appendix 3 for further information.

Thymic decreased corticomedullary ratio is determined subjectively by evaluating all of the cortical and medullary regions within a thymic lobe at low power; this can vary depending on species, strain, age, and the orientation of the thymus at trimming. The normal corticomedullary (CM) ratio is determined in the concurrent control animals. The ratio of cortex to medulla is approximately 2:1 (1:1:1 C:M:C). Some of the diagnostic features may be a decrease in size and weight of the thymus, loss of cortical lymphocytes via apoptosis or necrosis, and a medullary region that is normal in size or appears larger relative to the smaller cortex. Rarely, an increase in the medullary region may occur. A decrease in the CM ratio can result from conditions such as thymic involution, congenital malformations, and also from various exposures to chemicals or compounds in pharmaceutical development.



Decreased corticomedullary ratio in a rat thymus due to loss of cortical lymphocytes.

Thymic ectopia is a developmental abnormality of thymic tissue located outside of the normal anatomic location. These embryonic remnants can be located in the neck tissues, or within or adjacent to thyroid or parathyroid glands. The thymus, thyroid, and parathyroid share a common pharyngeal pouch origin, and during development the thymus separates and migrates caudally into the thorax. If separation is not complete, one or more remnants of thymic tissue may be retained with other tissues originating from the same pharyngeal pouch. Similarly, ectopic thyroid or parathyroid gland can be found in thymus. Thymic ectopic tissue is frequently structurally normal with cortical and medullary compartments and Hassall's corpuscles. It occurs at a low incidence and mostly in mice and rats. Ectopic thymus is generally an incidental finding, but exposures that adversely affect the anatomically correct thymus may also affect ectopic thymic tissue.



Ectopic thymus within the thyroid gland of a rat.

Thymic epithelial hyperplasia is characterized by tubules or cords composed of cuboidal to columnar epithelium within the thymus. This proliferative lesion may be focal or diffuse, and is a common age-related finding associated with thymic involution. Refer to **Lymphoid System** in Appendix 2 for further information.

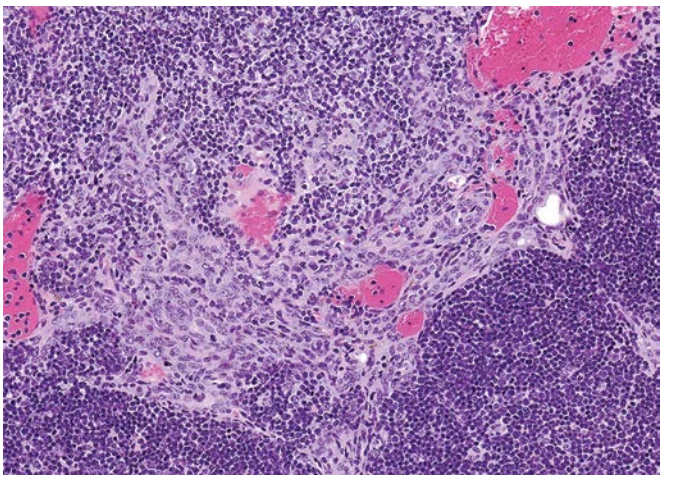
Thymic hypoplasia is a congenital condition of the thymus arising from developmental failure of the third and fourth pharyngeal pouches characterized by underdevelopment or incomplete development of the thymus. Histologically, there is a decrease in numbers of cortical and medullary lymphocytes. This condition can be the result of exposure to chemical and/or pharmaceuticals in development, or targeted mutations that disrupt the cortical thymic epithelial cells (TEC) such as alteration of the signal transducer and activator of transcription 3 (Stat3) gene, alteration of fibroblast growth factor [(Fgf)R2-IIIb] gene, or by disruption of the Forkhead box protein N1 (FOXN1) gene in heterozygous nude mice. B2-NC::noggin transgenics inhibit BMP signaling that causes a block of either the production or migration of neural crest cells, and results in thymic aplasia or hypoplasia. Although thymic hypoplasia can result from different causes, it is present in young animals and should be distinguished from thymic involution or thymic atrophy from any cause that occurs after development.

Thymic increased corticomedullary ratio is determined subjectively by evaluating all of the cortical and medullary regions within a thymic lobe at low power; this can vary depending on species, strain, age, and the orientation of the thymus at trimming. The normal corticomedullary (CM) should always be determined first in concurrent control animals. The medulla normally occupies about one-third of the lobular volume in the adult rodent, so the normal ratio is approximately 2:1. An increase in the CM ratio may be due to an increase in the cortical lymphocytes, a decrease in the medullary lymphocytes, or both. If there is an increase in the cortical lymphocytes, then lymphoma should be considered as a potential diagnosis.

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Increased CM ratio in a P53 ± C57BL/6 mouse thymus. Within this thymic lobe, there is an increase in cortical lymphocytes with an estimated average CM ratio of 3.5:1. All estimates of CM ratio must be compared to the range in untreated concurrent control animals.



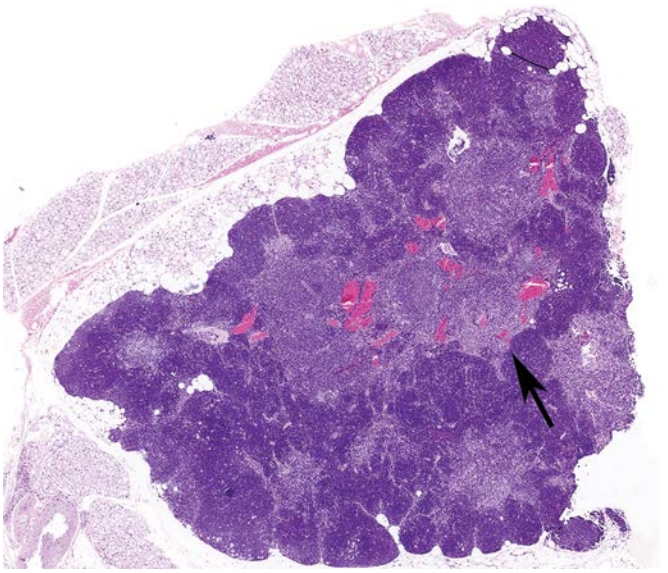
Higher magnification of the area with epithelial hyperplasia.

Thymic interlobular septae divide the lobes of this organ into smaller lobules. Although not usually apparent in a single histology section of thymus, the collagenous capsule is continuous with an interlobular septum, terminating at the corticomedullary junction. Numerous small branches of the internal thoracic and inferior thyroid arteries enter the thymus via the interlobular septae and supply the cortex and medulla. These vessels have fenestrated endothelium, allowing for the rapid exchange of molecules from the vessels to the surrounding tissue.

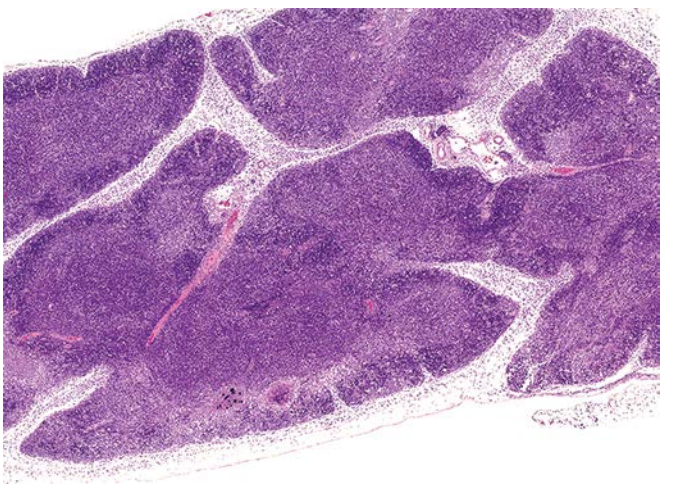
Thymic involution, age-related is the gradual and progressive decline in thymus size and weight during an animal's lifespan and is related to the natural decline of the immune system with a reduction in thymopoiesis (process in the thymus by which thymocytes differentiate into mature T lymphocytes), T-cell maturation. It is likely associated with sex steroid changes that naturally occur during aging. Involution begins at the onset of sexual maturity and becomes pronounced with advancing age. A spectrum of architectural changes may occur, including a decrease in cortical lymphocytes with thinning and irregularity of the cortex, presence of adipocytes within the capsule and septae, variable loss of the corticomedullary demarcation, prominent epithelial cells in the medullary region that may form tubules, cords, ribbons, or cysts, foci of B lymphocytes and plasma cells in the medullary regions, and an increase in perivascular spaces. Comparison to sex- and age-matched controls is necessary for critical assessment of treatment, or in toxicologic pathology, compound effects.

Synonym(s): **Thymic physiological involution**; **age-related involution**.

Thymic loss of corticomedullary distinction is characterized by the normally clear junction becoming less distinct when there is an overall loss of lymphocytes, and the cellular density of the small, basophilic lymphocytes is similar to those in both the cortex and medulla. The thymus may be grossly smaller and of decreased weight. Such a change may



Involution in a mouse thymus with thinning of the cortex, areas of medullary B-cell hyperplasia, and adipocytes in the capsule and septae. Arrow points to an area of epithelial hyperplasia.



Atrophy and loss of corticomedullary distinction in a 3-month-old Sprague Dawley rat treated once with 1 mg/kg dexamethasone and necropsied after 48 hours.

T

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occur in transgenic immunodeficient mice, or after treatment with xenobiotics, irradiation, viral infection, or age-related thymic involution. Normally, the thymus cortex and medulla have a well-defined junction where the dark, basophilic lymphocytes of the cortex occur next to the lighter, more eosinophilic cells of the medulla.

Thymic medulla contains fewer T lymphocytes than the cortex and also contains macrophages and a robust epithelial component, which is responsible for its pale, eosinophilic staining properties with hematoxylin and eosin (H&E) stain. These epithelial cells are important for the further development and maturation of T cells as they arrive from the cortex and become single positive cells—either $CD4^+CD8^-$ or $CD4^-CD8^+$ cells. Macrophages within the medulla can function to remove cellular debris or can function as dendritic interdigitating (antigen-presenting) cells. The medulla also contains Hassall's corpuscles. See **Hassall's corpuscles** for further information. See Appendix 3 for further information.

Thymic physiological involution, see the preferred term **Thymic involution, age-related**.

Thymidine kinase (TK) locus is an autosomal locus producing the enzyme thymidine kinase mutations, which are assessed in the mouse lymphoma assay. See **Mouse lymphoma test** for further information.

Thymoma, benign is a term used to classify a neoplasm of the thymus characterized by a neoplastic epithelial component, with or without neoplastic lymphocytes. Refer to **Lymphoid System** in Appendix 2 for further information.

Thymoma, malignant may be morphologically similar to its benign counterpart, but may extend through the capsule and into the adjacent surrounding tissue. Increased cellular atypia and nuclear polymorphism may also be features. Refer to **Lymphoid System** in Appendix 2 for further information.

Thymus arises on day 12 of gestation from the endoderm of the third and fourth pharyngeal pouches and adjacent mesenchyme. Lymphocyte precursors appear at this time, and the organ becomes adult-like in structure between gestation days (GD) 14–15. On GD 18 the thymus will reach its maximum size and structure. Functionally, the thymus is a primary or central lymphoid organ, essential for the normal development and function of the immune system. During fetal life it provides an important hematopoietic function, along with the liver and spleen. It is largest and most active during neonatal and preadolescent periods. Involution begins at onset of sexual maturity and becomes profound with advancing age. Thymus functions can fall into four broad, overlapping categories:

1. Development of immunocompetent T lymphocytes from bone marrow–derived T cell precursors to produce mature T helper ($CD4^+$) cells, cytotoxic ($CD8^+$) T cells, and regulatory or suppressor T cells (e.g., CD25, Foxp3).
2. Proliferation of clones of mature naïve T cells to supply the circulating lymphocyte pool and peripheral tissues.
3. Development of immunological self-tolerance.
4. Secretion of hormones and cytokines that regulate T-cell maturation, proliferation, and function within the thymus and peripheral lymphoid tissues.

The thymus is located on either side of the midline in the anterior portion of the thoracic cavity ventral to the base of the heart and the aortic arch. Macroscopic and microscopic morphology of the thymus varies by species. In general, the thymus is composed of two lobes, connected by a narrow isthmus, and invested by a thin capsule. Each lobe contains numerous lobules that are divided by septae. The lobules vary in size, but each contains a darkly basophilic cortex and a paler-staining, more eosinophilic medulla. Not readily apparent in both the cortex and medulla is a framework of simple cuboidal reticular epithelial cells that provide both structure and nurture functions for the developing T lymphocytes. Macrophages are also present that aid in the maturation of T lymphocytes and that remove apoptotic debris. See Appendix 3, **T Lymphocytes, Thymic Cortex,** and **Thymic Medulla** for further information.

Central tolerance is the mechanism whereby T cells are rendered nonreactive to self. As the T cells mature, they undergo gene segment rearrangement (variable, diversity, and joining: V(D)J rearrangement) to create receptor repertoire variety. V(D)J rearrangement or recombination is a mechanism of genetic recombination that occurs in the primary lymphoid organs (B cells in bone marrow and T cells in thymus) and is an important feature of adaptive immunity. The random gene combinations and base insertions of variable (V), diversity (D), and joining (J) gene segments allow for diversity of T-cell receptors and antibodies against antigens, which the host has never encountered. However, by chance, a subpopulation of these T cells is autoreactive and must therefore be eliminated via apoptosis. This is done by positive and negative selection to produce a functional and self-tolerant T-cell repertoire.

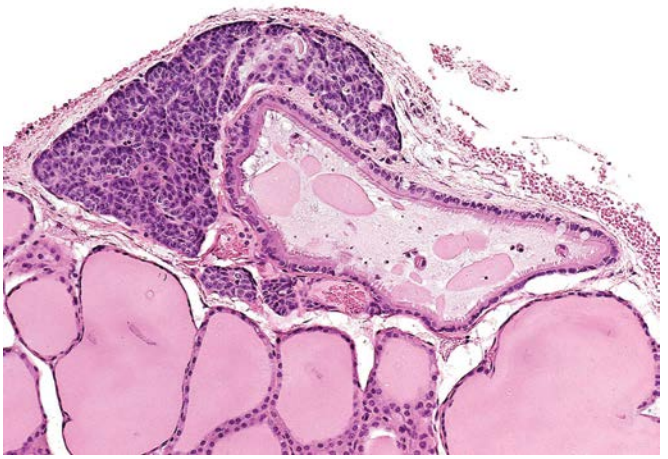
Thyrocyte, see the preferred term **Thyroid follicular cell**.

Thyroglossal duct cyst, see the preferred term **Thyroglossal duct persistence**.

Thyroglossal duct persistence is a small cystic or duct-like structure in the thyroid gland that is lined by cuboidal to columnar epithelial, sometimes ciliated, cells, and are often filled with mucin. They represent persistent remnants of an embryologic duct that connects the developing thyroid gland to the bottom of the pharynx.

Synonym(s): **Thyroglossal duct cyst**; **thyroid cyst**; **ultimobranchial cyst**.

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Thyroglossal duct cyst, B6C3F1 mouse, H&E. (Images provided courtesy of National the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

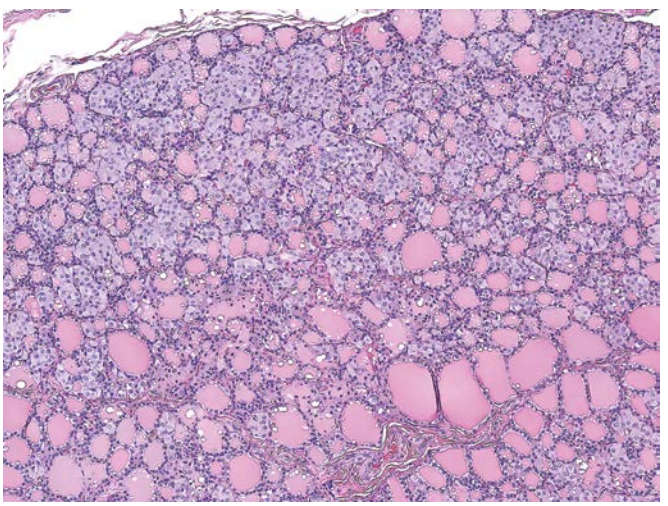
Thyroid C cell is a large, pale-staining neuroendocrine cell located in the connective tissue adjacent to the follicles of the thyroid gland. Their main function is to secrete the hormone calcitonin. See Appendix 3 for more information.

Synonym(s): **C-cell**; **thyroid parafollicular cell**.

Thyroid C cell adenoma, benign is a tumor in the thyroid gland comprised of normal-appearing C cells. These discrete masses are well demarcated and greater than five thyroid follicles in diameter. See **Endocrine Glands** in Appendix 2 for more information.

Thyroid C cell carcinoma, malignant is a malignant tumor of C cells in the thyroid gland. The cells in these masses can be very abnormal in appearance and have a high mitotic index. See **Endocrine Glands** in Appendix 2 for more information.

Thyroid C cell complex is a structural variation of the thyroid gland recorded in beagle dogs, in which cells form clusters, and in some cases large aggregates within the thyroid gland. These cells are remnants of the ultimobranchial body and differ from their mature counterparts in the thyroid gland by their fetal characteristics. They are typically immunopositive for vimentin and 19S-thyroglobulin.



Thyroid C cell complex, beagle dog, H&E.

Thyroid C cell hyperplasia is characterized by a focal or diffuse increase of C cells between thyroid follicles and/or within the follicular basement membrane. See **Endocrine Glands** in Appendix 2 for more information.

Thyroid cyst, see the preferred terms **Ultimobranchial cyst** and **Thyroglossal duct persistence**.

Thyroid follicular adenoma, benign is a neoplasm arising from the thyroid gland follicular cells that is usually well demarcated, may be encapsulated, compress the adjacent thyroid tissue, and have single or multilayers of cuboidal-columnar epithelial cells. See **Endocrine Glands** in Appendix 2 for more information.

Thyroid follicular carcinoma, malignant is a tumor of follicular epithelial cells that is subclassified as follicular, solid, papillary, and solid based on specific histologic features. See **Endocrine Glands** in Appendix 2 for more information.

Thyroid follicular cell is the lining cuboidal cell of the thyroid follicles. These cells are responsible for creating the colloid secreted into the follicular lumen by collecting and utilizing iodine and amino acids, and then retrieving the colloid for processing into the functional thyroid hormones T3 and T4. See image under **Thyroid gland**.

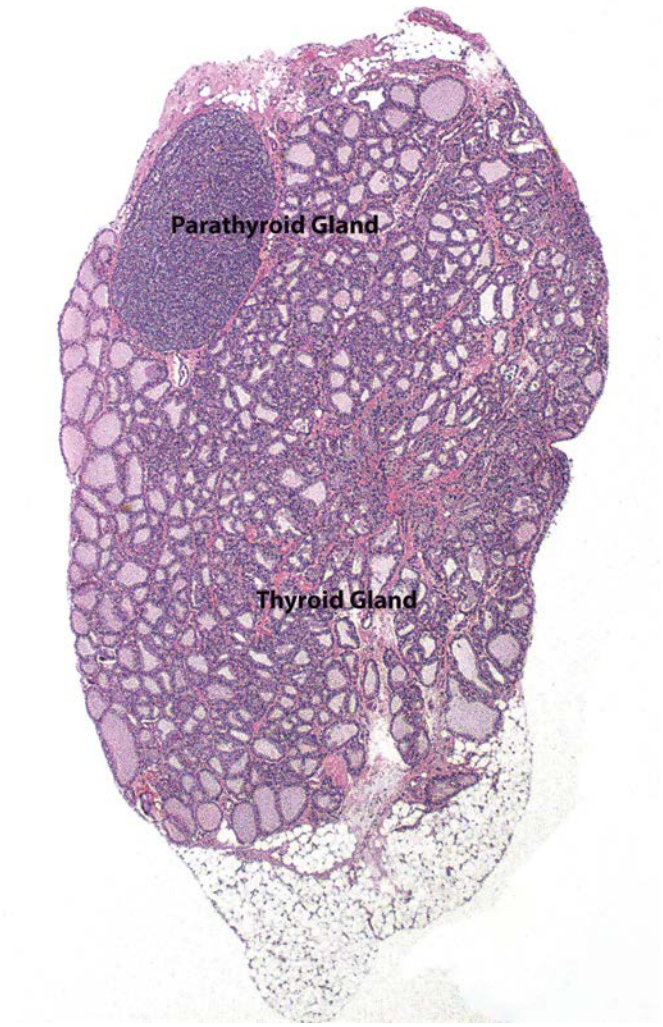
Synonym(s): **Thyrocyte**; **thyroid epithelial cell**.

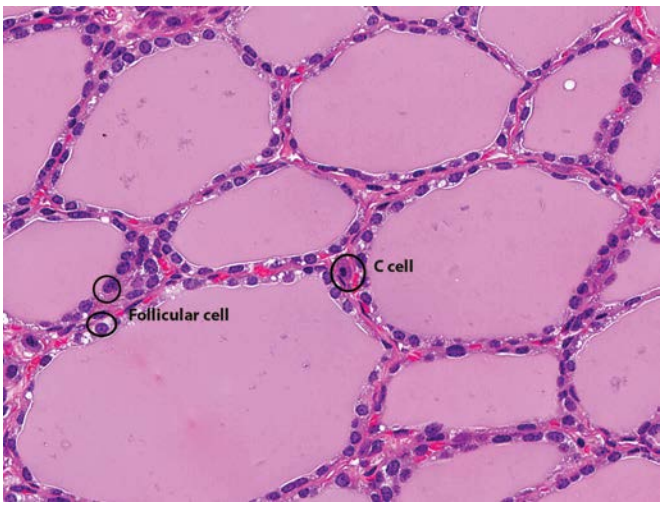
Thyroid follicular hyperplasia is a proliferative lesion characterized by increased numbers of thyroid follicular cells that may be focal or diffuse. See **Endocrine Glands** in Appendix 2 for more information.

Thyroid follicular hypertrophy is characterized by an increase in size and height of follicular cells and is normally diffuse in distribution. See **Endocrine Glands** in Appendix 2 for more information.

Thyroid gland is an endocrine organ responsible for the generation of the thyroid hormones thyroxine (T4) and triiodothyronine (T3) and for regulation of calcium homeostasis through production of calcitonin. Thyroid hormone precursors are generated from the follicular cells and secreted for storage into the lumens of the follicles as thyroglobulin bound to iodine (colloid). The constituent amino acids, tyrosine and others, are incorporated in the molecular structure of thyroglobulin as monoiodotyrosine (MIT) and diiodotyrosine (DIT). Under conditions requiring increased serum thyroid hormones, colloid is recollected through endocytosis by the epithelial cells and processed into T3 and T4, then secreted through the basal lamina into the bloodstream where it remains bound to thyroxine-binding globulins (TBGs) until

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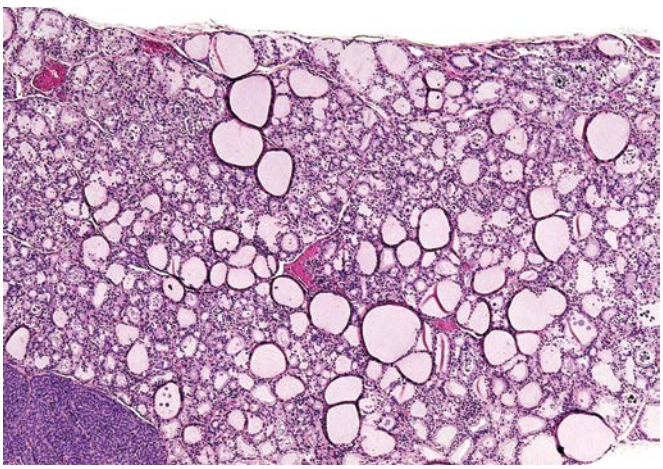


Thyroid gland: entire gland with parathyroid gland (Sprague Dawley rat) and with cell types labeled (cynomolgus monkey), H&E.

cell demand leads to cleavage from the transport protein and entry into the target cell. Calcitonin is produced by the thyroid C cells of the interstitium of the thyroid gland and is released into circulation when serum calcium levels increase.

The activity of the thyroid gland is under feedback regulation of its hormones, and those of the pituitary gland (TSH) and hypothalamus (TRH). See Appendix 3 for more information.

Thyroid gland atrophy is characterized by a decrease in size of the thyroid gland due to shrinkage of colloid within follicles and/or loss of follicular tissue. Histologically, atrophy is characterized by cuboidal to flattened epithelial cells with loss of intraluminal colloid. Epithelium may also become degenerate, and slough into the lumen. Atrophy most often occurs with a variety of conditions, but most commonly with inflammation of the thyroid gland (thyroiditis), and in the setting of disrupted thyroid hormone homeostasis. Symmetrical atrophy may occur secondary to lack of stimulation by thyroid-stimulating hormone (TSH), referred to as primary follicular atrophy. Asymmetric atrophy may arise secondary to a functional thyroid tumor (producing TSH) that results in atrophy of the contralateral gland due to excessive thyroid hormone production with a compensatory decrease in circulating TSH levels. In addition, atrophy may occur secondary to alterations in the hypothalamus or pituitary gland that results from loss or significant decrease in thyroid-releasing hormone (TRH) or TSH production. This condition usually leads to diffuse atrophy and hypothyroidism.

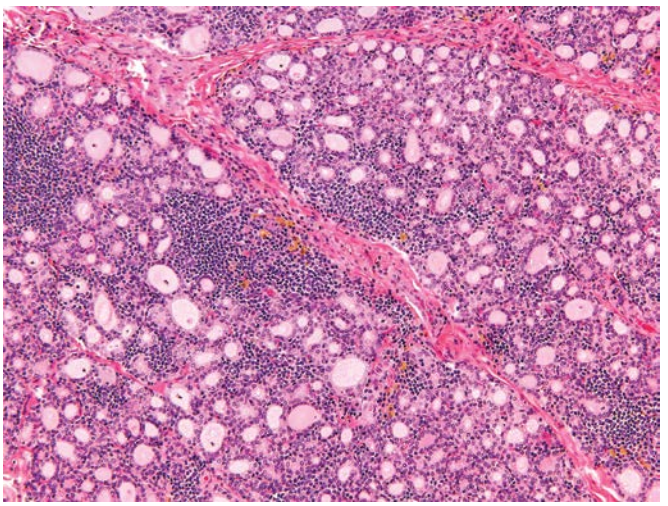


Thyroid, glandular atrophy, Harlan Sprague Dawley rat, H&E. (Images provided courtesy of National the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Thyroid gland inflammation is generally an uncommon finding as a spontaneous background lesion in rodents or primates. The presence of small numbers of inflammatory infiltrates may occur but has minimal to no functional or clinical significance. These infiltrates may be associated with other systemic diseases or, in the case of perivascular/vascular inflammation, may be related to polyarteritis nodosa in rats. Significant inflammation in the thyroid such that there is degeneration and/or loss of thyroid follicles may result in hypothyroidism similar to that in Hashimoto disease in humans.

Synonym(s): **Thyroiditis**.

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Thyroid gland, inflammation, Sprague Dawley rat, H&E. (Images provided courtesy of National the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Thyroid gland toxicity refers to adverse effects of a drug or chemical on the thyroid gland, either directly or through interactions with the hypothalamic-pituitary-thyroid axis and feedback loop.

Thyroid hormones include calcitonin, thyroxine (T4), and triiodothyronine (T3). See **Thyroid gland** for additional information.

Thyroiditis, see the preferred term **Thyroid gland inflammation**.

Thyroid parafollicular C cell, see the preferred term **Thyroid C cell**.

Thyroid parafollicular cell adenoma, see the preferred term **Thyroid C cell adenoma**.

Thyroid parafollicular cell carcinoma, see the preferred term **Thyroid C cell carcinoma**.

Thyroid-stimulating hormone (TSH) is a trophic hormone produced and secreted by thyrotrophs in the anterior pituitary gland. It functions to increase or decrease production, storage, and release of thyroid hormones at the thyroid gland in order to maintain a euthyroid state. The anterior pituitary and TSH production is part of the hypothalamic-pituitary-thyroid axis. The main control mechanism of TSH production and secretion is influenced by a negative feedback system in response to blood thyroid hormone levels via the axis, and thyrotropin-releasing hormone (TRH) produced by the hypothalamus, which promotes production of TSH.

Synonym(s): **Thyrotropin**.

Thyrotroph cell is a thyroid-stimulating hormone (TSH), or thyrotropin-producing cell, which constitutes a small percentage of the adenohypophysial (anterior pituitary) basophil cells. Thyrotrophs undergo hypertrophy and increase in size under certain conditions such as in hypothyroidism or after chronic treatment with goitrogens. See Appendix 3 for more information.

Thyrotropin, see the preferred term **Thyroid-stimulating hormone**.

Thyrotropin-releasing hormone (TRH) is a tripeptide hormone produced in the hypothalamus that stimulates the release of thyrotropin (thyroid-stimulating hormone [TSH]) from the anterior pituitary. TRH is produced and released by the hypothalamus after a decrease in plasma levels of thyroid hormone concentrations and is sensed by the neurosecretory neurons in the adenohypophysis. TRH is secreted into the hypophyseal portal circulation leading to the subsequent release of TSH-containing granules from the pituitary gland. Cold and various emotional stimuli can control secretion of TRH, and thus TSH. TRH has been implicated to have roles in the regulation of energy homeostasis, feeding behavior, thermogenesis, and autonomic regulation. Inadequate secretion of TRH from the hypothalamus has been implicated in the development of hypothalamic hypothyroidism.

Thyroxine (T4) is the thyroid hormone involved in overall thyroid hormone homeostasis. Thyroxine is under regulation by thyroid-stimulating hormone (TSH), and thyroid-releasing hormone (TRH) in the pituitary and hypothalamus, respectively. Under physiological condition, T4 remains bound to thyroxine-binding globulins (TBGs) in circulation until cellular demands lead to cleavage from this transport protein. Significant differences in rat and human T4 circulating plasma levels and transport proteins exist that make rats generally more sensitive to developing hyperplastic and/or neoplastic nodules in response to chronic TSH stimulation. In rodents, T4 has a shorter plasma half-life than in humans (12–24 hours vs 5–9 days, respectively). In addition, differential binding of T4 to albumin versus thyroglobulin (preferential protein binder in humans) affects the overall bioavailability and hormone turnover.

Thyroxine-binding globulin (TBG) is a protein primarily produced by the liver that has strong binding capacity for thyroxin (T4) and triiodothyronine (T3) in plasma. The globulins serve to transport the thyroid hormones to target sites. While bound to the TBGs, T3 and T4 have no impact on thyroid hormone homeostasis and are not available for uptake by the target cells. Cleavage of the thyroid hormone from its TBG releases the active product.

Thyroxine-binding proteins (TBPs) are proteins primarily produced by the liver that serve to transport thyroid hormones via plasma to their target cells throughout the body. TBPs include thyroxine-binding globulin (TBG), albumin, and transthyretin (TTR).

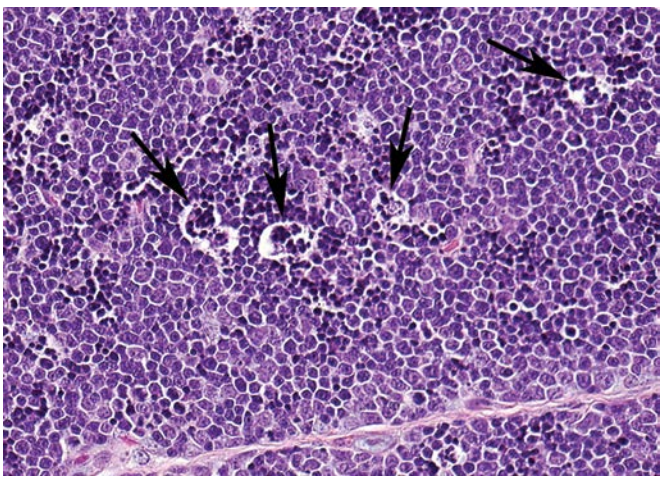
Time to tumor/time to tumor onset is the time period from exposure or dose initiation until tumor formation. It represents

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a statistically evaluated endpoint that may be used in carcinogenicity studies.

Tinctorial change refers to a change in color or staining in a cell body or cell fiber. As part of a degenerative or aging process, tissues may have a change in affinity for a stain, which is useful for identifying the process that has occurred (e.g., elastin fibers have a change in affinity for trichrome stains with aging).

Tingible body macrophage is a type of macrophage predominately found in the B cell–rich germinal centers of lymph nodes, mucosa-associated lymphoid tissue (MALT), and spleen, and in the T cell–rich thymus cortex, and are involved in the removal of apoptotic cell debris. Tingible body macrophages are normally present in these tissues and will be increased when there is an increase in lymphocyte apoptosis. In germinal centers, it is thought that they may play a role in down-regulating the germinal center reaction by the release of prostaglandins and result in reduced B-cell induction of IL-2. Histologically, these macrophages contain phagocytized, apoptotic cells in various stages of degradation, called "tingible bodies." When scattered among lymphocytes, there is a classic "starry sky" appearance.



Tingible body macrophages (arrows) in a rat thymus with engulfed apoptotic debris.

Tissue distribution is the uptake of a compound into various tissues and potential accumulation in these tissues. It may be assessed bioanalytically by estimating drug or metabolite levels in tissue homogenates, or by quantitative whole-body autoradiography.

Tissue-resident macrophages are heterogeneous populations of local immune cells that are generally established prenatally as permanent macrophages in individual lymphoid and nonlymphoid tissues, and in body cavities. Unlike circulating and transient monocyte-derived macrophages, resident macrophages are long-lived and self-renewing. Tissue-resident macrophages exhibit tissue-specific phenotypes, function, and transcription that contribute to innate and adaptive immunity, tissue development, and tissue repair and homeostasis. Tissue-resident macrophages will become activated and proliferate locally in response to a variety of exogenous stimuli. Circulating monocytes may transform into macrophages within tissues, but monocytes contribute minimally to macrophage activity within tissues and body cavities. Multiple and distinct populations of tissue-resident macrophages have been identified in some tissues and body cavities. Examples of tissue-resident macrophages include macrophages in yolk sac, bone marrow and fetal liver, alveolar and interstitial macrophages in the lung, Kupffer cells in the liver, tingible body macrophages, marginal zone, red pulp, and metallophilic macrophages in the spleen, microglia, meningeal and choroid plexus macrophages in the central nervous system, adipose tissue macrophages, osteoclasts, Langerhans cells and dermal macrophages in the skin, small and large peritoneal macrophages, pleural macrophages, synovial macrophages in joints, vasculature and perivascular macrophages, and macrophages in the bone marrow, gastrointestinal, reproductive, and urinary tracts, heart, mammary gland, and eye. These cells are often referred to by a tissue-specific name (e.g., microglia, Kupffer cells, and tingible body macrophages).

Synonym(s): **Resident tissue macrophages**.

T lymphocytes are produced in the bone marrow from hematopoietic stem cells and then migrate to the thymus, where they undergo cell division to create a large population of immature T cells. T cells can either be helper T cells or cytotoxic T cells based on whether they express CD4 (helper) or CD8 (cytotoxic) glycoprotein. The earliest T cells are double negative in that they express neither CD4 nor CD8, and are thus called double negative ($CD4^-CD8^-$) cells. As the T cells migrate from the periphery through the cortex, they mature to become double positive T cells ($CD4^+CD8^+$). As maturation of these double positive cells continues, they undergo positive and negative selection. During positive selection in the cortex, only T cells that can bind to a major histocompatibility complex (MHC) survive. During negative selection in the medulla, the T cells that cannot easily bind to self-antigens survive. The majority (~98%) of T cells fail either positive or negative selection and are eliminated by apoptosis. The few that survive undergo further developmental maturation, and each T cell will express a unique surface T-cell receptor (TCR). The TCRs are what recognize fragments of antigen as peptides bound to MHC molecules. As the T cells continue to mature in the thymus, they eventually become single positive T cells ($CD4^+CD8^-$ or $CD4^-CD8^+$). Only single positive T cells can leave the thymus and populate the peripheral lymphoid tissues such as the lymph nodes, mucosal associated lymphoid tissue (MALT), spleen, tonsils, etc. Naïve T cells, or those that have not yet encountered foreign antigen in the peripheral lymphoid tissues, can be activated by recognition of MHC-peptide complexes on the antigen-presenting cells (APCs) with subsequent proliferation and differentiation into effector or memory T cells. These activated T cells then become involved in T cell–mediated immunity in the peripheral lymphoid system

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to eliminate bacterial, viral, or parasitic infections as well as malignant cells. Cytotoxic T lymphocytes can kill cells infected with virus, bacteria, or protozoa as well as allografts such as transplanted heart, lung, and kidney, and cancer cells. T helper cells secrete cytokines that can activate B cells to produce antibodies and activate macrophages to destroy ingested microbes. They also help activate cytotoxic T cells to kill infected target cells. To date, four types of T helper cells have been identified: Th1, Th2, Tfh, and Th17. A subpopulation of cells, called T regulatory (Treg) cells, are thought to be derived from the same cell lineage as T helper cells. These cells are immunosuppressive and will down-regulate induction and proliferation of the T effector cells, or those that actively respond to a stimulus. Thus, a previous name for these cells was "suppressor T cell" because they help to maintain immunological tolerance. Natural killer T (NKT) cells also originate in the thymus from double positive T cells and represent a combination of T cell and natural killer (NK) cell attributes. They express a TCR complex and several NK cell markers. They do not recognize MHC but do recognize a glycolipid antigen presented by a molecule called CD1d. NKT cells will reciprocally activate antigen-presenting cells upon lipid/glycoprotein presentation. Once activated, these cells can produce Th1- and Th2-related cytokines and can perform functions ascribed to both T helper and cytotoxic T cells.

Synonym(s): **Suppressor T cell (for T regulatory cells)**.

Tonic is a type of seizure where a part of the body (usually the arms and the legs) becomes rigid due to increased muscle tone (stiffness) that persists and does not relax for a period of time (10–15 seconds).

Tooth fracture is a loss of normal tooth configuration resulting from trauma. There can be variable amounts of accompanying inflammation, malocclusion, and/or dental dysplasia, as observed in rodent incisors.

Differential diagnoses: **Dental dysplasia**; **Odontogenic tumor**.

Tongue inflammation is most commonly defined according to the nature, chronicity, and severity of the infiltrating cell types or other morphologic criteria (e.g., edema). The causes of glossitis are varied, ranging from incidental trauma and granulomatous reactions to foreign bodies, to local or systemic drug effects. Diagnostically, this term may be descriptively useful in the context of lesion description, such as in the necroulcerative tongue lesions that can occur in nonhuman primates infected by herpes viruses. Microscopically, focal infiltration of macrophages in the muscle layer has been noted as an incidental finding in beagle dogs. In monkeys, lymphoplasmacytic infiltrations are noted incidentally in the lamina propria, as are occasional erosions with associated inflammatory infiltrates.

Synonym(s): **Glossitis**.

Tooth necrosis occurs where there is disruption of the normal tooth structure by fracture, vascular compromise, or infection resulting in cell death. Necrosis is frequently observed in the pulp and can occur concurrently with inflammation.

Differential diagnosis: **Autolysis**.

Tooth thrombus is an obstruction of dental pulp vessels due to clotting activation. Impingement of blood flow due to accumulation of fibrin and platelets can lead to necrosis of pulp components and odontoblasts. This lesion has been observed following 2-butoxyethanol inhalation in rats.

Differential diagnosis: Postmortem clot.

Torpedo cells are segmental swellings or varicosities of Purkinje cell axons observed within the cerebellar granule cell layer. They have been observed in untreated aged mice but also following cerebellar injury of various types. Axonal swellings can also occur in other sites within the central nervous system (CNS), where they are more commonly referred to as axonal spheroids.

Synonym(s): **Axonal torpedo**; **axonal spheroids**.

Torsade de pointes ("twisting of points") is a type of polymorphic ventricular tachycardia that may occur in patients with delayed ventricular repolarization (QTc prolongation on electrocardiogram tracings). Torsade de pointes may lead to the potentially fatal arrhythmia of ventricular fibrillation. QTc prolongation may result from various mutations of genes that encode for ion channels. QTc prolongation may also be an effect of drugs that slow the efflux of potassium ions from cardiomyocytes, particularly through the potassium channel encoded by the human ether-à-go-go–related gene (hERG). Drugs associated with torsade de pointes liability include Cisapride, Terfenadine, and Haloperidol.

Total body clearance is the sum of clearance by all routes through which a drug is excreted from the body (e.g., biliary clearance, renal clearance, pulmonary clearance).

Tox21 is an abbreviation for "toxicology in the twenty-first century." Tox21 is a U.S. interagency collaboration and pooling of federal resources and expertise from the EPA, National Institutes of Environmental Health Sciences/National Toxicology Program, National Institutes of Health, and the Food and Drug Administration with the aim of developing better and more efficient toxicity screening methods. Using robotics, the program is in the process of evaluating and identifying the most promising in vitro screening methods for predicting toxicity, using a collection of 10,000 environmental chemicals and approved drugs (Tox21 Toolbox [10K library]; https://ntp.niehs.nih.gov/results/tox21/tbox/). Once the most predictive assays/tools are identified, the goal is to develop a cost-effective approach for prioritizing the thousands of chemicals that require toxicity testing.

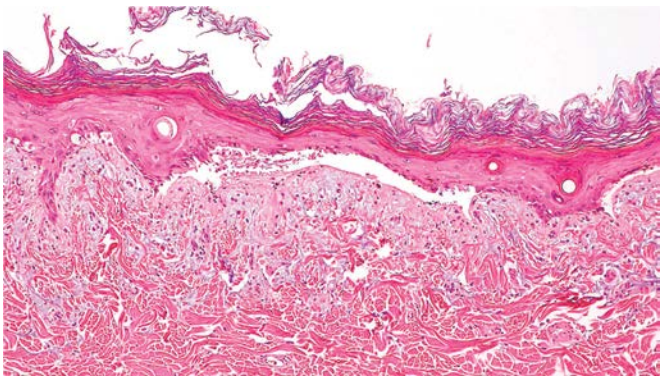
Toxic elements typically refers to elements in the periodic chart (table) that have a high degree of inherent toxicity based on the chemical/physical properties. Examples include Pb, As, Cd, F, and Hg. The term may also be used to refer to any

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individual component or components within a mixture that are primarily responsible for its toxicity.

Toxic epidermal necrolysis (TEN) represents part of a continuum of immune-mediated, typically drug-induced, skin lesions characterized by full-thickness necrosis of the epidermis, usually with mucocutaneous site involvement and separation of skin at the dermo-epidermal interface. Stevens-Johnson Syndrome (SJS) is a similar disease clinically, physiologically, and histologically, with less extensive overall skin involvement of the lesions (1–10%) versus those of TEN (over 30%). Skin involvement 10–30% clinically is considered SJS-TEN overlap disease. There are numerous drugs that have been implicated in the development of TEN in patients, but not all patients were exposed to a drug such that the pathophysiology of the disease is likely multifactorial and may have a genetic component. Drug-induced single cell necrosis of the epidermis is also described (see **Erythema multiforme** for further information). Lesions of TEN have been reported in macaques and dogs, and there are several rodent models of the disease. See **Epidermal necrosis** for further information.

Synonym(s): **Necrolysis**; **epidermal diffuse full-thickness necrosis**.



Toxic epidermal necrolysis in a monkey, H&E. Dermo-epidermal separation with full-thickness epidermal necrosis, dermal edema, and a paucity of associated inflammation.

Toxic metabolite is the metabolite ultimately responsible for the toxicity, which may be a reactive metabolite, as in the case of paracetamol toxicity, or a modified product of intermediary metabolism, as in the case of fluorocitrate formed from fluoroacetic acid. See **Reactive metabolite** for further information.

Toxic nephrosis, see the preferred term **Renal proximal or distal tubular or collecting tubular/ductular necrosis**.

Toxicodynamics (TD) is a change in a biological system that can be measured after dosing or exposure to a toxicant, representing the expression of an interaction between the toxicant and its target on a biochemical, cellular, or organ/tissue level, resulting in an adverse change. TD can be associated with a given exposure level (toxicokinetics) of the toxicant or provide evidence of exposure at a level that may be undetectable in serum/plasma. An example would include liver toxicity produced by a cholestatic effect of a chemical (toxicodynamics), indirectly monitored by increased serum liver enzymes and/or bilirubin (considered a biomarker), occurring at a certain exposure level (toxicokinetics). In cases where liver injury occurred at a plasma or serum concentration of the chemical that was undetectable by available bioanalytical techniques, the circulating increased serum liver enzymes and/or bilirubin levels would represent toxicodynamic biomarker(s) confirming exposure. The mechanism by which toxicity occurs in a nonclinical safety (toxicology) study can be monitored or assessed by use of specialized techniques including, but not limited to, flow cytometry, ECGs, EEGs, behavioral and clinical pathology endpoints, and specialized postmortem evaluations (e.g., immunohistochemistry). Toxicity testing for regulatory/safety purposes are generally descriptive in nature (e.g., determination of target organs, dose-response nature, and exposure/toxicokinetics); however, toxicodynamics can often be postulated from what is known of the pharmacodynamics, ligand binding profiles, ADME (absorption, distribution, metabolism, and excretion), or biologic targets, and endpoints incorporated into test protocols to monitor or assess relevant changes. For example, toxicity testing of a chemical with a structure related to known endocrine disruptors acting at the androgen receptor would include male reproductive assessments, and ideally, measurements of gonadotrophins or male hormones as biomarkers of possible toxicodynamics. For this reason, toxicity testing protocols require knowledge of the pharmacodynamics and biological targets of the test substance for proper design of the assessment and the ultimate evaluation of findings. See **Adverse effects** for further information.

Toxicokinetics (TK) is generally used in reference to systemic plasma levels of a test substance (and/or metabolite[s]) studied in a toxicology study, using analogous pharmacokinetic parameters (e.g., Cmax, AUC, Tmax, and T1/2) determined in groups of animals dosed or exposed to the test substance acutely (Day 1), at intervals during the study, and at study termination (at or near the last day of dosing) in repeat-dose studies. For protein-based substances, immunogenicity issues possibly affecting TK is also typically included and evaluated by determining the presence of antidrug (also referred to as antitherapeutic) antibodies at intervals during the study, and during a post-dose period (if included) where potential interference from the presence of the protein-based test substance is likely minimized. TK evaluations may be conducted in specific tissues in addition to or in lieu of systemic analyses, and may be included in studies where test articles are dosed into a specific compartment (e.g., eye vitreous) or known to distribute to certain tissues (e.g., kidney for antisense oligonucleotides).

Trabecular hypertrophy, see the preferred term **Bone increased**.

Transcriptome is the complete set of all mRNA in a cell, cell population, or a tissue that is encoded by the genome at a specific time and under specific conditions.

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Transcriptomics is the analysis and visualization of the transcriptome to determine gene expression changes following alteration of various factors, such as drug treatment, disease state, stage of development. See **Transcriptome** for further information.

Transitional cell carcinoma, see the preferred term **Urothelial carcinoma**.

Transitional cell epithelium, see the preferred term **Urothelium**.

Transplacental carcinogenesis involves the adverse effects of carcinogens that affect the embryo or the fetus, eventually leading to cancer after birth of the affected offspring.

Transplacental toxicity involves adverse effects, direct or indirect, that affect the embryo or the fetus in utero.

Transthyretin (TTR), see the preferred term **Thyroxine-binding proteins**.

Transudate is fluid with low protein content observed in a tissue or body cavity, as compared with exudates that have high protein content and are often associated with an inflammatory process. Transudates can frequently occur secondary to decreased serum albumin. See **Exudate** for further information.

Trichoepithelioma, see the preferred term **Hair follicle tumor, benign**.

Trichofolliculoma, see the preferred term **Hair follicle tumor, benign**.

Tricholemmoma, see the preferred term **Hair follicle tumor, benign**.

Triiodothyronine (T3) is the active thyroid hormone, converted from T4 by the cleavage of an iodide ion. While both T3 and T4 are found in circulation, T3 is in much lower concentration and is much more potent than the T4 precursor hormone. T3 is three- to four fold more active than T4, but has a shorter circulating half-life. Conversion from T4 to T3 usually occurs in the liver or pituitary gland. Under physiological conditions, T3 remains bound to thyroxine-binding globulins (TBGs) in circulation until cellular demands lead to cleavage from this transport protein. See **Thyroid gland** and **Thyroxine (T4)** for further information.

TSH is an abbreviation for thyroid-stimulating hormone (thyrotropin), See **Thyroid-stimulating hormone** for further information.

Tubular atrophy is a condition in which tubules (e.g., seminiferous tubules, renal tubules) were at one time normal in histologic appearance but have undergone a change in which the epithelial cells lining/comprising the tubules have undergone atrophy, leading to smaller, less dilated, or partially collapsed tubules with sparse, small or flattened lining epithelial cells. This must be distinguished from tubular hypoplasia in which the tubules/lining cells from the onset never attained their normal architecture. See **Atrophy** for further information.

Tubulointerstitial nephritis or nephropathy refers to renal disease with (nephritis) or without (nephropathy) an inflammatory component, that involves tubules and/or interstitium of the kidney with no or minimally noticeable glomerular changes.

Tumor refers grossly to any defined enlargement of a body organ and does not necessarily imply neoplasia. Microscopically, the term tumor is applied more specifically to enlargements, distortions, or effacement of the tissue architecture by neoplastic (tumor) cells, whether benign or malignant. See **Neoplasia** for further information.

Tumor differentiation describes the degree to which neoplastic cells resemble the parent cell type from which they originated. Well-differentiated cancer cells appear more like normal cells and tend to grow and spread more slowly (benign) than poorly differentiated or undifferentiated tumor cells (malignant). Differentiation is employed in tumor grading systems, which differ for each type of cancer. See **Malignancy** and **Undifferentiated tumor** for further information.

Tumorigen is any experimental compound or chemical that produces a tumor, either benign or malignant.

Tumor suppressor genes are genes that normally act via inhibition of cell proliferation and tumor development. In general, they slow down cell division to allow repair of DNA damage or trigger apoptosis. Inactivating mutations in tumor suppressor genes may cause cancer. Examples for tumor suppressor genes are p53, PTEN, and retinoblastoma gene.

Tympanic bulla calcification, see the preferred term **Tympanic bulla mineralization**.

Tympanic bulla edema is characterized by leakage of fluid (pale staining) into the lamina propria, which is expanded as a consequence. Edema is most often associated with other alterations, such as inflammation or alterations in the epithelium. It may occur with administration of saline.

Differential diagnosis: **Tympanic bulla hemorrhage**.

Tympanic bulla epithelia hypertrophy consists of enlargement of the epithelial cells lining the tympanic bulla. The cytoplasm may be vacuolated or granulated. This metaplasia is mostly associated with inflammatory processes due to infections, or administration of irritant material into the middle ear.

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Tympanic bulla fibrosis is characterized by proliferation and expansion of fibroblasts and the presence of increased loose connective tissue in the lamina propria of the tympanic bulla mucosa, but usually with minimal collagen deposition. Fibrosis usually occurs in association with inflammatory processes in the middle ear.

Differential diagnosis: **Tympanic bulla edema**.

Tympanic bulla granulation tissue is characterized by proliferation of new blood vessels, fibroblasts, edema, and loose connective tissue with only minimal collagen production in the lamina propria of the tympanic bulla. If progressive, granulation tissue will destroy the ossicles and hearing, and new bone formation and pseudoglandular structures (folding of epithelium) may be present. In severe cases, the entire tympanic cavity may be replaced by granulation tissue. Granulation tissue occurs in association with inflammatory processes due to administration of irritant material or infectious disease.

Differential diagnoses: **Tympanic bulla edema**; **Tympanic bulla fibrosis**.

Tympanic bulla hemorrhage is characterized by blood in the tympanic bulla or in the lamina propria of the tympanic bulla. Secondary findings include pigment deposition and granulation tissue or fibrosis. Hemorrhage may be part of an inflammatory process and can occur as a consequence of ulceration or necrosis of the lining epithelium or lamina propria and secondary to perforation of the tympanic membrane. Administration of severe irritants may cause damage and hemorrhage in the middle ear.

Tympanic bulla mineralization of the subepithelial region of the tympanic bulla is characterized by deposition of fine or coarse granules or plaques which stain intensely in hematoxylin and eosin, von Kossa, and Alizarin red–stained sections. Mineralization is observed as a spontaneous background finding, often in association with inflammatory processes, but may be increased in incidence and severity by the administration of test articles into the middle ear. Mineralization may cause foreign body reactions, epithelial necrosis, and fibrosis. Mineralization and middle ear new bone formation are described in several mutant mice (Tail-short and Enpp1 mutations).

Synonym(s): **Tympanic bulla calcification**.

Tympanic bulla new bone formation is characterized by thickening of the bone of the tympanic bulla by additional bone that is demarcated from the existing bone. The new bone may extend into the tympanic cavity and form spicules. New bone formation usually occurs in association with inflammatory processes due to trauma, infections, or administration of irritant material into the middle ear. Mineralization and increased ossification in the middle ear are also described for Tail-short and Enpp1asj mutations in mice.

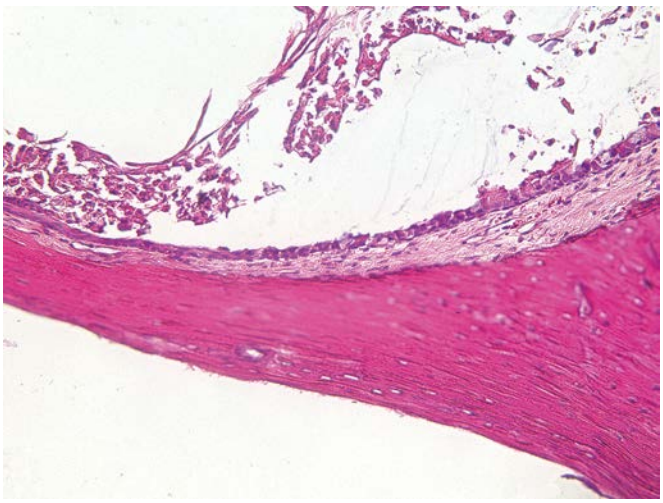
Synonym(s): **Middle ear hyperostosis**; **middle ear osteosclerosis**.



Tympanic bulla new bone formation, auditory bulla, rat, H&E. (Image courtesy of K. Schafer, Vet Path Services, Mason, Ohio.)

Tympanic bulla squamous cell metaplasia is transformation of the epithelial lining in most areas (except the ventral aspect) of the tympanic bulla from a monolayer of squamous cells (simple squamous epithelium) to stratified squamous epithelium, with or without keratinization. The ventral bulla contains simple cuboidal to columnar epithelium. This metaplasia is mostly associated with inflammatory processes due to infections or administration of irritant material into the middle ear.

Differential diagnosis: **Tympanic bulla tall cuboidal to columnar cell metaplasia**.



Tympanic bulla squamous cell metaplasia, rat, H&E. (Image courtesy of K. Schafer, Vet Path Services, Mason, Ohio.)

Tympanic bulla tall cuboidal to columnar cell metaplasia is transformation of the epithelium lining the ventral aspect of the tympanic bulla, which normally consists of a single layer of simple cuboidal to simple columnar cells. Most of the remainder of the bulla is lined by simple squamous epithelium. Metaplastic epithelium can be transformed into tall cuboidal to columnar cells with cytoplasmic vacuolation interspersed with numerous goblet cells. This metaplasia is

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mostly associated with inflammatory processes due to infections or administration of irritant material into the middle ear.

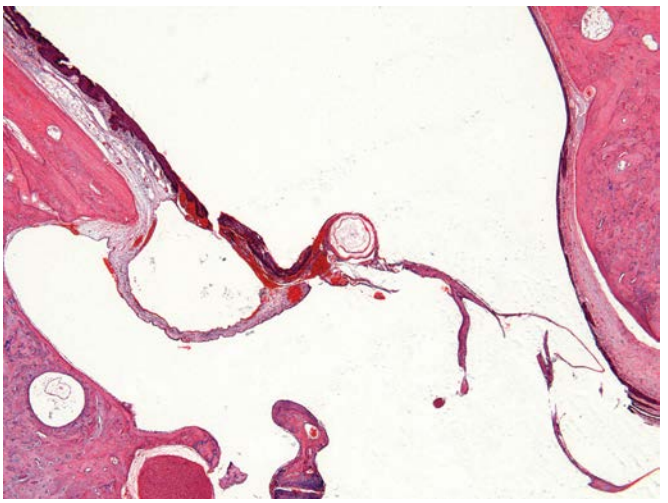
Differential diagnosis: **Tympanic bulla squamous cell metaplasia**.

Tympanic bulla ulcer is a defect or loss of the monolayer of epithelium lining the tympanic bulla. The cells are necrotic and slough into the lumen, leaving the underlying lamina propria exposed. Over time secondary alterations can occur, including middle ear inflammation and fibroplasia or fibrosis and epithelial hyperplasia. Instillation of irritants into the middle ear may induce ulcers.

Tympanic membrane coagulative necrosis, see the preferred term **Tympanic membrane necrosis**.

Tympanic membrane cyst is a spherical, thin-walled cavity lined by squamous epithelium with an internal core of effete squamous cells that arises from the external tympanic membrane epithelium. Cysts may arise within the tympanic membrane itself, or on its lateral (external) side, and they may progress to a nonneoplastic middle ear cholesteatoma.

Differential diagnosis: **Middle ear cholesteatoma**.



Tympanic membrane cyst, rabbit, H&E. (Image courtesy of K. Schafer, Vet Path Services, Mason, Ohio.)

Tympanic membrane necrosis consists of hypereosinophilia and necrotic debris which involves all layers of the membrane. Middle ear inflammation is also usually present. Necrosis of the tympanic membrane can be induced by foreign bodies, infections, and administration of severe irritants or xenobiotics into the external ear canal or middle ear.

Synonym(s): **Tympanic membrane coagulative necrosis**.

Tympanic membrane perforation results in a discontinuity of the tympanic membrane, a thin structure which transmits sound from air to the ossicles in the middle ear (refer to Appendix 3 for further information). Depending on chronicity of the rupture, additional changes may include hemorrhage, inflammation, epithelial hyperplasia, hemosiderin deposition, or fibrosis. Rupture of the tympanic membrane may be traumatic from a penetrating foreign object, or secondary to inflammation or necrosis of the tympanic membrane, or a combination of these factors. Xenobiotics administered by transtympanic injections may inhibit membrane healing. Artifact due to section or histologic processing should also be considered.



Tympanic membrane perforation, rat, H&E. (Image courtesy of K. Schafer, Vet Path Services, Mason, Ohio.)

Type I pneumocytes form the thin epithelial barrier (<0.1 μm in places) across which gas exchange occurs in the alveoli. Type I pneumocytes cover approximately 98% of the alveolar surface, and they also function to regulate solute and water movement between blood and the airspace. These cells are terminally differentiated, and normally lack mitotic activity. Aquaporin-5 is an ATI specific marker in the lung parenchyma.

Type II astrocyte or "Alzheimer type II astrocyte" refers to a structural alteration of astrocytes within the cerebral cortical gray matter that develops in conditions such as hepatic encephalopathy. Type II astrocytes have an enlarged round or lobulated nucleus and are frequently binucleate, with prominent nucleoli. The nuclei appear empty ("water clear") with a fine rim of marginated chromatin. The cytoplasm is indistinct, which differentiates them from reactive astrocytes. Additionally, disruption of the cytoskeleton leads to weak immunolabeling for glial fibrillary acidic protein (GFAP), a marker for normal and reactive astrocytes. The type II astrocyte change indicates a degenerative state associated with generalized cytoplasmic swelling or specific swelling of organelles that occurs after exposure to cytotoxic levels of circulating metabolites. Type II astrocytes occur most commonly with hepatic encephalopathy where the toxic metabolite is thought to be ammonia. Astrocytic processing of toxic metabolites, while cytotoxic to the astrocyte, is a sacrificial mechanism designed to spare and thus protect neurons. Type II astrocytes can occur throughout the brain but are most commonly found in the globus pallidus. See **Astrocyte swelling/vacuolation** and **Astrocytosis** for further information.

Synonym(s): **Astrocyte swelling**; **Alzheimer's type II astrocytes**.

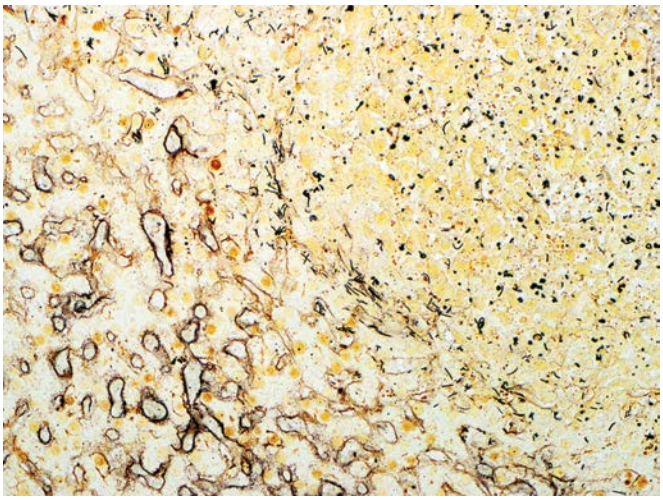
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Type II cell adenoma, see the preferred term Bronchioloalveolar adenoma.

Type II pneumocytes are located at the intersections of alveolar walls, act as progenitors for Type I pneumocytes, produce and secrete surfactant, and are involved in transepithelial fluid and electrolyte transport. By transmission electron microscopy, Type II pneumocytes are characterized by the presence of cytoplasmic lamellar and multivesicular bodies, and numerous microvilli are present on their apical surface. These cells may be demonstrated by alkaline phosphatase histochemistry or immunohistochemistry.

Typhlitis, see the preferred term **Cecum inflammation**.

Tyzzer's disease is caused by *Clostridium piliforme* infection, previously known as *Bacillus piliforme*. Ernest Tyzzer described this bacterium in a colony of Japanese waltzing mice in 1917. *C. piliforme* is a spore-forming, Gram-negative, filamentous microbe with spores that can survive in a nonhostile environment for up to 5 years. The infection spreads primarily by ingestion of spores. Tyzzer's disease is sporadic, due to poor husbandry practices, and is rare in current commercial rodent colonies. Mouse strain, age, and immune status are factors affecting animal susceptibility, ranging from DBA/2 mice susceptibility, to C57BL/6 mouse resistance. Gross lesions include hepatomegaly with single or multifocal necrotic areas, and reddening of the ileum and cecum. Microscopically, foci of degeneration, inflammation, edema, and necrosis are noted in the intestinal mucosa and muscularis. Focal or multifocal necrosis with inflammatory cell infiltration is noted throughout the liver parenchyma, being especially pronounced in immunodeficient mice. Lesions may be seen in the ventricular myocardium with myocyte degeneration and myocardial inflammation. Typical intracytoplasmic bundles of *C. piliforme* bacilli are usually seen in enterocytes, hepatocytes adjacent to necrotic foci, and in myocardial cells when stained with by Warthin-Starry or Steiner (silver staining), Giemsa, or periodic acid-Schiff (PAS) methods.



Tyzzer's disease, cat liver, Steiner silver. (Figure courtesy of R. Cattley, Auburn University.)

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UDPGA is an abbreviation for uridine diphosphate glucuronic acid, a cofactor for glucuronidation reactions.

UDP-glucuronsyltransferases (EC.2.4.1.17) is a superfamily of enzymes which catalyze the transfer of the glucuronic acid moiety from UDP-glucuronic acid to an oxygen- or nitrogen-containing drug, a process known as glucuronidation, which is a major Phase 2 reaction. Other names for the enzymes include glucuronyltransferase, UDP-glucuronyltransferase, UDP-GT, and UGT. In humans, there are 26 glucuronsyltransferase genes which code for 18 functional proteins (UGTs). There are two UGT families, UGT1 and UGT2, which based on gene sequence similarities are further divided into three subfamilies, UGT1A, UGT2A, and UGT2B. The UGTA1 subfamily consists of nine isoenzymes, UGT1A1, UGT1A3–UGT1A10. There are two isoenzymes in the UGT2A subfamily, UGT2A1 and UGT2A2, and seven isoenzymes in the UGT2B subfamily, UGT2B4, UGT2B7, UGT2B10, UGT2B11, UGT2B15, UGT2B17, and UGT2B28. See **Glucuronidation** and **Phase 2 reaction** for further information.

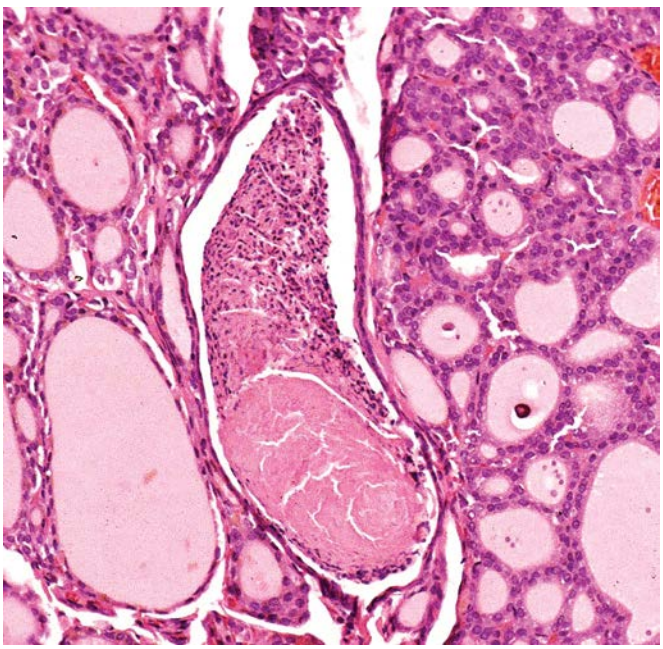
Ulcer is a focus of denuded epithelium, and applies to skin, mucous membranes, or epithelial surfaces of luminal organs, such as urinary bladder, stomach, or intestine. It involves disruption of the basement membrane, and therefore significant inflammation in contrast to erosions, which are superficial and do not extend past the basement membrane or elicit much inflammation.

Differential diagnosis: **Erosion**.

Ultimobranchial body, see the preferred term **Ultimobranchial gland**.

Ultimobranchial cyst is a congenital abnormality characterized by dilation of the ultimobranchial gland of the embryological fourth pharyngeal pouch and fusion with the thyroid gland and that persists into the post-neonatal period or beyond in mammals. Typically, these cysts are lined by squamous epithelium and may contain luminal eosinophilic material and may have associated inflammation.

Synonym(s): **Thyroid cyst**.



Ultimobranchial cyst, F344/N rat, H&E. (Images provided courtesy of National the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Ultimobranchial gland is an embryological endocrine gland composed of ectoderm (neural crest origin) that provides the thyroid C cell (parafollicular cell) population in the post-embryological periods of mammals. In other vertebrates (birds, fish, reptiles), the ultimobranchial gland is normally present after the fetal period.

Synonym(s): **Ultimobranchial body**.

Umbrella cells form the surface of transitional epithelium. See **Lower urinary tract** for further information.

Undifferentiated tumor refers to a heterogeneous group of neoplasms with little or no evidence of microscopic differentiation such that the tumor (neoplasm) cannot be subdivided into epithelial or mesenchymal origin. To aid in treatment and prognosis, delineation of an undifferentiated tumor into at least a broad category (e.g., epithelial, mesenchymal, melanocytic, hematopoietic) is crucial. Because poorly differentiated

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tumors may be heterogeneous in antigen expression, application of a broad panel of immunohistochemical markers that are anticipated to be either positive or negative should be used to determine the tumor lineage.

Unicameral bone cyst, see the preferred term **Bone cyst**.

Unmyelinated nerve fibers are small nerves whose axons lack a myelin sheath and are instead covered by a single fold of Schwann cell plasma membrane. A single Schwann cell typically ensheaths several nonmyelinated axons individually. Small unmyelinated nerves occur within the central nervous system (CNS) and in the peripheral nervous system (PNS) (e.g., olfactory nerves, sensory fibers of skin and muscle, postganglionic autonomic fibers). Nerve conduction along unmyelinated fibers occurs more slowly than along myelinated fibers. See **Blood-nerve barrier** and Appendix 3 for further information.

Synonym(s): **Nonmyelinated axon**.

Unscheduled DNA synthesis (UDS) test is a genotoxicity assay based on the detection of DNA replication during the nucleotide excision repair of DNA damage, which is distinct from the semiconservative replication of DNA during the S-phase of the eukaryotic cell cycle. Unscheduled DNA synthesis can be detected by elevated incorporation of [^{3}H]-thymidine into the DNA. In this case, the induction of DNA repair after treatment of a cultured cell or an animal with a compound is taken as an indication that the compound induced DNA damage and is genotoxic. In drug development such assays have largely been replaced by the Comet assay, which provides a more convenient method of determining such DNA damage.

Ureteral agenesis, see the preferred term **Ureteral aplasia**.

Ureteral aplasia is congenital absence of the ureter.

Synonym(s): **Ureteral agenesis**.

Ureteral dilation is distension of the lumen of the ureter from congenital, inherited, or acquired causes due to an obstructive process. Dilation is often noted with dilation of the renal pelvis. Histologically, dilation of the ureter lumen appears empty due to fluid removal during histological processing. As the ureter dilates, the urothelium becomes flattened, along with thinning of the underlying smooth muscle bundles. Minor degrees of ureteral dilation and/or pelvic dilation are common in laboratory rats and are potentially associated with spontaneous reflux in the absence of obstruction or pathologic changes in parenchyma.

Synonym(s): **Hydroureter**.

Ureteral inflammation is the infiltration of inflammatory cells into any part of the ureter.

Synonym(s): **Ureteritis**.

Ureteral leiomyosarcoma is a malignant tumor of smooth muscle surrounding the ureter. It is composed of pleomorphic spindle cells, with mitotic activity. Necrosis, cystic change, and mineralization are frequently present. Refer to **Urinary System** in Appendix 2 for further information.

Ureteritis, see the preferred term **Ureteral inflammation**.

Urethral inflammation is the infiltration of inflammatory cells into any part of the urethra.

Synonym(s): **Urethritis**.

Urethral occlusion is blockage of any portion of the urethra, most commonly by calculi. See **Obstructive uropathy** for further information.

Urethritis, see the preferred term **Urethral inflammation**.

Urinary bladder adenocarcinoma is a rare, malignant neoplasm composed of glandular structures that may contain mucous. They arise from the urothelium and differentiate from glandular metaplasia. Refer to **Urinary System** in Appendix 2 for further information.

Urinary bladder angiectasis represents a nonneoplastic dilation of blood vessels in the bladder submucosa. Angiectasis is most often a spontaneous lesion but may be observed following administration of vasodilating chemicals. It is more frequently observed in mice than in rats.

Urinary bladder calculi, see the preferred term **Urolithiasis**.

Urinary bladder carcinogenesis is the induction of tumors by genotoxic or nongenotoxic chemicals that cause trauma/irritation. Direct bladder carcinogens react with DNA, leading to mutations and cancer. Indirect bladder carcinogens (such as urinary solids) produce cytotoxicity by mechanical irritation, and subsequently increase cell proliferation by virtue of local trauma leading to cancer. The relevance of bladder tumors in laboratory animals to humans should be determined by defining the mechanism of induction. Refer to **Urinary System** in Appendix 2 for further information.

Urinary bladder carcinoma, see the preferred term **Urothelial carcinoma**.

Urinary bladder carcinosarcoma is a rare neoplasm composed of both malignant mesenchymal (e.g., fibroblasts or leiomyocytes) and epithelial cells. This tumor has the same features as a malignancy of the cell type of origin, but the epithelial cells are intermixed throughout the lesion. Refer to **Urinary System** in Appendix 2 for further information.

Urinary bladder dilation is distension of the bladder from congenital, inherited, or acquired causes due to an obstructive process. Dilation often accompanies dilation of the renal pelvis. Dilation of the urinary bladder may also arise from increased urine volume. Histologically, dilation of either the ureter or bladder lumen appears empty due to fluid removal during histological processing. In addition, as the bladder

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dilates, the urothelium becomes flattened along with thinning of the underlying smooth muscle bundles.

Urinary bladder diverticulum is an outpouching of the bladder mucosa extending into or through the muscle layer and fibroadipose tissue.

Urinary bladder inflammation is the infiltration of inflammatory cells into any part of the urinary bladder.
Synonym(s): **Cystitis**.

Urinary bladder leiomyosarcoma is a malignant smooth muscle tumor of the smooth muscle wall. It has spindle-shaped myocytes, nuclear anaplasia, and may exhibit local invasion or other features characteristic of malignancy. Refer to **Urinary System** in Appendix 2 for further information.

Urinary bladder lipomatosis consists of accumulations of normal-appearing adipose cells in the bladder wall. It has been associated with peroxisome proliferator–activated (PPAR) agonists. It is not clear if it represents a metaplastic or preneoplastic condition involving lipocytes.

Urinary bladder mesenchymal proliferative lesion is a nonneoplastic proliferation of pleomorphic epithelioid and spindle cells within the bladder wall. It has been described in mice but not rats and is regarded as a type of decidual change. Refer to **Urinary System** in Appendix 2 for further information.

Urinary bladder nematodiasis is parasitism by the roundworm *Trichosomoides crassicauda*. It is rarely reported now due to improved laboratory rodent housing practices. It usually leads to urolithiasis. Reports of urothelial hyperplasia and neoplasms are thought to be due to the urolithiasis rather than directly to the parasite. See **Urolithiasis** and **Urinary bladder calculi** for further information.

Urinary bladder papilloma is a benign tumor that mainly appears as an exophytic urothelial mass. Papillomas tend to be pedunculated, with a fibrovascular stalk. Papillomas contain little cellular atypia and do not invade the underlying submucosa. Refer to **Urinary System** in Appendix 2 for further information.

Urinary bladder polyp is a benign tumor composed of a cellular core lined by a thin layer of urothelium. The exact cause of this type of polyp is not known, but mechanical trauma, as from the parasite *Trichosomoides crassicauda*, can occur. Refer to **Urinary System** in Appendix 2 for further information.

Urinary bladder spindle cell carcinoma, see the preferred term **Urinary bladder carcinosarcoma**.

Urinary bladder squamous cell carcinoma is a malignant neoplasm composed primarily of squamous epithelium which arises from squamous metaplasia of the urothelium. These tumors are generally characterized by moderate cell atypia, invasion, and frequent metastases. Refer to **Urinary System** in Appendix 2 for further information.

Urinary clearance, see **Renal clearance** for further information.

Urinary excretion is the removal of drug or drug-related compounds from the body via the kidney into the urine. See **Excretion** for further information.

Urinary system, Anatomy and Histology, see Appendix 3 for further information.

Urogenital tract includes the combined tissues of the reproductive and urinary systems, which in mammals arise from a common developmental origin, the urogenital ridge.

Urolithiasis is the formation of mineral concretions (i.e., calculi), called uroliths, anywhere in the urinary tract. These structures vary in size, are either basophilic or eosinophilic, and freely lie within the bladder lumen. Calculi often result in inflammation, urothelial hyperplasia, and neoplasia. Concentric layering of some calculi may be present. Smaller calculi may be referred to as crystals or crystalluria (crystals present in the urine). The effects of calculi may be evident even though calculi themselves may be washed out during histologic processing. Calculi may form spontaneously or from xenobiotics that precipitate in the urinary tract due to a high concentration or low solubility.
Synonym(s): **Crystalluria**; **Urinary bladder calculi**.

Uroliths, see the preferred term **Urolithiasis**.

Urothelial attenuation is a thinning of the normal thickness of the urinary tract mucosa.

Urothelial carcinoma is a malignant tumor of the urothelium and can occur in any part of the urinary tract lined by urothelial cells. It is usually a solitary neoplasm but rarely can be multiple, large, and poorly demarcated. It is invasive and may be well-differentiated or highly anaplastic with variable mitotic figures. Refer to **Urinary System** in Appendix 2 for further information.

Urothelial cell hyperplasia, see the preferred term **Urothelial hyperplasia**.

Urothelial hyperplasia is a nonneoplastic (but potentially preneoplastic) increased number of urothelial cells occurring in the renal pelvis, ureter, or urinary bladder. It is a common response to infections, mechanical trauma (calculi), or xenobiotic exposure. Urothelial hyperplasia may be focal, multifocal, or diffuse, and simple, papillary, or nodular. This lesion may be reversible when the initiating agent is removed. Refer to **Urinary System** in Appendix 2 for further information.

Urothelial hypertrophy represents an enlargement of cytoplasm of the urinary tract lining cells in response to chemical stimuli.

Urothelial inclusions of superficial umbrella cells have been reported in mice as intracytoplasmic eosinophilic to

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basophilic granules of various constituents following chemical administration. Spontaneous urothelial inclusions are observed in nonhuman primates as eosinophilic inclusions representing keratohyalin granules. They have not been associated with other cytopathological conditions, preneoplasia, or neoplasia.

Urothelial metaplasia is a change from the normal-appearing urothelium to a different type of epithelium such as squamous, glandular, or mixtures of the two. Urothelial metaplasia may be observed in both nonneoplastic and neoplastic lesions associated with a wide variety of toxic, carcinogenic, or other stimuli. Refer to **Urinary System** in Appendix 2 for further information.

Urothelial necrosis is death of urothelial cells.

Urothelial vacuolation is the formation of cytoplasmic vacuoles in urothelial lining cells, which appear as clear vacuoles when viewed in hematoxylin and eosin (H&E)-stained sections.

Urothelium is the lining epithelium (i.e., mucosa) of the urinary tract. See **Lower urinary tract** for further information.
Synonym(s): **Transitional cell epithelium**.

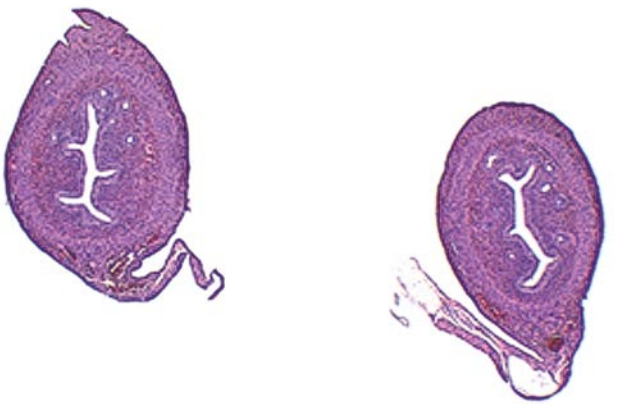
Urticaria (hives in the human) is a form of type I cutaneous hypersensitivity and is mediated by IgE antibodies bound to the surface of mast cells and basophils. Urticaria are characterized grossly by raised pruritic erythematous wheals, typically demonstrate the brightest erythema at the outer edge of lesions with rapid paling toward the middle. When a drug allergen interacts with IgE, the mast cells and/or basophils degranulate, releasing mediators such as histamine and leukotrienes, that manifest cutaneously as urticaria, angioedema, and pruritus. Histopathologically, urticaria are characterized by dermal angioedema, often with congestion of dermal vessels. The key differences between drug-induced and non-drug–induced urticaria is that in non-drug–induced urticaria there is often little else to see histologically, while drug-induced urticaria are characterized by the presence of a mononuclear infiltrates, with or without eosinophils, that are often perivascular. The mononuclear cells are T cells typically with $CD8^+$ cells in the epidermis and $CD4^+$ cells forming the superficial dermal infiltrate. In some cases vasculitis may be present, when the lesion is then referred to as a urticarial vasculitis.

U.S. Food and Drug Administration (FDA) is the federal agency which has oversight of food and drug safety. The FDA oversees clinical drug development Investigational New Drug (IND) application (or potentially a pre-IND meeting) submission of the registration dossier, assesses the regulatory submission and issues marketing authorization for the United States. The agency also collects pharmacovigilance data and monitors the safety of marketed drugs.

Uterine adenomatous differentiation, see the preferred term **Adenosis**.

Uterine angiomatous hyperplasia is a well-demarcated, noncompressive focus, often containing blood-filled vessels lined by normal-appearing endothelial cells in the endo- or myometrium. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Uterine atrophy is characterized by a reduced size and weight of the mature uterus and may involve some or all components of the uterus (i.e., epithelium, stroma, myometrium). It occurs with reproductive senescence or in response to xenobiotics. Histologically, atrophy may be characterized by decreased number and size of uterine glands, a low cuboidal endometrial epithelium with scant cytoplasm, compacted uterine stroma, or thinning of the myometrium.



Bilateral atrophy, uterus, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Dixon et al., 2014.)

Uterine cycle, see the preferred term **Menstrual cycle**.

Uterine dilatation, see the preferred term **Uterine luminal dilation**.

Uterine inflammation, see the preferred term **Endometrial inflammation**.

Uterine luminal dilation is characterized by a uterine lumen that is larger in diameter and often expanded by fluid. Distention of the uterine lumen may result in pressure-mediated atrophy or attenuation of the endometrial surface epithelium. There may be concomitant dilated endometrial glands, and the typical vaginal mucosa will include early keratinization and surface mucoid layer. An increased incidence of uteri with a dilated lumen indicates a xenobiotic-induced proestrogenic effect. In the mouse and rat, the proestral uterus is normally dilated due to estrogen-mediated fluid secretion.
Synonym(s): **Hydrometra**; **uterine dilatation**.

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Uterine myometrial hypertrophy is a diffuse or focal change characterized by increased cytoplasmic volume of myometrial smooth muscle. It can be induced by estrogenic or androgenic compounds, and by mechanical distention, such as during pregnancy. Myometrial hypertrophy is an unusual change in rats and mice and has not been reported as a spontaneous change in the nonhuman primate (NHP).

Uterine regenerative phase is the period of endometrial repair and reorganization immediately following menstruation in primates and preceding the proliferative phase of endometrial expansion prior to the next ovulatory cycle. See Appendix 3 for more information.

Uterine sarcoma is a malignant neoplasm of the myometrium. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Uterine squamous metaplasia is an adaptive, benign epithelial transition from a columnar or cuboidal mucosa to a stratified squamous epithelium in the uterus. It often occurs in response to local irritation. Squamous metaplasia of the uterine endometrial epithelium can occur secondary to metritis or pyometra. Squamous metaplasia of the endocervical mucosa commonly occurs when it everts during puberty or pregnancy to form the portio vaginalis. See **Female reproductive tract squamocolumnar junction (SCJ)** for further information.

Uterine stromal angiomatous hyperplasia, see the preferred term **Uterine angiomatous hyperplasia**.

Uterine stromal fibrosis is frequently observed in older rodents and is characterized by the expansion of the endometrial stroma and/or myometrium with fibroblasts and collagen. Overall the cellularity is reduced due to the mature connective tissue.



Thickened, fibrotic endometrial stroma, uterus, F344/N rat, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

Uterine tube, see the preferred term **Oviduct**.

Uterus is formed in females from the paramesonephric (Mullerian) duct. It is divided into a muscular layer, the myometrium, and the mixed epithelial, stromal, and vascular lining, which together compose the endometrium. The myometrium is predominantly composed of interlacing smooth muscle bundles that form the bulk of the uterine mass, and is capable of both expanding to contain the growing fetus(es) during pregnancy and appropriately contracting to expel them during parturition. The endometrium is the hormonally sensitive stromal and glandular lining that, in reproductively active females, undergoes expansion and regression or sloughing during the estrous or menstrual cycle in preparation for pregnancy. The uterus is connected to the ovaries via the fallopian tubes at the cranial end of each horn, and to the vagina via the cervix. In littering animals, such as the mouse, rat, rabbit, pig, and dog, the uterus is divided into two distinct horns, and in primates such as humans and macaques the uterine body is fused to accommodate a single fetus.

Uterus/ovary benign mixed mesodermal tumor, see the preferred term **Mullerian tumor, mixed**.

Uterus/ovary carcinosarcoma (for homologous malignant tumors), see the preferred term **Mullerian tumor, mixed**.

Uterus/ovary mixed mesodermal tumor (for heterologous neoplasms), see the preferred term **Mullerian tumor, mixed**.

Uveal leiomyoma is a rare, benign, intraocular tumor of smooth muscle originating from the smooth muscle myofibers of the iris or ciliary muscles in the uvea. The spindle-shaped cells with granular cytoplasm and an elongated nucleus may palisade around blood vessels and form interlacing bundles or whorls. Refer to **Special Senses** in Appendix 2 for further information.

Uveal malformation, see the preferred term **Optic fissure malformation**.

Uveal melanocyte hyperplasia in the rat and dog consists of aggregates of polygonal to poorly defined uveal melanocytes filled with usually large globules of pigment in the absence of other cellular or inflammatory changes. Refer to **Special Senses** in Appendix 2 for further information.

Uveal melanoma arises in the pigment cells (melanocytes) that reside within the iris, ciliary body, and choroid. Microscopically, tumors are often formed by spindle, epithelioid, or mixed-cell populations. Bundles or whorls of perivascular-oriented spindle cells have indistinct borders with scant cytoplasm and fusiform nuclei with indistinct nucleoli. Refer to **Special Senses** in Appendix 2 for further information

Uveitis, see the preferred term **Iris inflammation**.

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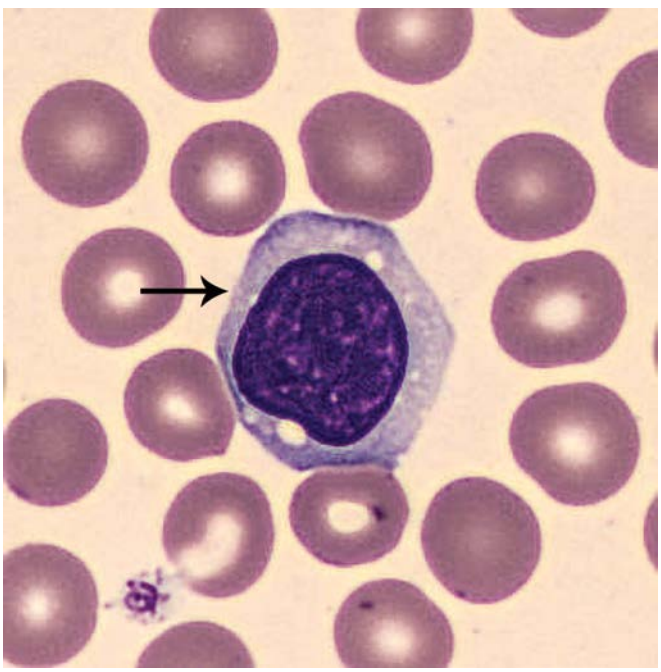
V

Vacuolar artifact is a synonym for white matter vacuolation, where the vacuolation is known to be artifact. See the preferred term **White matter vacuolation**.

Vacuolar degeneration is an early or mild form of injury to cells and is a potentially reversible change. Gross examination of the tissue may reveal some pallor (due to compression of capillaries), increased turgor, and an increase in weight of the organ. Microscopically, cells contain small, clear cytoplasmic vacuoles that when small or early in their development may be difficult to identify. Sensitivity is increased by ultrastructural evaluation, which often shows distended segments of the endoplasmic reticulum (ER) and mitochondria.

Synonym(s): **Hydropic change**; **hydropic degeneration**.

Vacuolated lymphocytes are large lymphocytes with small numbers of distinct, clear vacuoles. As reactive lymphocytes, they are nonspecific indicators of antigenic stimulation. However, they can also be indicators of storage disorders such as phospholipidosis. Cytoplasmic vacuoles can be observed in dogs with fucosidosis, an inherited disease due to a deficiency in L-fucosidase, an enzyme involved in glycoprotein metabolism. In drug development, phospholipidosis may result in vacuolated lymphocytes.



Vacuolated lymphocyte (arrow), blood smear, rat.

Vacuole is a cellular cytoplasmic cavity observed microscopically. Vacuoles are membrane-bound when viewed ultrastructurally, which separates them from tissue artifacts that may appear similar by light microscopy. Vesicles fuse and form vacuoles.

Differential diagnosis: **Vesicle**.

Vagina is the musculotubular terminal/distal segment of the female reproductive tract, extending from the cervix to the external vaginal orifice. The vagina is lined by a hormonally sensitive squamous epithelium that in some species (e.g., dog, rat) undergoes characteristic morphologic changes during the estrous cycle.

Vaginal carcinoma is an exophytic epithelial growth with squamous cell differentiation over a thin fibrovascular core that invades the submucosa. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Vaginal granular cell tumor is an expansile neoplastic cluster of a uniform population of cells with small basophilic nuclei, and abundant, granular, eosinophilic cytoplasm admixed with smaller cells containing small, dark, uniform nuclei, and fewer cytoplasmic granules. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Vaginal hypermucification, see the preferred term **Vaginal mucification increased**.

Vaginal imperforation is a congenital anomaly of the vagina resulting in an impatent external vaginal orifice. During fetal development, the vagina forms from the sinovaginal bulb and urogenital sinus and connects with the Mullerian duct components (uterus and cervix). Segmental anomalies of the developing vagina may range from imperforate hymen to complete atresia of the distal urogenital tract.

Synonym(s): **Imperforate hymen**; **persistent hymen**.

Vaginal inflammation is microscopically characterized by the presence of increased numbers of inflammatory cells in the mucosa, often accompanied by a mucopurulent exudate with activated and degenerate neutrophils, mucus, hemorrhage, cellular debris, and often numerous bacteria/bacterial colonies. Vaginitis is distinct from the typical inflammatory cell infiltrates (e.g., lymphocytes and neutrophils), and exudates observed during some phases of the estrous cycle in the mouse, rat, and dog, and during the menstrual cycle in nonhuman primates. Lymphocytic infiltrates in the lamina propria and submucosa are also typical for macaques during all phases of the menstrual cycle.

Synonym(s): **Vaginitis**.

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Vaginal mucification, see the preferred term **Vaginal mucification, increased**.

Vaginal mucification, increased is the presence of mucous-containing, superficial vaginal or cervical epithelium at a time other than in the proestrus stage of the estrous cycle. In normally cycling rodents, mucin is present in the superficial vaginal and cervical epithelium during proestrus. The presence of intracellular mucin at other times of the cycle, or in noncycling or abnormally cycling rodents, is reflective of hormonal imbalance (e.g., androgenic effect/relative decrease in estrogens). It is a nonspecific change that occurs spontaneously and is commonly observed in aging rodents accompanied by atrophy of the vaginal wall and uterus, and changes in the ovary consistent with senescence (see **Anestrus** for further information), and can also be induced by administration of hormonally active xenobiotics. The intracellular mucin stains readily with periodic acid-Schiff (PAS) and/or Alcian blue (see figures below).

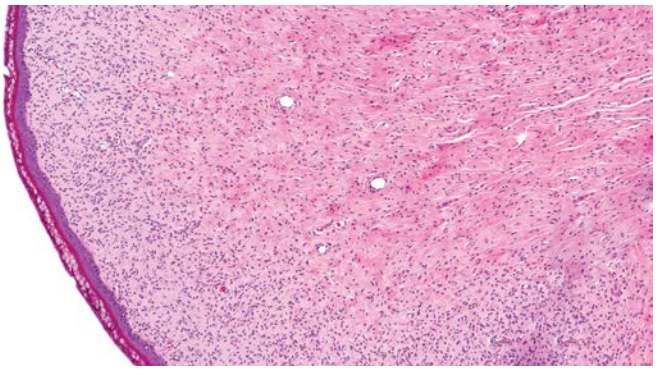
Differential diagnosis: **Proestrus vagina**.

Synonym(s): **Vaginal hypermucification**; **vaginal mucification**.

Vaginal papilloma is an exophytic epithelial growth with squamous cell differentiation over a thin fibrovascular core. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Vaginal polyp is an exophytic benign, well-differentiated mass of the vaginal mucosa and submucosa supported by a thin fibrovascular stalk. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

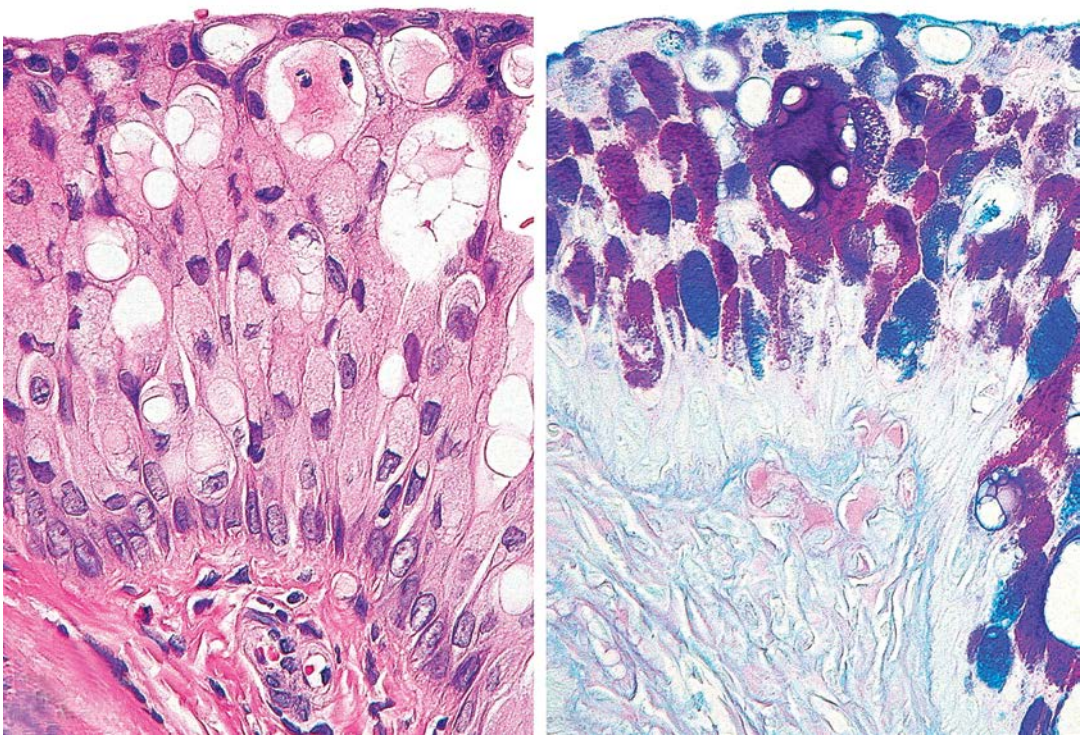
Vaginal stromal hypertrophy is the thickening or expansion of the fibrovascular stroma in the vagina proper. This lesion does not distort the surrounding tissue architecture.



Thickened fibrous stroma, vagina, F344/N rat. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

Vaginitis, see the preferred term **Vaginal inflammation**.

Valve degeneration is the thickening of heart valve leaflets due to increased amounts of glycosaminoglycans in the interstitium. Valvular insufficiency may occur in severe cases. Valve degeneration is considered a spontaneous, age-related change. Unlike in drug-induced valvular stromal proliferation (drug-induced valvulopathy), proliferation of valvular interstitial cells is not usually a prominent feature of spontaneous



Increased mucin in vaginal epithelium, rat, PAS-Alcian blue. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Dixon, D. et al. 2014. *J. Toxicol. Pathol.* 26 (3 Suppl):1S–107S.)

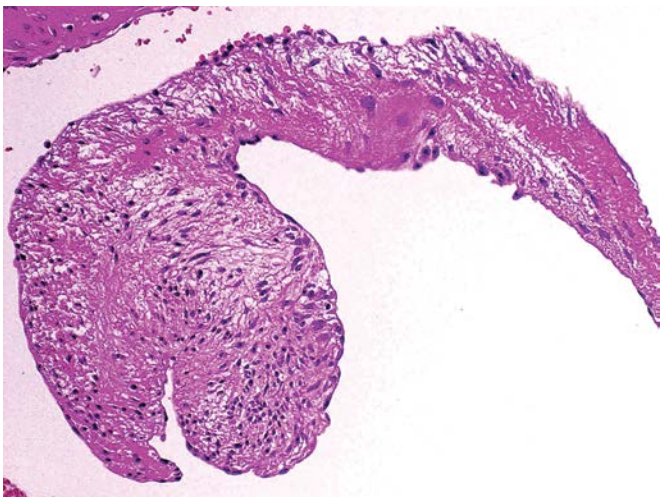
V

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valve degeneration. However, there is sufficient overlap in morphology between the two entities that may make distinguishing them difficult.

Differential diagnoses: **Valvular stromal proliferation**; **Valve inflammation**.

Synonym(s): **Myxomatous valvular degeneration**; **valvular endocardiosis**.

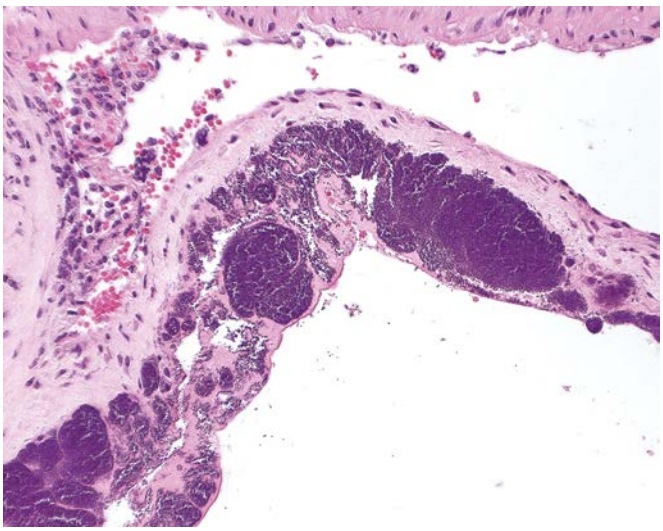


Valve degeneration, myxomatous, rat, H&E.

Valve inflammation is a rare finding in safety assessment studies, as valvular degeneration with myxomatous and stromal/fibrotic changes are seen more often than frank inflammation in laboratory animals. However, valve inflammation can occur spontaneously when septic emboli from another site spread hematogenously. Bacterial colonies establish themselves on the valve leaflets, resulting in suppurative inflammation and valvular endocarditis; this finding is generally characterized by neutrophilic inflammation with exudate and bacterial colonies. Reactive stromal and endothelial proliferation are also common features associated with valve inflammation. Impaired valve function can result in either regurgitation or stenosis, leading to congestive heart failure. Valve inflammation has to be differentiated from drug-induced valvular damage (valvular stromal proliferation) and spontaneous valvular degeneration. Valvular damage has been observed in humans following administration of the antiobesity drug, fenfluramine–phentermine, necessitating its withdrawal from the market. Models of valvular damage in laboratory animals have proved challenging to develop, although valvular damage has been induced in laboratory species with serotoninergic and 5-HT agonists, including ergotamine and benfluorex. Spontaneous valvular changes appear as myxomatous degeneration with increases in the interstitial component, sometimes accompanied by fibrotic changes.

Differential diagnoses: **Valvular stromal proliferation**; Valvular degeneration.

Synonym(s): **Valvular endocarditis**; **valvulitis**.



Valve inflammation with intralesional bacterial colonies, rat, H&E.

Valvular angiectasis is dilation of thin-walled vessels within an atrioventricular valve leaflet, resulting in a large, blood-filled chamber lined by endothelium. Valvular angiectasis usually does not affect heart function and is usually an incidental finding at necropsy.

Synonym(s): **Hematocyst**; **hemocyst**.

Valvular endocardiosis, see the preferred term **Valve degeneration**.

Valvular endocarditis, see the preferred term **Valve inflammation**.

Valvular stromal proliferation is an increased number of mesenchymal cells (valvular interstitial cells) within heart valve leaflets. The increased cellularity is often accompanied by increased amounts of extracellular matrix. Valvular stromal proliferation may result in valvular insufficiency and compromised heart function. Frequently, valvular stromal proliferation is the result of agonism of the $5HT_{2B}$ receptor (a serotonin receptor) on valvular interstitial cells. $5HT_{2B}$ receptors may be stimulated by excessive endogenous serotonin levels (e.g., in patients with carcinoid tumors) or by certain pharmaceutical agents (e.g., methysergide, pergolide, and fenfluramine).

Differential diagnoses: **Valve degeneration**; **Valve inflammation**.

Synonym(s): **Valvulopathy**.

Valvulitis, see the preferred term **Valve inflammation**.

Valvulopathy, see the preferred term **Valvular stromal proliferation**.

Vascular endothelial growth factor (VEGF) typically refers to VEGF-A, a homodimeric glycoprotein that is the major angiogenic growth factor in mammals. It is involved

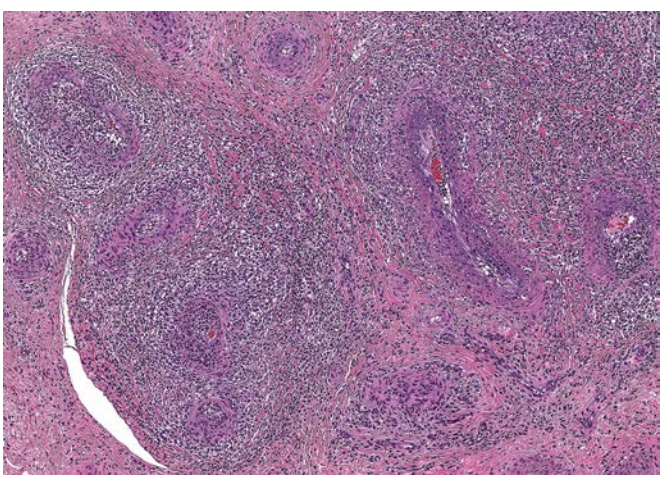
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in neovascularization during development, following injury, and in tumor growth. VEGF is induced in mesenchymal and epithelial cells under conditions of hypoxia or inflammation, and signals via receptor tyrosine kinases. Its major effects are to increase vascular permeability, induce proliferation and migration of endothelial cells, and promote endothelial cell survival in growing vessels. VEGF is a target of several licensed therapeutics primarily for solid tumors and neovascular ocular disease such as the wet form of age-related macular degeneration. Other members of the VEGF family include VEGF-B (involved in embryonic angiogenesis), and VEGF-C and -D (which stimulate both vascular and lymphatic angiogenesis).

Vascular endothelial growth factor receptor (VEGFR) blockers may inhibit the signaling capacity of vascular endothelial growth factor receptors (VEGFR) by inhibiting ligand binding, receptor dimerization, or receptor tyrosine kinase activity. Direct toxicity related to inhibition of VEGF signaling has been noted in preclinical toxicity studies, and consists of physeal dysplasia in long bones, and decreased ovarian and uterine weight with absence of corpora lutea. The majority of marketed VEGFR blockers are small-molecule inhibitors of VEGFR tyrosine kinase activity, while ramucirumab is a monoclonal antibody directed against VEGFR2. VEGFR blockers are used to inhibit angiogenesis in the treatment of several solid tumors.

Vascular inflammation is characterized by infiltration of inflammatory cells that disrupt the normal architecture of a blood vessel wall and may be accompanied by edema, hemorrhage, necrosis, or fibrosis depending on the inciting cause, severity, and chronicity of the lesion. Vascular inflammation may be seen as a background lesion in commonly used preclinical species or may be a test article–related effect or secondary to immune complex disease in association with antidrug antibody formation to biologics. Vascular inflammation can be induced by several xenobiotics; see **Drug-Induced Vasculitis**.

Synonym(s): **Vasculitis**.



Vascular inflammation, mesenteric vessels, cynomolgus monkey, H&E.

Vascular occlusion is characterized by complete obstruction of a blood vessel lumen, most commonly due to thrombosis. Surrounding tissue may exhibit congestion, hemorrhage, and/or necrosis depending on the type of vessel affected, presence of collateral circulation, and chronicity of the lesion.

Vasculitis, see the preferred terms **Vascular inflammation** and **Arterial inflammation**.

Vasoconstrictor is any endogenous or exogenous molecule that causes narrowing of vascular lumens, particularly arteries and arterioles, via contraction of the smooth muscle (medial) wall.

Vasodilator is any endogenous or exogenous molecule that causes widening of vascular lumens, particularly arteries and arterioles, via relaxation of the smooth muscle (medial) wall.

Vasopressin, see the preferred term **Antidiuretic hormone**.

Vasopressor agent is a drug used to increase blood pressure primarily by causing systemic vasoconstriction. Examples include synthetic hormones such as epinephrine and vasopressin.

Vehicle is any medium used to carry, dissolve, suspend, and/or dilute a test substance, thereby enabling its administration or delivery into a biological system. Examples include water, saline, dimethylsulfoxide (DMSO), carboxymethyl cellulose, and polyethylene glycols.

Ventricles of the brain are a communicating series of cerebrospinal fluid–filled spaces within the center of the lobes of the brain and are continuous with the central canal of the spinal cord and subarachnoid space surrounding the brain and spinal cord. The ventricular system is composed of two lateral ventricles within the cerebral hemispheres, the third ventricle, the cerebral aqueduct, and the fourth ventricle. Refer to Appendix 3 for further information.

Ventricular dilatation (neuronal) is a synonym for hydrocephalus and is more often used in nonclinical necropsy reports, since it is a descriptive term. Ventricular dilatation is due to excess cerebrospinal fluid (CSF) in the ventricles of the brain, which may be congenital or acquired. Hydrocephalus may be due to obstruction of CSF flow, increases in CSF production, and/or decreases in CSF egress via the arachnoid villi. See **blood-CSF barrier** for information on CSF flow. A related term is hydromyelia, which is excessive CSF within the spinal cord. See **Hydromyelia** for further information.

Ventricular dilatation (cardiac) is characterized by abnormal enlargement of the ventricular lumen that is best assessed via in vivo techniques such as echocardiography. Ventricular dilatation may be a compensatory response to increase stroke volume and may or may not be accompanied by changes in ventricle wall thickness and/or microscopic changes involving cardiomyocytes.

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Vesicle is a cellular structure containing fluid. These cytoplasmic components have a lipid bilayer wall and function in the secretion, uptake, metabolism, storage, and transport of cellular materials. This term is also used to indicate the presence of a fluid-filled space within the epidermis; vesicles are a diagnostic feature of infection by a number of viruses. See **Cutaneous vesicle** for further information.

Differential diagnosis: **Vacuole**.

Vesicoureteral reflux is the reverse flow of urine from the urinary bladder into the kidney(s). It may be congenital due to a defect at the terminal end of the ureter or occur later in life due to any obstruction interfering with urine outflow from the bladder.

Vessel dilatation, see the preferred term **Angiectasis**.

Vestibular neuritis, see the preferred term **Inner ear inflammation**.

Vestibular organ necrosis is characterized by damage and loss of vestibular organ epithelium or hair cells, or the entire organ (refer to Appendix 3 for further information). After toxic injury, epithelial cells become shrunken and eosinophilic with pyknotic, karyorrhectic, or karyolytic nuclei. Coagulative necrosis of all cells of the vestibular organ may occur with nonspecific irritants.

Differential diagnosis: **Hair cell necrosis**.

Vestibulocochlear axonal degeneration of cranial nerve VIII (vestibulocochlear nerve or the vestibular or cochlear branches; refer to Appendix 3 for further information) consists of axonal swelling with eosinophilia followed by fragmentation and formation of digestion chambers within the nerve. Damage to this nerve or its branches may result in dying back with loss of hair cells of the organ of Corti, crista ampullaris, or vestibular organ, and ultimately the loss of neuronal and axonal connections to the brain.

Virilization is a syndrome encompassing androgen-induced changes to females such that they appear more male-like. Adult-onset virilization may be related to administration of androgenic substances or may be secondary to androgen production by a testosterone-producing tumor. Phenotypic changes may include female reproductive tract atrophy and masculine pattern musculature, hair growth, and vocalization. Virilization can also occur secondary to in utero exposure to high levels of androgens during critical windows of development in females. Virilization may include development of the Wolffian duct to form epididymides, vas deferens, seminal vesicles, and/or prostate gland, and may occur in parallel with complete or partial development of the Mullerian-duct origin female reproductive tract. Early to mid-gestation exposure to testosterone in rodents and macaques is used as a model for polycystic ovary syndrome.

Visceromotor nervous system is a synonym for the autonomic nervous system, which has components in both the central and peripheral nervous systems, interacts closely with the hormonal (or endocrine) systems, and innervates smooth muscle, cardiac muscle, and glands of the visceral system. The enteric nervous system is a fairly autonomous subdivision of the autonomic nervous system that controls the gastrointestinal tract.

Vitreal agenesis is a congenital failure of the vitreous to develop, which commonly occurs in conjunction with other internal ocular structural malformations and microphthalmia. Genetic mutations in mice such as Pax6, infectious diseases, and toxicities may cause mutations in the vitreous and other internal structures.

Vitreal bone or cartilage metaplasia consists of well-differentiated cartilage and less frequently, mineralized bone that forms in the vitreous secondary to chronic fibrosis (see vitreal fibroplasia). Vitreal hyalocytes, retinal Müller cells and astrocytes, migrating retinal pigment epithelium (RPE), and scleral fibroblasts may transdifferentiate and are thought to participate in the formation of vitreal fibroplasia. These cells may also differentiate into cartilage or bone under anoxic or hypoxic conditions. See **Metaplasia** for further information.

Differential diagnoses: **Vitreal mineralization**; **Vitreal fibrosis**.

Vitreal dystrophic calcification, see the preferred term **Vitreal mineralization**.

Vitreal fibroplasia forms from neovascularization and proliferating fibrous connective tissue (fibrovascular proliferation) as a response to trauma, penetrating injury, and inflammation in the vitreous. Loose connective tissue or fibrous membranes may form as thin fibrous sheets (epiretinal membranes or retinal fibroplasia) or fill the vitreal space and progress to fibrosis that replaces the vitreous (vitreal fibrosis). Fibroplasia may be accompanied by hemorrhage, vitreal hemosiderin-laden macrophages, and inflammation. Fibroplasia attaches to ocular structures and contributes to lens dislocation and retinal detachments. Vitreal hyalocytes, retinal Müller cells and astrocytes, migrating retinal pigment epithelium (RPE), and scleral fibroblasts may transdifferentiate and contribute to fibroplasia. See **Lens capsule hypertrophy** for illustration.

Differential diagnosis: **Vitreal fibrosis**.

Synonym(s): **Vitreal membranes**; **fibrovascular proliferation**.

Vitreal fibrosis is a chronic form of vitreal fibroplasia in which connective tissue fills the vitreal space with mature connective tissue that replaces the vitreous (vitreal fibrosis).

Differential diagnosis: **Vitreal fibroplasia**.

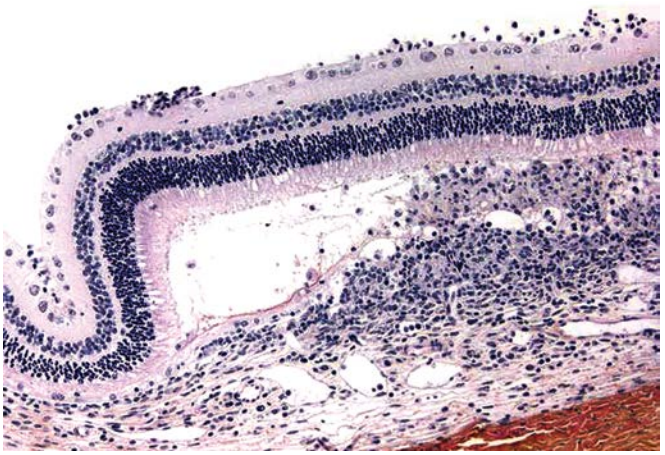
Vitreal hemorrhage is the presence of extravasated red blood cells in the vitreous as a spontaneous change in some strains of mice (DBA/2), secondary to trauma, inflammation, retinal detachment, intravitreal injections, retroorbital bleeding procedures, or rarely, bleeding from persistent fetal vasculature.

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Vitreal hemosiderin–laden macrophages results when whole blood cells in the vitreous break down, and the released hemosiderin is engulfed by macrophages. See **Vitreal hemorrhage** for further information.

Vitreal inflammation consists of focal or diffuse accumulations of systemically derived leukocytes inflammatory cells (granulocytes or heterophils [rabbit], macrophages, lymphocytes, plasma cells, and multinucleated giant cells) and local proliferation of the tissue-resident hyalocytes within the vitreous chamber. The cell types are dependent on the chronicity and initiating agent. As part of systemic immune surveillance, leukocytes transiently cross the blood-retinal barrier (refer to Appendix 3 for further information), but these leukocytes may persist and release proinflammatory secretions to attract additional leukocytes. Tissue-resident hyalocytes will also proliferate as part of the protective inflammatory response. Inflammation occurs with trauma, penetrating injury such as intravitreal injections, infectious organisms, autoimmunity, toxicities, extension of inflammation from the retina or iris, and secondary to rupture of the lens capsule. Vitreal fibroplasia and fibrosis may occur with chronic inflammation.

Synonym(s): **Vitritis**.



Vitreal inflammation with subretinal fibroplasia and retinal detachment; experimental uveitis, Dutch belted rabbit, hematoxylin phloxine saffron stain.

Vitreal inflammatory cell infiltrate consists of a few systemically derived leukocytes (granulocytes or heterophils [rabbit], macrophages, lymphocytes, and plasma cells) or increased numbers of the tissue-resident hyalocytes (hyalitis) within the vitreous chamber. As part of systemic immune surveillance, leukocytes can transiently cross the blood-retinal barrier (refer to Appendix 3 for further information). A few hyalocytes are normally present in the vitreous to provide phagocytic activity, but these tissue-resident macrophages will proliferate locally (hyalitis) in response to trauma or a penetrating injury such as intravitreal injections.

Synonym(s): **Hyalitis**.

Vitreal membranes, see the preferred term **Vitreal fibroplasia**.

Vitreal metastatic calcification, see the preferred term **Vitreal mineralization**.

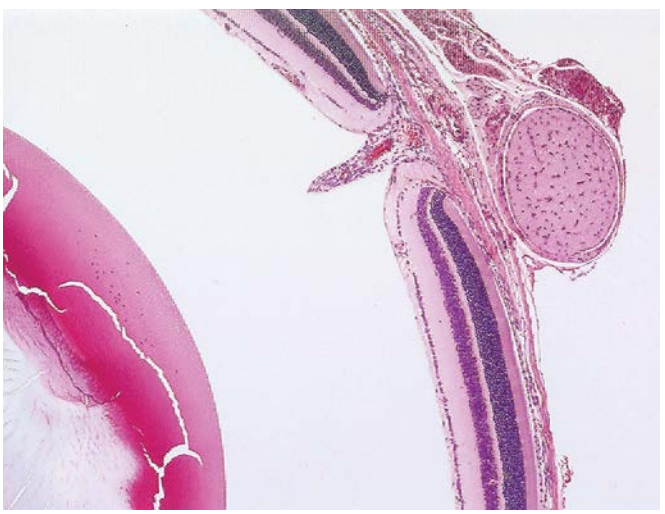
Vitreal metastatic mineralization, see the preferred term **Vitreal mineralization**.

Vitreal mineralization consists of granules or larger extracellular deposits of basophilic material consistent with calcium salts within the vitreous. Mineralization may precede or be concurrent with inflammation, vitreal fibroplasia, and cartilaginous/osseous metaplasia.

Differential diagnosis: **Vitreal bone or cartilage metaplasia**.

Synonym(s): **Metastatic mineralization**; **metastatic calcification**; **dystrophic calcification**.

Vitreal persistent fetal vasculature (PFV) is a developmental abnormality of failed regression of the hyaloid vasculature (hyaloid artery, vasa hyloidea propria, and tunica vasculosa lentis) that extends from the fetal optic nerve to the lens, or persistence of other intraocular vasculature. This occurs as a spontaneous finding in all animals. The expression of abnormalities in the hyaloid vasculature affecting the vitreous, retina, optic nerve, and lens depends on the location and severity of the retained vasculature. Anomalies of persistence of uveal, scleral, retinal, and other intraocular vessels are less well characterized. In animals, the most common spontaneous expression of PFV is a variable-length, membrane-like remnant that projects from the optic nerve into the vitreous that may extend as far as the lens (persistent hyaloid vessels or persistent pupillary membranes). Often there are little to no other changes in tissues along the involution pathway, but posterior cataracts and retinal detachments may be present. More severe forms of hyaloid vessel PFV include hemorrhage, a vitreal fibrosis mass (persistent hyperplastic primary vitreous), cataracts or distorted lens, retinal atrophy or detachment, and microphthalmia as reported in genetically engineered mice with mutations in pro-apoptotic and Wnt signaling (Arf, p53, Bax, and Bak null mutations).



Vitreal persistent fetal vasculature (remnant of the hyaloid artery), vitreous, Sprague-Dawley rat, H&E.

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Vitreal persistent hyaloid vessels, see the preferred term **Vitreal persistent fetal vasculature (PFV)**.

Vitreal persistent hyperplastic primary vitreous, see the preferred term **Vitreal, persistent fetal vasculature (PFV)**.

Vitreal traction band, see the preferred term **Retina fibroplasia**.

Vitreous persistent hyperplastic primary vitreous, see the preferred term **Vitreous, persistent fetal vasculature**.

Vitritis, see the preferred term **Vitreal inflammation**.

Volume of distribution (V_D) is the theoretical volume (in liters or L/kg) that would be required to contain the total amount of drug administered if it were at the same concentration as in the plasma. After an intravenous dose of a drug, the concentration at time zero (C_0) is equal to dose/volume of distribution.

Vomiting, see the preferred term **Emesis**.

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W

Wallerian degeneration/Wallerian type degeneration are synonyms for axonal degeneration that imply that the cause is surgical or chemical transection of an axon. Due to the implied cause in this diagnosis, **Axonal degeneration** is the preferred term, but if it is known that the cause of axonal changes is surgical or chemical axonal transection, then Wallerian degeneration may be appropriate.

Weaning index is a term used in fertility studies for the ratio of pups alive at the end of weaning (postnatal day 21 in the rat) to those alive on postnatal day 4, expressed as a percent. It is a measure of the mother's ability to raise the offspring through the weaning period.

Wear and tear pigment refers to a golden-brown to yellow pigment that results from oxidation of cellular contents, frequently age-related degeneration of carbohydrate, lipid, and protein moieties in the cell. It is often associated with senescence and/or increased metabolic activity within the cell. These pigments may be seen in neurons within the brain, myofibers of the heart, hepatocytes, and many other cell types. Accurate identification of a golden pigment as lipofuscin requires a weight of evidence such as use of histochemical stains for oxidated lipids. Wear and tear pigments such as lipofuscin may contain certain metal ions (e.g., Fe, Ca, Cu, Al, Zn, and Mn). Therefore caution is necessary when selecting and interpreting special stains such as Prussian blue and von Kossa for the interpretation of pigments. Abnormal intracellular accumulation of lipofuscin is termed lipofuscinosis.

Differential diagnoses: **Ceroid pigment**; Lipofuscin pigment; **Hemosiderin pigment**.

White blood cell (WBC) (also known as leukocyte) is a general term for nucleated cells found in peripheral blood including neutrophils, lymphocytes, monocytes, eosinophils, and basophils. They develop from hematopoietic stem cells that reside in the bone marrow and are mature when released into the peripheral blood. Absolute numbers and proportions of WBCs are commonly evaluated using a hematology analyzer. WBCs are an important part of the immune system and are involved in innate (neutrophils, monocytes, eosinophils, and basophils), and acquired (lymphocytes) immunity providing protection against invading organisms. Depending on the species, there is usually a predominance of either neutrophils (humans and dogs) or lymphocytes (nonhuman primates, rabbits, guinea pigs, and rodents). There are many causes of increased WBCs, and the cause is generally related to the type of WBC affected. Causes include infection, inflammation, leukemia, stress, allergies, and immune disorders. Decreased WBC count is less common and may be caused by viral infections, autoimmune disease, chemotherapy, radiation, and sepsis.

White matter vacuolation is a descriptive term that refers to discrete, rounded, generally clear spaces (holes) in the white matter of nervous tissue that could represent either an artifact or a pathologic change. Recent international lexicon harmonization efforts have proposed that the term "white matter vacuolation" be reserved for changes caused by factors such as autolysis, careless handling during collection, improper fixation, or prolonged immersion in ethanol prior to or during histologic processing versus a pathologic process. Other terms that may be used in reference to artifactual spaces in the central nervous system (CNS) white matter include vacuolar artifact and alcohol artifact. An analogous clear-space artifact in the myelin sheath of peripheral nerves may be referred to as myelin bubbles. The occurrence of vacuoles unaccompanied by additional features such as gliosis, axonal swelling, leukocytic infiltrates, or necrotic neurons may be helpful in distinguishing artifactual vacuolation from pathologic changes that can cause clear spaces within white matter (e.g., demyelination, intramyelinic edema). In some cases, ultrastructural evaluation is necessary to differentiate artifactual and pathologic vacuolation. See **Vacuolar artifact**, **Alcohol artifact**, **Myelin bubbles**, **Demyelination**, and **Intramyelinic edema** for further information.

Synonym(s): **Vacuolar artifact**; **vacuolation artifact**.

Whole-body autoradiography (quantitative), see **Quantitative whole-body autoradiography** for further information.

Wilms tumor is the most commonly used term for nephroblastoma in humans. See the preferred term **Nephroblastoma**.

Wolffian duct remnants, see the preferred term **Mesonephric duct remnants**.

Woven bone is a result of unaligned osteoblasts which do not secrete type I collagen in an orderly lamellar pattern. The type I collagen in woven bone is randomly oriented and appears as scattered linear structures with no particular orientation under polarized light microscopy. Osteocyte lacunae are also irregularly placed and may appear larger than normal. Woven bone can be generated very quickly and is to be expected during early callus formation of fracture healing, and in very small amounts on primary spongiosa. Beyond these two instances, the presence of woven bone generally indicates a large, sudden increase in osteoblast activity occurring before the osteoblasts can become appropriately oriented to the bone surface. Because of the haphazard arrangement of the collagen lamellae, woven bone is weaker than lamellar bone. In rodents, woven bone often resolves by osteoclastic resorption shortly after the discontinuation of a chemotherapeutic agent administration.



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X

Xenobiotic-induced exocrine injury is a type of toxicity that occurs in the pancreas, albeit infrequently. This likely occurs as all potential toxicants absorbed from the intestines must pass through the liver via the portal vein before reaching the systemic circulation. The liver has a high capacity to bind, actively transport, and metabolize xenobiotics, thus detoxifying (or activating) compounds before they reach the pancreas. There is little information on the relative capacity of acinar cells to bind and transport xenobiotics into the cytoplasm. Pancreatic acinar cells contain the enzyme systems necessary for the metabolism of xenobiotics, including phase I (cytochrome P-450-containing monooxygenases), and phase II (conjugation) reactions. Isozymes of cytochrome P-450, an important enzyme system involved in the activation of carcinogens, are present within acinar cells. These enzymes are inducible by methylcholanthrene and dioxins. Three isozymes of glutathione S-transferase have also been shown to be present. In rat, the pancreatic acinar cells oxidize xenobiotics at rates several orders of magnitude lower than those of hepatocytes, but they appear to conjugate the resulting products at comparable rates. A variety of chemically related nonneoplastic lesions can occur in the exocrine pancreas. These include cell swelling, fatty change (ethanol, PCB 118), autophagocytosis, formation of residual bodies (azaserine, ethionine), necrosis (azaserine, ethionine, 2-aminoanthracene), atrophy (1-cyano-2-hydroxy-3-butene from cruciferous plants, cassava feeding accompanied by malnutrition, dietary iron, and androstenone in females), and hepatocyte metaplasia. Pancreatitis can also be experimentally induced by using caerulein or 2-aminoanthracene. Alcohol does not induce pancreatitis directly but predisposes to ectopic exocytosis upon postprandial stimulation.

X zone, see the preferred term **Adrenal gland X-zone**.



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Y

Yolk sac carcinoma is a malignancy derived from endodermal sinus germ cells which form two distinct layers characteristic of the parietal and visceral layers of the yolk sac. Refer to **Reproductive System and Mammary Gland** in Appendix 2 for further information.

Yolk sac tumor, see the preferred term **Yolk sac carcinoma**.



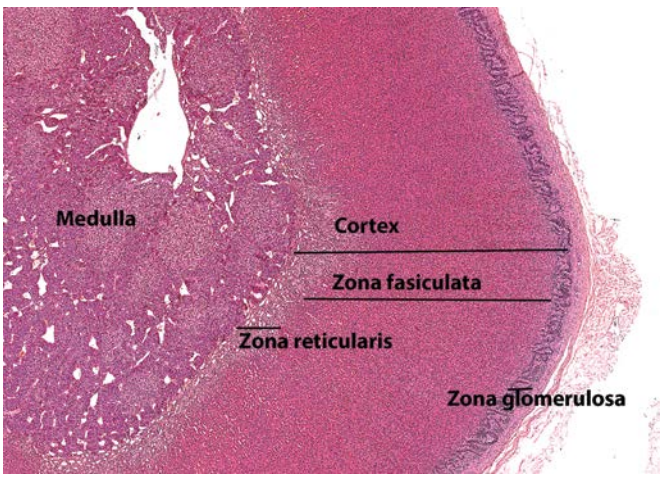
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Z

Zona fasciculata is the middle and widest zone of the adrenal cortex, where cells are arranged in bundles, or "fascicles." Its primary function is to produce glucocorticoid hormones, although it can produce small amounts of androgens. See Appendix 3 for more information.

Zona glomerulosa is the region of the adrenal cortex directly subjacent to the outer capsule, comprised of small, columnar cortical secretory cells. The cortical cells form curved cords and are contiguous with the zona fasciculata. The cells are surrounded by abundant capillaries, and typically have cytoplasmic lipid. Mineralocorticoids, such as aldosterone, are the primary secretory product and assist in sodium and potassium homeostasis and fluid regulation. See Appendix 3 for more information.

Zona reticularis is the innermost zone of the adrenal cortex, where cells are arranged in intersecting cords creating a reticulated or "net-like" appearance. Its primary function is to produce precursor androgen hormones (gonadocorticoids) from cholesterol, which are released into the blood to be taken up by the reproductive organs where they are converted to estrogen and testosterone. See Appendix 3 for more information.



Adrenal cortex with zona reticularis, zona fasciculata and zona glomerulosa labeled; minipig, H&E.

Zucker diabetic fatty (ZDF) rat is used in research as an animal model of type 2 diabetes (diabetes mellitus). ZDF rats are directly related to and derived from Zucker fatty (ZF) *fa/fa* rats. ZF rats are a partially outbred rat strain that carry a spontaneous mutation of the leptin gene (*fa*). These animals are hyperphagic and obese. Though insulin resistant, they are able to maintain normal blood glucose levels through increased insulin production and secretion. Occasionally, ZF rats spontaneously develop hyperglycemia; these animals are selectively inbred to derive the ZDF rats. Male Zucker diabetic fatty *fa/fa* (ZDF) rats develop obesity and insulin resistance at a young age, and then with aging, progressively develop hyperglycemia. This hyperglycemia is associated with impaired pancreatic β-cell function, loss of pancreatic β-cell mass, and decreased responsiveness of liver and extrahepatic tissues to the actions of insulin and glucose. Of particular interest are the insights provided by studies of these animals into the mechanism behind the progressive impairment of carbohydrate metabolism. This feature, among others, including the development of obesity- and hyperglycemia-related complications, is common between male ZDF rats and humans with type 2 diabetes associated with obesity.



Zucker diabetic fatty rat. (Image courtesy of Chares River Preclinical Services, Reno, NV.)

Zygote is a fertilized egg.

Zygotene spermatocyte is an intermediate type spermatocyte that develops from a leptotene spermatocyte over a 3-week meiotic prophase. Zygotene spermatocytes have thin, threadline chromatin which thickens as they develop into pachytene spermatocytes. In rats the zygotene spermatocytes are mostly present in stages XII and XII of the spermatic cycle. See **Spermatocyte** for further information.

Zymbal's gland adenocarcinoma, see the preferred term **Zymbal's gland carcinoma**.

Zymbal's gland carcinoma in rodents is a malignant tumor originating in sebaceous cells (sebaceous cell subtype), or duct epithelium (squamous cell subtype), or as a mixture of both subtypes in the Zymbal's (auditory) gland located near the opening of the outer ear canal. As this gland is unique to rodents, the presence of Zymbal's gland carcinoma in carcinogenicity

assessment is of questionable relevance to humans. Refer to **Special Senses** in Appendix 2 for further information.

Zymbal's gland duct cyst is a rare finding that occurs only in rodents and consists of distended ducts lined by attenuated or flattened stratified squamous epithelium, filled with sebum or sloughed keratin, respectively.

Zymbal's gland hyperplasia in rodents consists of a focal or rarely diffuse proliferation of sebaceous cells (sebaceous cell subtype) or duct epithelium (squamous cell subtype) in the Zymbal's (auditory) gland located near the opening of the outer ear canal. As this gland is unique to rodents, the presence of Zymbal's gland hyperplasia in carcinogenicity assessment is of questionable relevance to humans. Refer to **Special Senses** in Appendix 2 for further information.

Zymbal's gland hypertrophy consists of clusters of acini with enlarged epithelial cells containing increased pale eosinophilic, foamy or lacy cytoplasm. Increased numbers of cells may also be present.

Zymbal's gland inflammation consists of focal or diffuse accumulations of inflammatory cells (granulocytes, macrophages, lymphocytes, and plasma cells) in and around the acini, ducts, and interstitial stroma accompanied by other indicators of inflammation including interstitial edema, congestion, hemorrhage, and necrosis or cellular debris.

Differential diagnosis: **Duct-associated lymphoid tissue**.
Synonym(s): **Dacryoadenitis**.

Zymbal's gland sebaceous cell adenoma in rodents consists of a well-defined, but not encapsulated, normal-sized or larger than normal lobule of sebaceous cells in the Zymbal's (auditory) gland located near the opening of the outer ear canal. As this gland is unique to rodents, the presence of Zymbal's gland sebaceous cell adenoma in carcinogenicity assessment is of questionable relevance to humans. Refer to **Special Senses** in Appendix 2 for further information.

Zymbal's gland squamous cell papilloma in rodents consists of multiple papillary growths of cornified and stratified squamous epithelium covering connective tissue cores that extend into the lumina of the ducts of Zymbal's (auditory) gland located near the opening of the outer ear canal. Cellular atypia is usually absent, but adjacent sebaceous glands may be hyperplastic. As this gland is unique to rodents, the presence of Zymbal's gland squamous cell papilloma in carcinogenicity assessment is of questionable relevance to humans. Refer to **Special Senses** in Appendix 2 for further information.

Appendix 1: Overview of Drug Development, Nonclinical Safety & Toxicologic Pathology, and Important/Special Topics

John E. Burkhardt, Roy L. Kerlin*, James D. Fikes, Famke Aeffner, Deepa B. Rao**, and Shayne C. Gad*

DRUG DEVELOPMENT OVERVIEW

In modern pharmaceutical product development, new therapies are designed to treat a wide variety of clinical indications. Such treatments are intended to produce specific therapeutic effects that are often based on known mechanism/s of action. Typically, a common action may be an agonist or antagonist activity of a specific entity, such as an enzyme or other molecule possessing a regulatory function within a complex cascade or cell signaling pathway. The pharmaceutical product itself can range from being an endogenous or synthetic compound, a small molecule drug, to being a recombinant protein, a monoclonal antibody, an antibody-drug conjugate, an antibody-device combination drug product, or any one of numerous other modalities, such as the delivery of vaccines, cells, or genetic material to the patient.

This section focuses on traditional synthetic small molecule drug development, in order to inform the reader of key salient points related to the role of nonclinical safety assessment in the drug development process. A broad overview of the phases of drug development is depicted in Table 1. It includes a research and discovery phase, a nonclinical phase, a clinical phase, and a post-marketing phase. The drug development program for each therapeutic product is unique and is dependent on the drug type, indication, proposed dosing regimen, and specific inherent properties of the drug product impacting safety and efficacy. The following narratives are not intended to cover all aspects of product development; however, they do illustrate principles to provide a general overview for toxicologic pathologists.

Typically, toxicologic pathologists are involved in multiple stages of drug development. In the research and discovery phase, toxicologic pathologists are usually in a non-good laboratory practice (GLP) environment, working on various pathology endpoints conducted in animal studies. Other toxicologic pathologists are involved in a GLP environment evaluating safety in the nonclinical phases (GLP) of drug development. In safety evaluation, anatomic and clinical pathologists routinely evaluate tissues and body fluid samples from general toxicology studies (acute, chronic, single dose, and repeat-dose toxicology studies) for potential signals of drug-related toxicity as reflected by morphological and functional changes. Usually, with successful nonclinical testing in general toxicology studies and/or successful Phase 1 clinical trials, nonclinical animal toxicology studies often extend into Phases 2 and 3 of clinical development (e.g., longer-term repeat-dose toxicity, reproductive toxicity [fertility, embryo-fetal development, peri/postnatal development], and carcinogenicity studies). Tissues from reproductive toxicology and carcinogenicity studies (also conducted in a GLP environment), are evaluated by toxicologic pathologists for signals of drug-related toxicity affecting reproductive systems and carcinogenesis, respectively.

In the research and discovery phase of drug development (typically within large pharmaceutical companies), an ultra-high throughput (UHT) screen may be utilized to screen large numbers (e.g., thousands) of compounds from an even larger library of reference compounds. Medicinal chemists analyze data from UHT screens and compare structure-activity relationships with emerging hypotheses to design a molecular structure that confers a desirable mix of "drug-like" properties, including selectivity, potency, half-life, physicochemical properties, pharmacologic properties, and safety. The safety profile of a new compound derives from the pharmacological activity at its intended biological target (primary pharmacology), as well as other unintended activity, all of which are related to the chemical structure. Drug safety scientists work with chemists and discovery biologists to assess cohorts of compounds in primary and secondary pharmacology studies (described below in the Nonclinical Studies section) conducted in a variety of in vitro and short-term in vivo assays, to achieve an optimized balance of the drug's properties. Groups of structurally similar compounds, referred to as a "series," will often have similar biological characteristics. Safety team scientists evaluate many compounds to find the series possessing desirable properties, and subsequently select an individual compound with a superior profile. Usually, a single superior target compound, and occasionally a small subset of multiple target compounds with similar structure and desirable properties is/are nominated to go into the next phase of drug development—the nonclinical (also referred to as preclinical) phase. The term nonclinical is preferred over preclinical as the animal studies are continually conducted during the various

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** Contributions to the section Drug Development Overview co-authored by Deepa B. Rao reflects her own views and should not be construed as representing views or policies of her employer, the U.S. Food and Drug Administration.

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TABLE 1
Overview of Phases of Drug Development

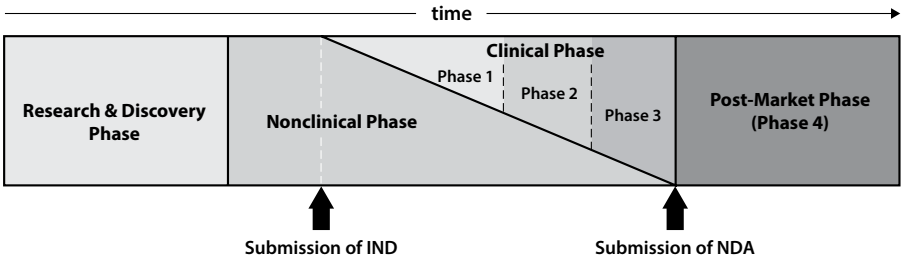


TABLE 2
Representative Nonclinical Toxicology Studies Relative to the Phases of Drug Development

Nonclinical Phase (Prior to First in Human Dosing)	Clinical Phase		
	Phase 1	**Phase 2**	**Phase 3**
Pharmacology studies	Basic ADME	Complete ADME	Special toxicology studies
Safety pharmacology studies	Toxicology studies to support dose/duration in 2 species	Chronic toxicology studies in 2 species	Pivotal toxicology studies
Genotoxicity studies (in vitro)	Complete genotoxicity (in vivo)	Male and female fertility	Carcinogenicity
Short-term toxicology studies in 2 species		Embryo-fetal development	Pre-postnatal development and offspring fertility

clinical phases of drug development and not limited to those conducted prior to the Phase 1 clinical trials.

The nonclinical phase of drug development typically involves initial safety testing of a single target compound via in vitro and animal toxicology studies to demonstrate safety prior to dosing in humans. Such nonclinical studies (described below in the Nonclinical Studies section) include safety pharmacology studies, genotoxicity testing, and general toxicology testing prior to dosing in humans. Each nonclinical program is unique and dependent on the inherent properties of the drug product impacting safety and efficacy under the proposed indication, population, and dosing regimen. The primary objective is protecting healthy volunteers/patients in the first-in-human and/or Phase 1 clinical trials. The typical nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals are outlined in the ICH M3 (R2) Harmonised Tripartite Guideline for Industry. Table 2 depicts a general overview of the various nonclinical studies in the context of drug development phases.

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) was established in 1990 to standardize drug development regulatory recommendations between Europe, Japan, and the United States. The ICH comprises global health authority professionals, academic experts, and industry experts from around the world, and has worked to produce a number of guidelines that describe expectations for new drug development, including nonclinical safety assessment. A complete list of the ICH Guidance documents can be found on the ICH website (http://www.ich.org/products/guidelines/safety/article/safety-guidelines.html). Compliance with ICH guidelines typically allows the sponsor to apply for marketing a single drug product across different geographical regions. Often, ICH participants have regional guidance documents as well, such as the Food and Drug Administration (FDA) guidances for marketing within the United States, the European Medicines Agency (EMA) guidelines for marketing within Europe, and the Pharmaceutical and Medical Devices Agency guidelines (PMDA) for marketing within Japan. For countries that participate in ICH, an ICH guideline will supersede a regional guidance. Countries not participating in ICH have guidances and expectations that are often similar to those of ICH countries and may be found on their respective websites.

Nonclinical Studies

This section provides an overview of the various pharmacology and toxicology studies that evaluate safety prior to clinical dosing. Table 3 illustrates the ICH Guideline documents most relevant to the nonclinical phases of drug development.

Pharmacology Studies (Typically Non-GLP)

Pharmacology studies are focused on understanding *what the drug does to the body*. Primary pharmacodynamic studies are geared toward understanding the mechanism of intended action, binding affinity to intended receptors, and showing proof-of-principle that the drug does what is expected when examined both in vitro and in vivo.

Secondary pharmacodynamic studies are geared toward understanding off-target effects, or those effects of a substance

TABLE 3
International Council on Harmonization (ICH) Guidelines on New Drug Development Relevant to Nonclinical Issues

Guidance Number[a]	Title
S1A-S1C	Carcinogenicity studies
S2	Genotoxicity studies
S3A-S3B	Toxicokinetics, pharmacokinetics
S4	Toxicity testing
S5	Reproductive toxicology
S6	Biotechnological products
S7A-S7B	Pharmacology studies
S8	Immunotoxicology studies
S9	Nonclinical evaluation for anticancer pharmaceuticals
S10	Photosafety evaluation
S11	Nonclinical safety testing in support of development of paediatric medicines (in progress)
M3 (R2)	Nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals
M7	Assessment and control of DNA-reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk

Note: Complete guidance documents can be accessed at: http://www.ich.org/products/guidelines/safety/article/safety-guidelines.html

[a] Guidelines starting with "S" represent safety subject matter; those starting with "M" represent multidisciplinary subject matter. Additional suffixes, such as "R," refer to Revisions.

and mechanism of action not related to the desired actions of the therapeutic product. Pharmacodynamic studies help elucidate the relationship between drug concentration and effect, or dose-response.

Pharmacokinetic Studies

Pharmacokinetic studies examine *what the body does to the drug*, and are designed to obtain information on the extent and duration of exposure to the drug, detect any potential active metabolites, and delineate routes or pathways of elimination. The results among several animal species are then compared to identify species-specific differences that help establish an exposure profile that can then be compared to those seen in humans. Specifically, a drug is investigated to yield information about absorption, distribution, metabolism, and excretion (ADME). Absorption studies involve determination of drug concentrations in blood with time after oral or parenteral administration. Common parameters include area under the curve (AUC), maximum (peak) plasma concentration (C_{max}), time to peak plasma concentration (T_{max}), and half-life of the drug ($t_{1/2}$). Comparison of animal and human pharmacokinetics should be considered once the human data are available to compare metabolic pathways and exposure differences, so that any toxicities seen in animals can be interpreted in a clinically relevant context. Distribution studies provide information on the extent and time course of drug distribution to and accumulation in various tissues. The "volume of distribution" is a parameter that is useful to assess drug distribution and uptake by cells. Clearance is a measure of elimination or excretion of a drug. The drug's metabolic profile is essential to the understanding of the drug's efficacy and toxicity, particularly when comparing effects seen in animals to those encountered in human clinical trials. When appropriate, the potential impact of drug-drug interactions on pharmacokinetics and pharmacodynamics of the test agent will need to be assessed. Toxicokinetic evaluations are generally conducted as part of most GLP toxicology studies. Toxicokinetic evaluations are generally not as comprehensive as other pharmacokinetic studies but provide data that allow direct comparison of exposures in animal toxicity studies to human exposures.

Safety Pharmacology Studies

These studies assess potential adverse effects on major organ systems. They typically include evaluation of effects on vital organs such as the central nervous system, and the respiratory and cardiovascular systems that may be related or unrelated to the desired therapeutic effect. The core battery of GLP-compliant safety pharmacology studies should be conducted prior to first-in-human exposure, according to the ICH M3 (R2).

Genotoxicity Studies

Genotoxicity studies are used to assess a drug's potential to cause genomic damage that could cause cancer and/or heritable defects. Short-term studies include a spectrum of in vitro and in vivo tests in mammalian and nonmammalian species to detect a compound's ability to cause an increase in genetic alterations, such as gene mutations and/or chromosomal aberrations. Per ICH M3 (R2) guidance document, results from in vitro tests are generally needed prior to conducting Phase 1 clinical trials. In vitro tests to evaluate whether a compound induces a genetic mutation or chromosomal aberration include the bacterial reverse gene mutation assay (Ames), mouse lymphoma TK assay, and/or Chinese hamster ovary (CHO) cell chromosomal aberration assay. Depending on the nature of the proposed Phase 1 study, a single-dose trial can be conducted with supporting data from an Ames assay, whereas a multiple-dose trial requires an in vitro or in vivo mammalian assay in addition to an Ames assay. In vivo

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tests for chromosomal aberration include tests in bone marrow cells or micronucleus assays in blood erythrocytes. A complete battery is needed prior to Phase 2. Specific guidance on optimizing the standard genetic toxicology battery for prediction of potential human risks and on interpreting results is detailed in the ICH S2(R1) guidance document.

General Toxicology Studies

Nonclinical data from general toxicology studies are used to characterize target organs, dose dependence, and the reversible nature of toxicity. Data generated from nonclinical studies are used to determine the initial clinical dose (based on allometric scaling between species or physiologically based pharmacokinetic [PBPK] models), dose escalation, and clinical monitoring. Typically, these studies are conducted in two mammalian species, one rodent and one non-rodent species, under GLP conditions. Appropriate species are selected based upon metabolism and pharmacokinetic profiles as well as ability to respond pharmacodynamically to the compound. The rodent species is usually the rat, or less commonly the mouse, and the non-rodent is usually the beagle dog or the cynomolgus monkey. More recently, the minipig is being used as a non-rodent model in general toxicology studies. Occasionally, animal models of disease can be used to evaluate the biological plausibility of the target compound for treating a specific disease. The duration of general toxicology studies is contingent upon the duration of the proposed drug dosing regimen. The route of administration tested is preferably the intended clinical route, while the duration and dosing frequency should, at least, be equal to the proposed clinical dosing regimen. Often the dose range finding nonclinical toxicity studies provide information on the maximum tolerated dose (MTD), the no observed adverse effect level (NOAEL), dosages and for longer-term repeat-dose studies, potential target organs, information on possible acute toxicity in humans, and an estimate of the safe starting doses for humans used to support initial clinical testing. Following single-dose short-term studies (1–10 days), the sponsor will usually conduct repeat-dose short-term studies (2 weeks to 1 month) or subchronic (13 weeks) or chronic studies (at least 6 months) to evaluate the toxic potential, reversibility, secondary effects, and pathologic effects over a longer period. Depending on the duration of intended clinical exposure (Table 4), chronic studies are generally 6 months' duration in rodent and 9 months' duration in non-rodent species. Chronic studies help identify the NOAEL and specific target organs or other toxicities that may develop upon prolonged exposure to the drug. Completion of nonclinical chronic toxicity studies (and carcinogenicity studies, when appropriate) will enable up to lifetime duration of dosing in humans unless there is an unusual safety concern that is specific to an individual program.

TABLE 4
ICH Table

Maximum Duration of Clinical Trial	Recommended Minimum Duration of Repeated-Dose Toxicity Studies to Support Clinical Trials	
	Rodents	Non-Rodents
Up to 2 weeks	2 weeks	2 weeks
Between 2 weeks and 6 weeks	Same as clinical trial	Same as clinical trial
>6 months	6 months	9 months

Note: Excerpted from ICH M3 (R2).

Reproductive Toxicology Studies

Although several strategies can be used to assess reproductive toxicity, the following three types of studies are generally used to assess toxicity across the complete reproductive cycle, before a drug product can be marketed:

1. A fertility study in at least one species (usually rat): Although standard histopathological evaluation of male and female reproductive organs in repeat-dose toxicology studies (≥2 weeks duration) is considered sufficient for early phase clinical trials, specific studies that address male and female fertility endpoints are required prior to large-scale or long-duration clinical trials (e.g., large-scale Phase 2 or Phase 3 clinical trials) in men, or in women of childbearing potential (WOCBP).
2. Embryo-fetal developmental toxicology studies in two species (usually rat and rabbit): The goal is to detect adverse effects on the pregnant female and the development of the embryo and the fetus consequent to the exposure of the female from implantation to closure of the hard palate. Unless there are specific concerns (indication, patient population) regarding potential effects on male/female reproductive systems, studies on embryo-fetal development are generally required to support large-scale Phase 2 or Phase 3 clinical trials. In the United States, assessment of embryo-fetal development can be deferred until before Phase 3 for WOCBP by using adequate precautions to prevent pregnancy in clinical trials.
3. Finally, a peri-/postnatal development study in one species (usually rat) is generally needed in order to support filing of the product for registration or marketing authorization. This study is designed to detect adverse effects on the pregnant and lactating female as well as on the conceptus and the neonates following exposure of the female from implantation through weaning.

All female reproduction toxicity studies and the standard battery of genotoxicity tests should be completed before inclusion, in any clinical trial, WOCBP not using highly effective birth control or whose pregnancy status is unknown.

Contingent upon the intended patient population for the drug, if pregnant women are included in clinical trials, all reproductive toxicology studies must be completed prior to clinical dosing (in addition to all genotoxicity studies). Women *not* of childbearing potential (permanently sterilized, postmenopausal) may be included in clinical trials without animal reproduction studies.

Carcinogenicity Studies

For products in which patients will be taking the drug continuously for 6 months or longer, or are taken intermittently to treat chronic or recurrent diseases, 2-year carcinogenicity studies in both mouse and rat are required to assess the risk for the product to cause or promote the growth of tumors. Increasingly, based on scientific validity, regulatory agencies may accept substitution of a 6-month mouse study utilizing various transgenic strains of mice, such as TgH-Ras mutant mice, in place of the 2-year mouse study. The route of administration selected should be the intended clinical route or a route that provides the greatest systemic exposure. Generally, carcinogenicity studies are not needed in advance of initial clinical trials "unless there is cause for concern" (such as belonging to a class of drugs with suspected carcinogenic potential), and are conducted concurrent with Phase 3 clinical trials. Harmonization of scientific and technical requirements by ICH guidances helps ensure that duplication of these studies is minimized. The FDA offers consultation or Special Protocol Assessment (SPA) on dose selection and study design issues for carcinogenicity studies for products submitted to the Center for Drug Evaluation and Research (CDER).

Special Toxicology Studies

The requirement to conduct special toxicity studies depends on specific variables impacting the proposed use of the drug. For example, local tolerance studies may be needed for drug products with new proposed routes of administration.

Drug Development Process

Following the conduct of above-mentioned nonclinical studies and prior to entering human clinical trials, final reports of all nonclinical studies supporting the proposed clinical dose and dosing regimen are filed together along with a collated summary of the nonclinical safety studies (a nonclinical overview), in the Investigational New Drug (IND) application along with the proposed clinical protocol to the FDA within the United States, in the Clinical Trial Application (CTA) to EMA within Europe, or in the Clinical Trial Plan Notification (CTPN) to PMDA within Japan. The application is essentially a process by which a sponsor informs the respective geographical regulatory authority of the intention to dose the candidate compound in humans.

Dosing in humans is the clinical phase of drug development that is subdivided into three pre-marketing phases of clinical trials (Phases 1, 2, and 3) and at least one post-marketing (Phase 4). Typically, human clinical studies conducted prior to marketing cannot be of a dosing duration greater than the dosing duration of the supporting nonclinical general toxicology studies for the proposed clinical trial. After approval of the proposed clinical protocol by the appropriate health regulatory authority, the first-in-human, or Phase 1, clinical trials generally are carried out in healthy volunteers (i.e., not the disease population) who may be compensated to participate in the study. Clinical study design usually includes a single ascending dose (SAD) paradigm that is often followed by a short-duration (e.g., 1–2 weeks) multiple ascending dose (MAD) paradigm. It is a goal of the Phase 1 human clinical trials to define the full range of tolerated doses and attendant pharmacokinetic parameters under conditions of a carefully monitored inpatient or outpatient setting. Ideally, pharmacodynamic properties, such as surrogate markers of drug activity, can also be assessed in this setting. In certain situations, the Phase 1 studies may be conducted in the intended patient population so as to expedite the benefit to patients. Examples include drugs approved for expedited review (such as those with serious unmet medical need that can be submitted via the Fast Track expedited program) or drugs that are unusually toxic (and exposure to heathy volunteers is unethical such as with some anticancer agents), or if the drug activity involves a mechanism of action that is only disease specific and scientifically irrelevant in healthy volunteers (not found in normal physiological conditions).

Upon completion of Phase 1, the sponsor will design the small-scale Phase 2 studies to investigate the drug in the intended patient population, with an objective to attain positive proof of concept (POC) that the drug will beneficially impact the disease process. The endpoints used to demonstrate POC are chosen by the sponsor and are used to help select appropriate doses for a pivotal Phase 3 trial. A drug that achieves positive POC is an asset of considerable value to the sponsor. Many new drug candidates fail to achieve a positive POC and are consequently terminated from development or repurposed for treatment of a different disease. Careful planning for pivotal, registration-quality Phase 3 studies is initiated and includes direct dialogue with the prevailing health regulatory authority about the primary (and secondary) clinical endpoints that, if achieved, will enable registration and marketing of the drug to patients. Generally, two separate pivotal clinical trials must successfully achieve primary endpoints in order for a drug to become a candidate for regulatory submission and marketing approval, although one well-conducted trial may be sufficient if the drug is shown to impact serious endpoints, such as prevention of hospitalizations or death. In the United States, expedited programs can include application via Fast Track, Breakthrough Therapy, Accelerated Approval, and Priority Review following application and approval with the FDA. Such approaches are often utilized for anticancer, antiviral agents, and orphan drugs with promising therapeutic potential.

In the United States, under the Pediatric Research Equity Act (PREA), sponsor companies are required by health regulatory authorities to consider whether their new drug is appropriate for treatment of juvenile or pediatric patients. Consequently, the sponsor must develop a pediatric plan, usually after Phase 1 in Europe after some initial human pharmacokinetic (PK) data are available, and prior to Phase 3 in the United States and Japan. Although many new drugs may not be required to undergo pediatric testing, those that do may need to have a juvenile animal toxicity study conducted prior to dosing in children. Juvenile animal studies are conducted on a case-by-case basis. In some cases, the juvenile toxicology studies (and the pediatric program) can be conducted after marketing approval for adults has been achieved, and this is termed as a "post-marketing" commitment or requirement.

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In general, as more clinical data become available, there is a gradual tapering in the number of nonclinical studies during later stages of drug development (Phase 3 clinical trials and beyond) compared to Phases 1 and 2 of clinical trials. Some safety issues that might arise during later stages of drug development include increased levels of impurities that may occur in batches/lots of drug product material being tested in clinical studies, with an increased likelihood that these impurities may be present in the to-be-manufactured product. These impurities may need to be assessed for genotoxicity and may require additional toxicity testing. Moreover, when clinical trials reveal major metabolites (i.e., $\geq$10% of total exposure to drug-related material) of the drug that are not present in animal studies at comparable levels, then such metabolites need to be qualified through additional nonclinical toxicology studies.

The testing paradigm outlined above covers a basic overview of the drug development process. Several specific topics such as immunotoxicity, phototoxicity, and hypersensitivity are not covered in this overview. Further, it should be noted that every drug is evaluated for safety on a case-by-case basis contingent on variables specific to the drug's pharmacologic and toxicologic profile, proposed indication, route of administration, selective target organ(s), and any off-target toxicity. As nonclinical safety studies are conducted, undesirable effects are often observed, and the sponsor company determines whether the target compound is safe to further advance. Toxicologists, pharmacologists, chemists, statisticians, clinicians, and clinical pharmacologists work together to understand cause-and-effect relationships of any adverse effects seen, and assess whether findings in animals are relevant to humans. In addition, it may be beneficial to identify biomarkers for toxicity that are premonitory to more severe effects, as a way to detect and prevent human adverse effects before they occur or become irreversible. Investigative or mechanistic types of repeat-dose nonclinical safety studies may be undertaken to better understand initiation, progression, reversibility, and ability to clinically monitor undesired new drug effects. Such investigative studies may utilize nontraditional endpoints, assays, and study designs to bring forward new information that may shed light on possible mechanisms for the effects seen and whether they possess relevance for humans under therapeutic conditions.

Depending on the proposed clinical dosing regimen, duration, and the intended patient population, general toxicology studies are designed to evaluate safety prior to first-in-human or Phase 1 clinical trial. Target organ toxicities, determination of doses or exposures at which they occur, and reversibility are assessed to determine the risk-benefit ratio for the proposed drug, dosing regimen, and indication.

It should be noted that the nonclinical phase in drug development continues during the clinical trial phases.

TOXICOLOGIC PATHOLOGY

What Is Toxicologic Pathology?

In the United States, toxicologic pathology is a subdiscipline of veterinary pathology, which is one of the specialty groups encompassed by the American Board of Veterinary Specialties of the American Veterinary Medicine Association. In other countries, similar bodies oversee the accreditation of veterinary pathologists, such as the European College of Veterinary Pathologists, the Royal College of Pathologists, and so forth. Veterinary pathology is principally composed of the major subspecialties of anatomic pathology (the study of diseases of tissues and organs, mainly through macroscopic and microscopic examinations) and clinical pathology (the laboratory analysis of bodily fluids such as blood, urine or cavitary effusions, or tissue aspirates). These subdisciplines incorporate modalities such as light microscopy, electron microscopy, immunohistochemistry, morphometrics, flow cytometry, imaging, stereology, biomarkers, and others.

According to the Society of Toxicologic Pathology, the subdiscipline of toxicologic pathology "is a medical discipline that applies the professional practice of pathology—the study of diseases—to toxicology—the study of the effects of chemicals and other agents on humans, animals, and the environment." As outlined in previous sections, pharmaceutical agents, or chemicals to which humans or animals may be either intentionally or unintentionally exposed, must be subjected to tests in order to reveal their inherent toxicity. The chemical or biological agents are exposed to animals, animal cells, or organ systems, and toxicologic pathologists are usually involved in the team of scientists that interpret the responses, which must be reported to governmental agencies that oversee the safety of human exposure at large. Much of the safety profile of a chemical or drug product depends on the interpretations of a toxicologic pathologist who studies the responses of cells, tissues, organs, and fluid components derived from animals exposed under the conditions of a toxicity or safety study.

Who Are Toxicologic Pathologists?

Toxicologic pathologists are the scientists responsible for studying and interpreting the toxic effects of pharmaceutical and chemical agents on cells, tissues, organs, and whole bodies. Because this is a medical subspecialty, and because nonclinical tests are conducted in a variety of animal species, most toxicologic pathologists have been, and still are, veterinarians. However, some physicians have trained themselves in animal pathology and work as toxicologic pathologists, especially in Europe. Individual members of some other scientific disciplines have also found a niche as toxicologic pathologists, although they will have some formal training, usually a PhD in a pathology-based subject. In the classical model, a toxicologic pathologist usually takes 4–5 years to achieve the Doctor of Veterinary Medicine degree (DVM, VMD, BVSc, or other equivalent degree) after a 4-year Bachelor's degree (BA, BS, BSc, etc.). The most common path is for a future toxicologic pathologist to subsequently undertake a formal residency training of 3–4 years in diagnostic veterinary pathology, earn a Master's and/or PhD in a scientific discipline (4–5 years), and often one or more postdoctoral appointments conducting basic or applied research. This adds up to approximately 18–22 years of post-high school education, meaning that entry

level positions are often filled by candidates in their early 40s. It is no wonder that toxicologic pathologists are highly paid professionals and are generally in short supply.

The Role of Toxicologic Pathologists

Toxicologic pathologists are pivotal in bridging the preclinical/clinical interface by virtue of their insight into the pathophysiologic mechanisms underlying toxicities observed in nonclinical studies. Pathologists interpret changes in the morphologic appearance of cells and tissues exposed to a chemical or biologic agent and integrate this with other effects measured in a study, using a thorough knowledge of clinical and basic sciences and a general knowledge of species differences in responses, including the likelihood that any particular effect may occur in humans. The first step in this role is that of hazard identification.

Hazard Identification

Toxic effects in preclinical studies are limited to clinical/behavioral signs observed in-life and in laboratory-based assays and observations, most of which are usually obtained after euthanasia of the test animals. Without interpretation and synthesis, isolated changes in any parameter may be real or spurious, may be caused directly by the test article, or may be a secondary effect of the primary toxicity, and may be important or unimportant. Pathologists have a unique insight into all of these questions, since they are trained to understand the range of normal variation and can link effects in clinical signs or laboratory-based assay data to changes in the morphology of cells and patterns of tissue or organ effects.

A well trained and experienced pathologist can tell whether cytoplasmic clearing in the liver is due to accumulation of lipid or glycogen or is the first indication of a degenerative effect on hepatocytes. Each of these effects may have quite different consequences, and the input of a pathologist can be a very efficient way to identify the hazards and possible pathogenesis of an effect at very small cost of resources and time. A critical component of this is the use of ancillary procedures to help define the exact nature of the hazard. Special stains including immunohistochemistry, electron microscopy and image analysis can be conducted, depending on the diagnoses and interpretations of the study pathologist. Within a very short time, a diagnosis of clear droplets within hepatocytes can be diagnosed as lipid with a special stain and thereby determined to be of limited consequence, or observed to be microvesicular, and resolved as swollen mitochondria under electron microscopy, quickly leading the team to look for new molecules which may be screened using a functional assay for mitochondrial toxicity.

A critical piece of hazard identification is effective communication in reports. The nonclinical safety or toxicity study report along with the data tables constitute raw data for pathology (discussed later) and is the main conduit to transfer information from the pathologist to physicians and regulators who are making decisions regarding human safety. In general, toxicity data should be identified and interpreted within the study report only as they pertain to the study at hand. Extrapolation to future studies or relationships between the current and past studies should be mostly avoided, unless they are critical to explain something within the current study. Furthermore, speculation about relevance for humans or about patients suffering from a specific clinical indication should be avoided. The reason to avoid dealing with human relevance within a study report is that, except in a few well understood cases, it is usually speculative and may be wrong. Even in cases where a finding may appear clear, further information may show otherwise. For example, test article—related exacerbation of chronic progressive nephropathy in rats, which has no counterpart in humans, may actually be a rat-specific response to a subtoxic effect on the kidney that may also affect humans. In another example, neuronal necrosis that appears to be a result of very low blood glucose may be partly caused by a neurotoxic test article effect. Both of these cases may really be relevant to humans, despite our first thoughts that this was a rat-specific, or secondary, phenomenon. The relevance to a clinical indication should be avoided because the clinical indication for a compound often changes over time. Something that may appear of low importance for a drug used to treat end-stage head and neck cancer may be critical to the development of a compound to treat pediatric asthma.

Another critical component of the nonclinical report, which is very relevant to pathology, is the assignation of adversity to toxicity. This is discussed in greater detail below, but in regard to hazard determination, a finding is adverse if it causes harm to the species under test. Furthermore, adversity should not be modified by conjectured human relevance, by speculation about potential pathogenesis, or by predicting the possible outcome in longer studies. In this regard, adversity should also not be predicated by whether or not a finding is reversible, or whether there are biomarkers of the effect identified in the study. Both of these are often critical to drug development decisions within a company, but not to the adversity decision. This is because adverse findings can be reversible (as in necrosis within a parenchymal organ without damage to infrastructure), or irreversible (such as retinal or neuronal necrosis). Similarly, both adverse and nonadverse effects may or may not have biomarkers. The importance of the determination of adversity for toxic effects is that they contribute to the establishment of the no adverse effects level (NOAEL) for the study, from which are established clinical dosing regimens and the designs of the clinical studies themselves.

Risk Assessment

Pathologists are uniquely positioned to understand the relevance of many toxicities and thereby allow a well-founded assessment of human risk. The appropriate place to integrate information across multiple studies and assess relevance for humans and risk for patients is in the nonclinical overview documents that populate the Investigational New Drug application (within the United States), marketing applications (within Europe) or investigators brochures, and so forth. In these documents, information about results from studies that either help rule in or rule out an effect as being relevant to humans may be discussed. This is not to

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infer that species relevance or the pathogenic implications of a finding for humans cannot be discussed within a study report, as it may provide important substrate for use within the overview documents. However, what is not helpful is undue speculation without appropriate data. For example, renal tubular degeneration in rats may cause consternation in a drug development team when identified as a hazard in a toxicity study. However, further experiments in dogs may not show this effect in that species. Subsequent experiments demonstrating that this effect in rats is due to a metabolite that is not produced in dogs or humans may effectively de-escalate that issue as a problem for the team. On the other hand, if the subsequent work identified the target receptor in rat and human renal tubular epithelial cells, but not in the dog, this immediately raises the likelihood that the effect is a real consequence of target modulation, which may be of relevance to human subjects.

Risk Management

Clearly the toxicologic pathologist is deeply involved in identifying and characterizing the hazards uncovered by administration of test articles to animals. In addition, their knowledge of comparative medicine and pathobiological pathways and mechanisms is invaluable for assessing the potential risk to humans of any changes occurring in the animal test species. It should therefore be obvious that the study pathologist, or at least the pathologist's opinion expressed within reports and represented by someone else knowledgeable in such matters (such as a peer review pathologist), should be a major influence when developing strategies to manage the risks inherent in dosing humans. In cases where the study pathologist is unavailable, such as when studies are conducted by external contractors, an experienced pathologist from within the company should be utilized to ensure that the pathology perspectives are accurately represented in compiled documents or at strategic meetings.

On-Target and Off-Target Toxicity

A critical question when conducting toxicity studies for pharmaceutical agents is whether an effect is a consequence of modulating the targeted ligand or receptor (on-target), or whether it is due to unintentional effects unrelated to the target (off-target). Off-target toxicity is relatively simple to deal with because it can either be considered acceptable as an inherent hazard of the test article after establishing a risk profile, or it may be eliminated by testing different molecules with differing structures in order to maintain target binding while attempting to engineer out the off-target effects. Pathologists can play a key role to help identify the nature and possibly the mechanism for the off-target effect to potentially steer the team toward building in vitro models in order to more quickly and cheaply screen compounds and develop structure/activity maps for the undesirable effect. However, when the toxicity is determined to be related to target binding, and especially if the toxicity is directly related to efficacy, the pathologist may be able to serve in an even more pivotal fashion.

Efficacy and Safety: A Continuum

Artificial separation of efficacy and safety issues is an old and erroneous notion in the pharmaceutical industry. Examples of this are legion, but a simple one is glucose lowering for diabetes treatment. As you increase doses of a drug to lower glucose into a harmfully low range, it is likely that the low blood glucose may reach levels that can cause neurological signs and even progress to tremors, convulsions, and neuronal death. The advantage of involving pathologists in efficacy model studies in the early phase of drug discovery is that they develop an understanding of all the changes associated with target modulation, and begin to understand the target organs for exaggerated efficacy and even the potential for target modulation at tissue sites other than those that were expected. An example of this is the way prostaglandin inhibitors used for pain relief may affect vascular tone and perfusion of sensitive, target-rich areas such as the renal papilla.

Small Molecule and Large Molecule

Another erroneous dogma that has largely disappeared is the idea that only small molecules have off-target effects because large molecules (i.e., biologics), which are usually proteins, are a "natural" component of the body and only bind to their associated ligand, thereby eliminating the issue of off-target toxicity. While this has some merit in that it is much less likely that a protein such as a human antibody will bind to hitherto unknown entities, this naïve concept does not take into account the possibility for "normal" binding to all sorts of receptors to which antibodies naturally bind (e.g., Fc, complement fragments, etc.), bringing them into close proximity to the ligand which the antibody is targeting. Furthermore, the natural redundancy built into most important ligand receptor systems within the body is staggering, and if we actually find a therapeutic target to which an antibody binds with no unexpected effects due to the unanticipated engagement of untargeted cells expressing a receptor with some affinity for our agent, we should consider ourselves lucky. Pathologists can avail themselves of target mapping using protein binding (immunohistochemistry) or gene expression (in situ hybridization) to assist with identification of such large-molecule off-target effects.

Why Is Pathology Data Different from Other Forms of Data?

What Is Pathology Raw Data?

Raw data under the good laboratory practice (GLP) regulations (U.S. Code of Federal Regulations – Title 21, Part 58) is defined in the General Provisions, Part 58.3. It has two components, namely that raw data are the original observations, and that these data are necessary for the reconstruction of the study. This means that any notes, even if on scrap paper, made about animals during clinical observation are considered to

be raw data and would have to be retained under these regulations. However, this is NOT the case for histopathology data. In the preamble to the GLP regulations, raw data for histopathology is defined as both the data tables and the pathologist's narrative describing the "pathology syndrome." The regulations state that a signed pathologist's report is required to create the raw data. This means that interim notes made during the pathologist's review of the specimens are not raw data and do not have to be retained. The key to this puzzle lies in the second component of the raw data definition—"are required for the reconstruction of the study." As a pathologist looks at more slides, including control tissues, they will refine their diagnoses and modify their interpretations based on understanding what the spectrum of changes in the tissues are telling them about the nature and etiopathogenesis of the lesions. Earlier iterations of the data tables are of no value in reconstructing the study since they are superseded by the final version containing the most accurate and refined diagnoses.

The Pathologist's Opinion and the Interpretative/Integrative Narrative

The point that the pathologist's narrative is necessary as a component of the raw data can be understood by the notion that the diagnoses in the data tables may not fully describe or define the nature of the morphological changes in the tissues. Fundamentally the diagnoses in the tables are simply a concise way for a pathologist to record their opinions about what they see, succinctly synthesized into a pathophysiologic mechanistic term. However, the nomenclature for a given lesion may vary for many reasons, and it may only be in the narrative that the pathologist can explain the understanding that underpins the particular spectrum of diagnoses in a particular study. For example, a diagnosis of "inflammation and necrosis, multifocal, random" in the liver could be interpreted in a number of ways. It could indicate that there is a primary inflammatory lesion scattered throughout the liver, which has some foci of necrotic cells present within the lesions interpreted as being produced secondary to inflammation. Or it could mean that there is multifocal necrosis as the primary event, with secondary inflammation. Such critical distinctions may be clear to the reviewing pathologist, and the pathologist's narrative may be the only place where such opinions are linked to morphological descriptions and thereby described, explained, and recorded.

Pathology Diagnoses in Nonclinical Studies

Incidence and Severity

As outlined above, the diagnoses made by pathologists reviewing specimens and other data from a study are succinct subjective opinions that attempt to best portray the often complex and sometimes subtle pathophysiologic mechanisms caused by administration of a test article. Integral to this are the additional modifiers of the diagnoses used to describe severity (minimal, mild, moderate, severe), distribution (focal, multifocal, diffuse), location, sub-location, cell type, and so forth. Although many modifiers may be used, it is most common to see only severity, or severity and distribution used, in order to simplify the data tables. Sometimes a descriptive note can be added to the diagnosis in order to describe other components of the lesion rather than add everything in to an unnecessarily long diagnostic string. The decision to use any or none of the available modifiers (lesions may be simply marked as "present" in some systems) is a prudential choice by the study pathologist in order to best depict the nature of each lesion. For example, a particular lesion may have varying distribution as well as varying severity. It may be that using both of these modifiers makes it confusing to illustrate the overall impact of the effect at each dose. For example, there may be a diffuse distribution of an effect at a minimal level which may need to be compared with a mild, focal distribution covering less than 10% of the tissue section. In such cases, it may be better for the pathologist to make a judgment of the overall severity alone using that single modifier, basing that decision on both the intensity of the lesion and the amount of tissue affected within the organ in a particular animal. It is important to allow the pathologist freedom to use the best method to show effects at each dose without tying them to a predetermined expectation, unless the protocol was designed for that purpose.

The Use and Abuse of Statistics with Pathology Data

Statistics must be used with caution when dealing with histopathology data. In 2-year carcinogenicity studies where just the incidence of the presence or absence of a lesion such as a neoplasm in treated groups is examined statistically with respect to control incidence, it seems simple enough. However, even in that case, there are a number of difficulties:

- The number of animals in each group may be different.
- Do you separate out benign and malignant neoplasms of the same cell type?
- There may be a multiplicity of neoplasms in a single animal—do you count all the tumors as separate incidences or do you combine and give them a value of one incidence per animal?
- Do you separately record a benign and a malignant neoplasm in the same animal, or just diagnose the most malignant?
- There may be two control groups used—should they be combined or treated separately?
- Animal survival is likely to be different in controls and treated groups, with older animals having a greater likelihood for tumor development.

Most of these difficulties have been generally well debated, and good methods exist for obtaining valid statistical conclusions from these types of studies; however, this highlights the difficulties that exist even with what appears to be relatively simple histopathology data.

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The problem of using statistics with histopathology data outlined above becomes even more of an issue with data that are more qualitative measurements, containing subjective assessments of severity, distribution, or other attributes that subcategorize the diagnoses. Histopathology data is a qualitative assessment which is often converted to a numerical system within many of the electronic data capture systems available in the industry. For example, a severity grade system such as minimal, mild, moderate, severe, and marked is often depicted as grades 1, 2, 3, 4, and 5, respectively within data tables for ease of reporting. However, this may create an illusion that these grades actually represent the proportional severity of a particular lesion; for example, that grade 2 is twice as bad as grade 1, and grade 3 is three times more severe, etc. Unless numerical data have been obtained objectively (e.g., using histomorphometry), this is usually not the case. In most cases the spread of severities is from grade 1, which represents the most minimal lesion possible, to grade 4 (or 5, depending on the system), which represents an end-stage effect of that change on the tissue or organ involved. The grades in between represent increased stages of the effect that may be characterized by more tissue affected, or by additional features such as progression from degeneration to individual cell necrosis to multifocal necrosis to regionally extensive damage and loss of tissue, perhaps with hemorrhage, and so forth. Therefore, statistics should not be generally applied to such data. The question "what is the average severity grade in each group?" is usually not logical. However, judicious use of statistics could be appropriate as long as they are applied with full knowledge of the caveats described here, and with the involvement of the pathologist who recorded the diagnoses.

Peer Review

Peer review is a regularly discussed and often misunderstood topic of great importance to the practice of toxicologic pathology. The definitive statement about peer review was published by Morton et al. (2010) as a series of recommendations endorsed by the major societies supporting toxicologic pathology around the world. This current narrative will not document every aspect of peer review, which is already achieved in the referenced paper, but will principally discuss the major points of confusion regarding the principles and practice of peer review.

The first point is to emphasize that this practice was not mandated by any regulations and was developed voluntarily by toxicologic pathologists in order to improve the quality of diagnoses and interpretations made to support nonclinical toxicity studies. Pathology peer review is something that occurs informally all the time, as a normal part of consultation and refinement of diagnoses. Multiple opinions help form the perspectives of the study pathologist (SP) as they review more material and gather opinions from colleagues who may have more recent experience with a particular lesion or organ system. What we refer to as "peer review" is simply a more formal documentation of this process. The outcome is a single set of tables and a narrative report which is agreed to by both pathologists (both PRP and SP), documented by a short memorandum containing the methods and materials used in conduct of the work, and signed by the peer review pathologist (PRP) with a statement that they agree with the diagnoses and interpretation of the SP. There is no raw data created by the PRP in this process. The final pathology report is signed by the SP and does not need to be signed by the PRP.

It is not recommended that peer review is conducted as a "reread" of the tissues with generation of a set of tables from both the SP and the PRP, with a documented reconciliation process to end up with a final set of tables. Since earlier iterations of pathology data are not raw data (as discussed above), they are not required to be archived and can be discarded. Indeed, they should be discarded (if they were ever created), since they do not reflect the opinions of either pathologist (either SP or PRP), who would only support the final iteration of the data tables and the final signed report narrative. This is the principle reason why pathology peer review should be conducted before the pathology raw data has been created (i.e., before the report has been signed). Pathology diagnoses or report narratives created prior to a final version therefore serve no purpose except to illustrate where pathologists may have differed in their opinions prior to an agreement on the final version.

If there is substantive disagreement between the SP and the PRP prior to report signoff, a formal pathology working group (PWG) formed by other pathologists (usually 3–7 members) who may be subject matter experts can be formed to conduct the peer review and document the outcome in a similar way to that done with the single PRP. In the event that a PWG is called together after the pathology report is completed and signed, the outcome of the review can be documented in a small report that should be archived with the study data.

Peer review of standard nonclinical studies usually requires review of all tissues from at least 30% of rodents or 50% of non-rodents of each sex in the highest dose group. Control animal review is not usually mandated but can be performed at the discretion of the PRP. Tissues designated as "targets" for toxicity in a study should be examined from all high dose and controls and all animals in the highest non-affected group. In recovery animals, only target organs identified at the end of the dosing period are required to be examined. Due to their size, carcinogenicity studies are treated differently. All tissues from 10% of rodents per sex are examined from the high dose. All neoplasms and all organs with neoplastic test article—related effects in a particular sex are examined. In addition, non-test article—related effects are looked for in all control animals, and in all animals in the highest non-affected dose group, as well as at least 30% of animals in affected doses (or at least sufficient to verify the effect at that dose).

It is critical to emphasize that the PRP is not only responsible for examining glass slides and verifying diagnoses but also for reviewing other study data to understand and concur with the interpretations of the SP as written in the pathology report. To do this, the PRP would need to review the report narrative and in-life clinical findings, organ weight tables, clinical pathology data, and other ancillary data such as any special stains, electron microscopy findings, and so forth. The understanding gained from these analyses helps the PRP

to understand how the SP created the diagnoses and crafted the narrative. Iterative consultation between the SP and PRP during peer review helps craft the best possible study report and tables of diagnoses. It must be emphasized though that the SP is entirely responsible for the content of the narrative and pathology tables. The job of the PRP is only to review, read, and suggest changes as necessary. It is only at the end of the process where both pathologists agree that the PRP can create and sign the memorandum documenting the interaction and eventual agreement by both partie.

REFERENCE

Morton, D. et al. 2010. Recommendations for pathology peer review. *Toxicol Pathol* 38: 1118–1127.

IMPORTANT/SPECIAL TOPICS IN NONCLINICAL SAFETY AND TOXICITY

Adversity/NOAEL in Toxicity Studies

The notions of "adversity" and the consequent "no adverse effect level" (NOAEL) have been used for over 40 years to assist regulators and clinicians to understand the effects of test articles used in nonclinical toxicity studies designed to assess the potential for human risk. However, despite general acceptance of these terms and numerous publications addressing various aspects of their use or abuse, there has been no universally accepted definition or guidance for their application in nonclinical drug development and regulation. Consequently, the Society of Toxicologic Pathology sponsored a working group to develop a set of recommendations addressing the use and communication of "adversity and the NOAEL" best practices (Kerlin 2015). The idea was to convey a universally accepted set of guidelines that would help sponsors communicate the nature of test article effects in nonclinical studies, and importantly assist regulators to develop greater confidence in the reports of these effects by the scientists most familiar with the tissue changes and laboratory parameters altered by the test article administration.

The STP article featured 10 recommendations that are outlined below with a short review of the reasons, concerns, and caveats associated with each.

REFERENCE

Kerlin, R. 2015. Scientific and regulatory policy committee: Recommended ("Best") practices for determining, communicating, and using adverse effect data from nonclinical studies. *Toxicol Pathol* 44: 147–162.

Adversity Is a Term Indicating "Harm" to the Test Animal

Many articles have attempted to encapsulate the meaning of the term "adverse." However, none of them encompass all possibilities, since as soon as there is an attempt to delineate the meaning in some practical way, a caveat can be found which is outside of wherever the lines were drawn. The beauty of the current definition is that it is so simple and complete, and it is up to the author to define exactly what "harm" means in the context of their particular study and their specific use of the word. Similarly, nonadverse connotes a lack of "harm" to the animal subjects, and the onus is on the authors to define exactly why.

The Decision about Whether or Not to Test Article-Related Effects (or a Group of Related Effects) in a Nonclinical Study are Considered "Adverse" or "Non-Adverse" Should Be Unambiguously Stated and Justified in Sub-Reports and/or the Study Report

Once an effect has been established to be related to the test article, the next choice for a report author is to determine whether the effect is adverse itself, or part of a cluster of effects that together are adverse. It should be made clear to readers which findings are adverse and which are not, and the reasons for the decisions. It is important to note that effects of a test article are usually associated with perturbations of a variety of parameters, and when these are clearly related to a single effect, the adversity decision can be applied to the spectrum of changes. This is most evident with effects on clinical pathology parameters, some of which may be designated adverse in and of themselves, such as low erythrocytes or platelets, but many of which are not in and of themselves adverse, but rather are "markers" of an adverse effect. For example, hepatocellular necrosis will result in an increase in the concentrations of markers in the blood such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST). These enzymes do not themselves "cause harm" but are markers of the harmful effect of the test article on hepatocytes. An example sentence:

> Hepatocellular necrosis observed in rats administered the high and intermediate dose was considered adverse, and was reflected in increased levels of ALT and AST.

In a similar fashion, many small effects that may or may not be etiologically or mechanistically linked may be "lumped together," if together they do not constitute an adverse effect. An example sentence:

> Small decreases in serum electrolytes (Na, Cl, Ca) and serum proteins (albumin and globulins) in high dose animals, coupled with a small decrement in body weight gain, with no significant effect on final body weight were not considered to be adverse due to the low magnitude of effect, no clinical evidence of poor body condition, and no change in food intake.

"Adversity" as Identified in a Nonclinical Study Report Should Be Applied Only to the Test Species and under Conditions of the Study

This recommendation refers to addressing adversity only with regard to the species being tested within the study. The three main components to this issue are human relevance, therapeutic indication, and exacerbation of background effects.

Human relevance can be discussed in a report as it pertains to test article effects, but the decision about adversity must be predicated only on effects on the test species within a study. Specifically, an otherwise adverse effect on a test animal

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should not be dismissed on the basis that this effect is "specific" to the test species and does not occur in humans. Such decisions are usually speculative and may be incorrect. The best place to make such decisions is in the nonclinical overview documents where multiple studies are pulled together to either reinforce or refute such speculation. An example may be an exacerbation of chronic progressive nephropathy (CPN) in rats caused by a test article. CPN is not known to occur in humans, so there may be a temptation to dismiss an otherwise adverse increase in incidence and severity of CPN at a particular dose as not relevant. However young rats usually do not have CPN to the extent that it would be determined to be adverse, so a test article effect that does this may be due to an "occult" toxicity to renal tubules which may manifest in rats as an exacerbation of CPN. Studies in other species may support lack of relevance (where no renal findings are noted) or refute it (where tubular degeneration may be observed in the other species), reinforcing the notion of limiting such speculation to the overview documents rather than primary study reports.

Therapeutic indication has been used inappropriately to modify adversity decisions because, for example, something that could be tolerated in late-stage human cancer patients may be completely unacceptable for patients with pediatric asthma. However, this is not appropriate because indications for drugs often change over time. If a study report written initially for a drug destined to treat cancer allows quite harmful toxicities to be designated as nonadverse, it will be problematic if the indication switches to a much less severe disease, or a much more sensitive patient population. Adversity decisions based only on effects on the test species and independent of the presumptive therapeutic indication are objectively accurate and able to be appropriately positioned within the overview documents used to support applications to run human trials, whatever the indication.

Exacerbation of background effects have been also inappropriately used to dismiss an otherwise adverse effect. But as stated above (with the CPN example given for human relevance), there is usually little evidence to discount the potential effects of a toxicity that causes the exacerbation. More often than not, the justification given is that the exacerbation is a consequence of stress, body weight loss, or debilitation resulting in higher levels of whatever background effect is being discounted. However, what is usually not discussed is the large number of studies from the same laboratory where similar levels of debilitation or stress may exist, but which do not show a concordant increase in the background effects in question. Where there is evidence such as a publication to back up these contentions, the reasoning is strengthened. But where such evidence is lacking, the presumption is that this may still be a direct toxicity that may be simply be expressed in the test species in a manner consistent with that species.

Toxic Effects on Cells, Tissues, Organs, or Systems within the Test Animal Should be Assessed on Their Own Merits

Speculation about whether a toxic effect is due to a primary toxicity or whether it is secondary to that effect, such as liver or kidney damage secondary to cardiac failure, may be important to discuss within a study report. However, such mechanistic pathophysiological speculations should rarely be used to dismiss such secondary effects as unrelated to the test article, since there are usually little data to verify such notions within the individual study. Even if the connections are very compelling, there may be an additional direct adverse toxic effect on a given organ.

Attributing an effect to suspected excessive pharmacology may also be important to discuss, but similarly, should not predicate the adversity decisions. Again, the idea may be wrong, and more importantly, suprapharmacological effects may actually occur in humans, need to be considered as a potential toxicity, and should not be dismissed as an "expected effect of pharmacology."

Finally, a tissue change may be adaptive and protective, and on that basis may be considered nonadverse. However, if the adaptive change is so extreme that it actually causes harm to the test animals, then it should be determined to be adverse.

In all three of these examples (primary vs secondary, excessive pharmacology, adaptation) it may be important to discuss these scenarios within the text of the report. However, none of these should be used to determine or dismiss an adverse effect, which should be established by evaluating the phenotype rather than the potential pathogenesis of the test article effects on the test species.

Communication of What Is Considered "Adverse" and Assignment of the NOAEL in the Overall Study Report Should Be Consistent with, and Supported by, the Information Provided in the Study Sub-Reports

Adverse effects established within sub-reports should carry through to the study report and be discussed, sometimes with additional information, as an adverse effect. On occasion, particularly with clinical pathology or safety pharmacology, there may be insufficient information to determine whether an effect of the test article is adverse. In these cases, the effect may need to be integrated with other information and the determination of adversity made within the study report only. An example of this is where the clinical pathology report is finalized prior to the anatomic pathology report, so that increases in markers of toxicity are not able to be coupled with the related adverse effect observed by the anatomic pathologist. Importantly, a NOAEL should only be established within the study report, built from the constellation of adverse and nonadverse effects recorded in the sub-reports, such as the anatomic and clinical pathology reports. However, a NOAEL should not be established within the sub-reports.

Communication of Adverse Findings and the NOAEL Should Include Direct Interaction between Staff within Different Contributing Scientific Disciplines

Communication between contributing scientists and the study director are critical to insure clear, cogent, and complete integration of study findings within and between sub-reports

(such as anatomic pathology, clinical pathology, safety pharmacology, etc.) and the overall study report. This is most important when a test article produces a series of effects that themselves may be of modest importance, but when reviewed together indicate an adverse effect. For example, slight hemoconcentration with modest neutrophilia, coupled with slightly decreased food intake, minimal individual cell necrosis in parenchymal organs, and slightly increased fibrinogen may paint a picture of a dose level that is adversely affected by the test article, but where each finding alone could be arguably determined to be nonadverse. Conversations between all key study scientists are necessary to insure complete understanding and consequently clear communications in and between sub-reports and the study report.

The NOAEL for a Test Article Should Be Communicated in an Overview Document Based upon Data from Multiple Studies

As discussed above, determination of the relative value of the individual adverse effects and NOAELs from multiple studies should be determined in an overview document, usually used as part of a regulatory submission (IND, NDA, marketing application, etc.). In these documents, it may be determined that a NOAEL established in a rat study due to marked exacerbation of CPN can be discounted since the rat did not express receptors for the test article ligand, and the monkey does, but did not exhibit renal toxicity. Similarly, the importance of the toxicities in light of the therapeutic indication, or the assessment of the potential for exaggerated pharmacology which may be able to be tracked with a biomarker, can be given weight in these documents, which can be rewritten for different indications if desired in the future.

In Order to Place Them in Appropriate Context, the Use of NOAELs in Data Tables Should Be Referenced to Explanatory Text

Removal of the NOAEL from contextual references is not recommended. The scientific context for establishment of the NOAEL may provide critical insight into appropriate risk assessment and risk management. For example, a NOAEL established from liver toxicity may be easily managed in human trials through biomarker monitoring. But understanding that retinal toxicity was observed as an adverse effect at the next highest dose may be more important as a possible risk for humans. Simply working from NOAELs in a table to set human doses or design clinical trials, devoid of the scientific narrative used to determine them, may result in unnecessary risks to human volunteers or patients.

Nonclinical Scientists, Including Toxicologists, Pathologists and Other Contributing Subject Matter Experts Who Interpret Data from Nonclinical Studies Should Be Active Participants in Assessing and Communicating Human Risk

It is well understood that there is variable concordance between preclinical and clinical toxicity, with some organ systems better than others. Similarly, although it is often true that studies in nonhuman primates predict human responses better than rodents, this is not always the case. When human clinical trials are being designed and the possible risks of toxicity are being reviewed, it is important to include the nonclinical scientists responsible for the studies being reviewed, or at least scientists with similar qualifications (toxicologists, pathologists, safety pharmacologists, etc.). These scientists are trained, and have experience in understanding species differences, including humans, and can bring appropriate information to help manage risks and design safe human trials.

All Available Data from All Nonclinical Studies Must Be Evaluated Together to Define Any Potential Toxicities and to Predict Human Risk

Risk assessment is an iterative process whereby information from multiple studies along with human trial data are reviewed and a risk management strategy applied. It is critical that all the data currently available be assessed together. For example, studies designed to understand potentially limiting toxicities may profoundly alter the risk profile. Knowing that a ligand receptor is or isn't present on human tissues may accentuate or diminish the risk for a toxicity identified in animal studies. Similarly, knowing if the toxicity is due to the parent compound or metabolite of a drug may be important if humans do not share the same metabolic pathway for the drug as the animal species demonstrating the relevant toxicity. In addition, as clinical trials continue and longer or different (i.e., reproductive toxicity, carcinogenicity, etc.) animal studies are conducted, the risk profile changes and thus the risk management strategy evolves.

Nonclinical Safety in In Vivo Testing: Use of Conventional Animals versus Alternative Toxicology Models

The biopharmaceutical industry constantly strives to improve the safety predictability of in vivo testing and the translation of these findings to the clinical setting. One foundational assumption in our approach to nonclinical safety assessment is that our animal model(s) can serve as accurate predictive models of human hazard. Perceived and actual weaknesses in this assumption serve as motivation to nonclinical safety scientists to search for the optimum use of animal models in the evaluation of new therapeutic candidates.

The concordance of findings in standard preclinical testing to human toxicity is reported to run as high as 71% for rodent and non-rodent species when combined (Olson et al., 2000). Alone, non-rodents and rodents have been predictive for 63% and 43% of human toxicities, respectively. Although the concordance is adequate, there is room for continued improvement. Safety issues in clinical trials have been reported as a major issue in Phase 1, with 62% of projects closed due to safety concerns, and this has remained an important problem in later development, with 33% of projects failing due to safety in Phase 2a and 12% failing in Phase 2b (Cook et al., 2014).

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Therefore, using the optimal animal model(s) for safety assessment may have significant benefit in enhancing our identification of bad actors and good candidates during the discovery phase, enhancing the translation of findings to humans, and therefore decreasing attrition during clinical development due to unexpected safety findings.

Traditionally, our choice of the animal species and models used in our toxicology studies has been influenced by experience, historical precedence, and regulatory requirements. However, with increasing complexity in therapeutic modalities, the greater sophistication with which we can create and evaluate animal models must also influence our thinking about animal model selection in nonclinical safety assessment. In addition, as guiding principles for ethical use of animals in testing, the 3Rs (replacement, reduction, and refinement) must be considered, as they have been included in international legislation and compulsory guidelines regulating the use of animals for scientific purposes.

Each type of animal (normal healthy or alternative animal model) chosen for nonclinical safety assessment will have strengths and weaknesses. Although using animal models such as knock-in transgenic mice containing the human target or a breed or strain with the spontaneous occurrence of the disease for toxicology testing may potentially improve the safety assessment, even optimal use of alternative animal models in preclinical testing will not result in an absolutely perfect predictability or understanding of toxicities that may be encountered in a clinical setting.

Regulatory Guidance

There are several health authority guidances available that comment on the use of animal models (conventional normal healthy animals or alternative animal models) in nonclinical general toxicology studies. Combined efficacy/tolerability studies are increasingly accepted by health authorities as components of nonclinical development programs such as those for cell and gene therapy products. It is important to start a dialogue with regulatory authorities early when considering the intense use of alternative animal models as part of nonclinical safety assessment program for efficient preclinical to clinical development transition. In general, ICH M3 and ICH S6 guide nonclinical studies to support clinical development. However, other information is incorporated into some other guidance documents that are primarily focused on the development of disease-specific therapies or indications. Some of the major guidance regarding animal model include the following.

FDA Guidance, Product Development under the Animal Rule

This guidance provides information and recommendations on product development when human efficacy studies are not ethical or feasible. Circumstances where this is most applicable would encompass the development of medical countermeasures for chemical, biological, or nuclear threat agents. This guidance provides information on the use of animal models of disease to support filing from an efficacy, but not a nonclinical safety assessment perspective. The guidance anticipates that the preclinical safety development program is conducted largely like those in a traditional regulatory pathway.

ICH M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals (January 2010)

This guidance provides direction on the length and timing of studies in order to support clinical trials as well as when studies in two species (rodent and non-rodent) versus one species may be required. There is no specific mention of using conventional normal healthy animals in these studies, but it is generally assumed to be the default. The guidance refers the reader to ICH S6 for appropriate nonclinical safety studies for biotechnology derived products.

ICH S6 Safety Studies for Biotechnological Products

This guidance is directed at biotechnology-derived pharmaceuticals. It supports a science-based, "case-by-case basis" for animal model selection for safety assessment and asks that toxicity testing is completed in biologically relevant species. If there are two pharmacologically relevant species (one rodent and one-non-rodent), then both species should be used for short term toxicology studies. This guidance notably recognizes that alternative approaches may be needed for nonclinical safety assessment by acknowledging that animal models of disease, to include spontaneous and induced models of disease, gene knockout(s), and transgenic animals, may provide some insight in nonclinical safety assessment. In addition, the guidance clearly states that in certain circumstances, studies performed in animal models of disease may be used as an acceptable alternative to toxicity studies in normal animals (e.g., in circumstances where the target is only expressed in animal models of disease). However, the principles of safety evaluation for biotechnology-derived pharmaceuticals are not different than that for new chemical entities.

FDA Guidance: Preclinical Assessment of Investigational Cellular and Gene Therapy (CGT) Products

The FDA CGT guidance is consistent with ICH S6 with respect to the importance of using a relevant species, and states that the assessment of bioactivity and safety should demonstrate a biological response to the investigational cellular and gene product similar to that expected in humans in order to generate data to guide clinical trial design. The guidance highlights that studies performed using alternative animal models may provide insight regarding the relationship to dose and toxicity. Due to specific features of CGT products (e.g., potentially prolonged duration of intended product effect, in vivo product persistence, complex mechanism of action involving interactions between the CGT product and the disease environment, invasive routes of administration), animal models of disease/injury may be preferable to healthy animals to assess the activity and safety of these products. Therefore, preclinical studies in disease/injury models are encouraged to better define the risk-benefit ratio associated with investigational CBT products. In addition, use of disease/injury models provides the

opportunity for possible identification of activity-risk biomarkers that may be applicable for monitoring in clinical trials.

EU/EMA: Guideline on the Nonclinical Studies Required before First Clinical Use of Gene Therapy Medicinal Products

Similarly to the FDA guidance, this guidance also considers and encourages the use of relevant models for preclinical testing including safety studies when considerations warrant such a decision. It stresses the species used should be one relevant for the expected toxicological effects based on the available biological/pharmacological data, and the choice should be scientifically justified.

Disease-Specific Regulatory Guidance

EMEA Guidance: Guideline on the Evaluation of New Medicinal Products in the Treatment of Primary Osteoporosis

In the EU, it is mandatory for stimulators of bone formation to have a preclinical safety package demonstrating the safety of the tested material in terms of bone quality. The guidance recommends use of the ovariectomized rat and others with estrogen deficiency, but the guidance acknowledges there are no completely satisfactory models of osteoporosis.

Hypertension (EMA/CHMP/29947/2013/Rev.3) and Lipid Disorders (EMA/CHMP/748108/2013)

Guidance for both of these therapeutic indications stress the need for preclinical data in relevant animal models evaluating the hypothetical effects on key safety aspects. More specifically, the guidance indicates that nonclinical data in relevant animal models evaluating the potential effect of the test drug on different safety aspects, including cardiovascular safety risk, should be conducted and provided as an instrumental element of the safety evaluation. Animal studies should focus, among others, on atherothrombotic findings, fluid retention, blood pressure, renal function, electrolyte homeostasis, cardiac functionality, repolarization, and conduction abnormalities (pro-arrhythmic effects), as outlined in ICH Guidelines (e.g., S7A and S7B). For certain agents, reactions relating to muscle and liver toxicity are of particular significance, as are local tolerance and immunogenicity depending on the nature of the medicinal product.

Standard Paradigm Using Conventional Animals The use of normal healthy (conventional) animals from two species, usually one rodent and one non-rodent, is generally considered to be the standard animal model paradigm for toxicity testing. Species selection is general based on a comparison of the pharmacologic activity, potency, and metabolic profiles between the proposed species and humans. Two species are generally considered necessary, because a therapeutic candidate may induce changes in one species differently than it does in another. As mentioned earlier, adverse effects found in two separate and diverse species have a much higher predicative power for the outcome of exposure in humans. Conventional models such as the CD-1 mouse, Sprague Dawley and Wistar rats, cynomolgus monkey, beagle dog, and increasingly the minipig are used almost exclusively for nonclinical safety assessment.

In rodents, usually the study is conducted in healthy rats, and less commonly mice are used. The non-rodent species is usually either healthy dog or monkey, but occasionally rabbit or minipig may also be used. Considerations for which species to use in the standard paradigm is influenced and guided by what is reported in the literature, previous experience of the investigator with the same class of drug, presence of target (monkeys may express a target molecule that is similar to that in humans, whereas dogs may not), drug availability (mice require significantly less compound than rats), costs (monkeys are very expensive to buy and maintain compared to dogs), as well as other considerations.

The standard paradigm is not restricted to small molecule development. Guidelines for species selection for biologics also indicate that toxicologic assessment should be performed in two relevant species if available—one rodent and one non-rodent. A relevant species is one in which the test material is pharmacologically active due to the expression of the receptor or an epitope. However, due to the high degree of species specificity that may be encountered with many biotherapeutics, a specific, although healthy animal model (i.e., genetically modified animals containing the target) may be required rather than conventional models to assess some aspects of safety (evaluate on-target activity).

Alternative Animal Models Alternative models are routinely used for nonclinical efficacy testing and are seeing increased use in animal toxicity testing. Alternative animal models or animal models of disease are diverse in nature, but can generally be placed into one of the following categories:

- *Spontaneous*: Result from a genetic (dogs with factor VIII deficiency), metabolic, or anatomical feature of a specific species/strain.
- *Induced*: Can be surgically, chemically, or immunologically induced.
- *Infection*: Includes bacterial, viral, fungal, protozoal, and parasitic pathogens.
- *Xenograft*: Patient-derived and cell-line−derived tumors in immunocompromised mice.
- *Transgenic*: Broad category of animals with a specific genetic modification induced by transfer of genetic material from another organism or removal of an endogenous gene.

Alternative animal models can be used to provide early safety assessment by incorporating safety-associated endpoints and biomarkers into efficacy studies using animal models of disease. This can provide early identification of potential target tissues and the impact of exaggerated pharmacology.

Alternative animal models are commonly leveraged to pursue hypothesis-driven investigation of findings in nonclinical toxicity studies or clinical trials. A better understanding of adverse effects observed in conventional animals and

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their potential significance to humans can be gained through the use of animal models of disease. This can be especially helpful if the adsorption, distribution, metabolism, and excretion (ADME) or pharmacodynamics of the therapeutic in development are different in conventional animals versus in the disease condition. Examples of this include testing agents for weight loss in normal animals, antihypertensive agents in normotensive animals, glucose-lowering agents in normoglycemic animals, and the use of transgenic animals with altered Phase 1 or 2 metabolism to better dissect and characterize any potential relationship between metabolism and toxicity. Animal models can be considered to investigate the pathogenesis of unexpected findings in a clinical trial.

Regardless how they are leveraged in nonclinical safety assessment, it is commonly found that alternative animal models are better for hazard identification than for establishing specific safety margins.

The use of animal alternative animal models must be carefully considered, as there can be many confounding factors (Table 5). When considering the use of a model, it is essential

TABLE 5
Considerations for Using an Alternative Animal Model

Functional/anatomic analogy to the human disease/injury of interest
- How similar are the animal model's genetic basis of disease and pathophysiology to that of the human disease? The majority of human diseases are not the result of a single gene mutation and the pathophysiology is frequently influenced by environmental factors as well as the complexity of a multiorgan physiology.
- How closely does the model recapitulate the human condition as far as signs and symptoms, laboratory parameters, and pathology (organ involvement and histologic features).
- Is the disease progression and outcome similar?

Inherent variability of the model
- How consistent is the model in the way it manifests the disease?
- Does it have low long-term survival?

Specific to genetically engineered animals
- Alterations in target may have significant adverse effects (embryonic lethal) that are not relevant to the therapeutic setting. This is most commonly associated with the global loss of a function due to gene deletion. A global loss of function from birth in a transgenic animal may have little relevance to the way candidate therapeutic are administered to patients for a limited period or on an intermittent basis. Conditionally modified animals can be used to control the temporal and spatial expression of the genetic mutation to enhance survival and/or better recapitulate the disease in humans.
- May have uncharacterized compensatory mechanisms or redundant pathways to augment or replace knocked out target.
- Pharmacological challenges and physiologic stressors may unmask subtle phenotypes.
- Using random transgenic integration techniques, insertions may not occur at the natural site of the genome. However, more frequently now, target gene mutation techniques are used to insert an engineered gene to a specific location to inactivate expression of the normal gene and creating a null mutation (i.e., "knock-out") or replacing an endogenous gene with a different functional gene (i.e., "knock-in").
- Regulatory sequences around the inserted sequence may function differently, thereby altering the spatiotemporal patterns and level of expression.
- May express one or a few human products of interest, but other proteins that interact with the human molecules are still of mouse origin.
- The physiological effects of human-mouse protein interactions may differ from the normal human-human protein associations.

Limited historical/baseline data for the model, sufficient knowledge of model-specific background lesions
- Is there sufficient information on the incidence, severity, and uniformity of background changes?
- Interpretation of findings may be difficult as to whether to attribute them to incidental age-related changes, anticipated primary or secondary manifestations of the modeled disease or condition, or true test article—related adverse and nonadverse effects.
- Animal models when compared to conventional animals may have unique pharmacokinetic/toxicokinetic characteristics, metabolic capabilities (CYP enzyme profile), and liver or kidney function that results in a model-specific ADME profile.

Technical limitations with the physiological and anatomical constraints of the model
- Immunodeficient mice may be too small for surgical implantations or other experimental manipulations.
- Is it feasible to access the target site for product administration and deliver a specific absolute cell dose (cell and gene therapy products)?

Operational considerations
- Is the model readily available?
- Are animals pathogen free?
- Genetically modified models may need to be rederived prior to scaling up production (takes months to years)
  - Expense to genotype each animal during the rederivation process.
- Can sufficient animals be prepared to perform an adequately powered investigative or toxicology study?
- Colony may be expensive and difficult to establish and maintain.
- GLP compliance of studies may be difficult, but may not be required.

Animal care issues
- Immunodeficient animals will require special housing and operational support due to their susceptibility to secondary infections.
- Can the animals be maintained over the intended duration of the study? Sufficient numbers of animals may have to be prepared (chemically or surgically induced) to guarantee enough animals are successfully modified to power the study to account for individual animal variation in creation of the disease and loss of animals during the study.

to understand it as well as possible. Any findings must be considered in the context of how well the model reflects the disease in humans.

It is important to remember, as previously stated, that there is not a single animal model that addresses all features of a disease or safety assessment nuances. Rather, alternative animal models tend to address certain aspects of the disease or disease process, for instance the development of characteristic lesions in tissues/organs. In addition, most models are applied in acute settings rather than chronic. The difference in temporal progression may limit the value of many animal models. Therefore, investigators need also to take into consideration the model and the time window suited to test the hypothesis in order to meet the aim of the study.

When implementing the use of an alternative animal model, a staged approach may be best initially. Performance of pilot studies involving the intended investigational product may assist in evaluating the suitability of a particular animal model in advance of a definitive nonclinical safety study. Moreover, multiple animal models may be necessary to adequately identify functional aspects and potential toxicities for a single product under study. In these situations, the preclinical testing paradigm may include the use of a combination of large and small animal models, multiple small animal models, or only large animal models.

Decision Tree

Use of alternative animal models of disease is generally driven by scientific necessity and/or to test a specific hypothesis that is difficult or impossible to address in conventional animals. This consideration is followed by whether there is an appropriate alternative model available, understanding relevant human pharmacology, human and animal model ADME, and the challenge of confounding effects inherent to the model, the indication of the drug, as well as the targeted human patient population. If these questions are satisfied, a final check is whether any limitations of the animal model still support its use in the anticipated context of use in nonclinical safety assessment. This can be best illustrated with a decision tree (Figure 1).

A Few Specific Examples The following section will provide a few examples of using animal models (focused on transgenic applications) in a nonclinical safety setting to highlight points previously made.

Conventional animals used for toxicity testing may have limited ability to predict treatment-related effects linked to the disease condition. As an example, recombinant human acid sphingomyelinase (rhASM) is being developed as an enzyme replacement therapy for patients with acid sphingomyelinase deficiency (Niemann–Pick disease types A and B), which causes sphingomyelin to accumulate in lysosomes. In

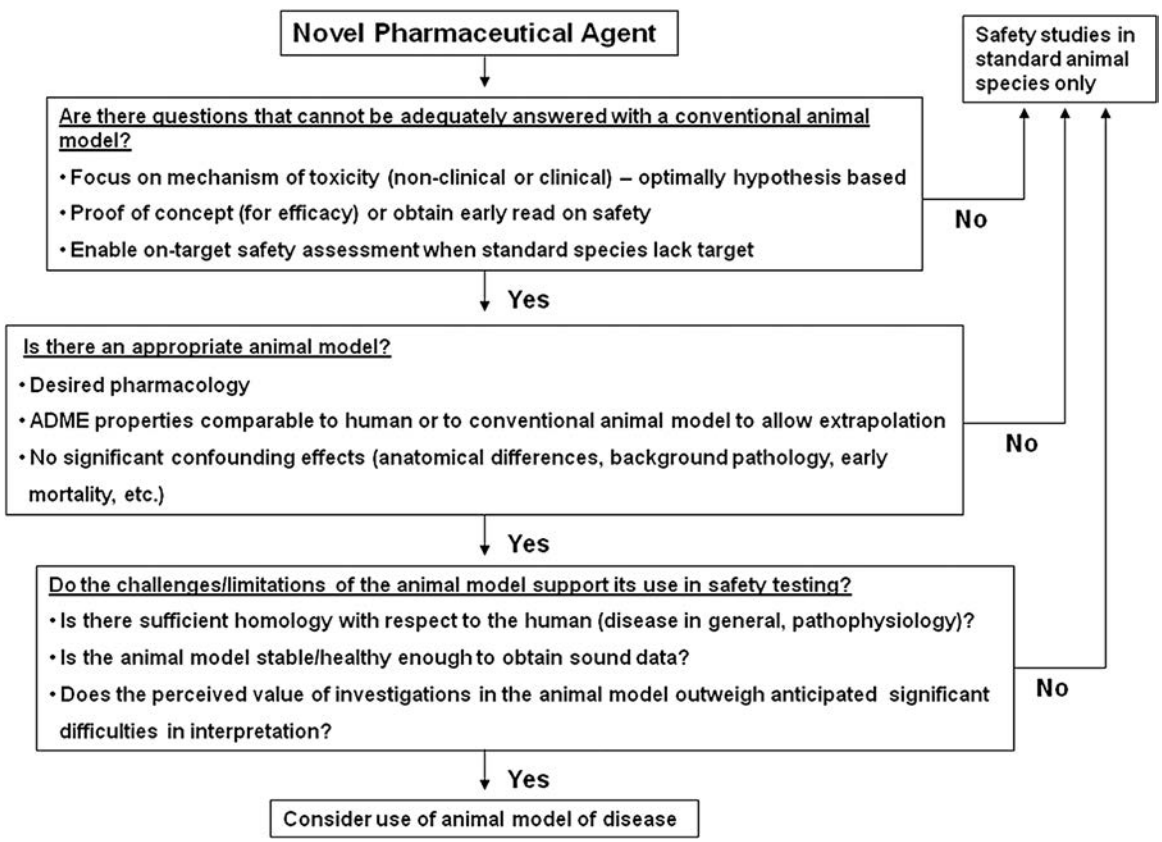


FIGURE 1 Decision tree. Selection of animal disease models for conducting nonclinical safety studies. (From Morgan, S.J. et al. 2013. *Toxicol Pathol* 41:508–518. With permission.)

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the acid sphingomyelinase knockout (ASMKO) mouse, intravenously administered rhASM reduced tissue sphingomyelin levels in a dose-dependent manner, demonstrating efficacy (Murray et al., 2015). When rhASM was administered to normal rats, mice, and dogs, no toxicity was observed. However, high doses of rhASM administered to acid sphingomyelinase knockout ASMKO mice resulted in unexpected toxicity characterized by cardiovascular shock, hepatic inflammation, adrenal hemorrhage, elevations in ceramide and cytokines, and death. The toxicity could be completely prevented by the administration of several low doses of rhASM prior to single or repeated high doses. This work in the transgenic animal model of disease characterized the mechanism of the observed toxicity as the rapid breakdown of large amounts of sphingomyelin into ceramide and/or other toxic downstream metabolites, which are known signaling molecules with cardiovascular and proinflammatory effects, and allowed the program to proceed.

One area seeing significantly increased use of transgenic models as a part of a core nonclinical safety assessment program is the area carcinogenicity testing. In regard to the identification of cancer hazard in humans, there is much debate on the use of the standard 2-year mouse bioassays. In the late 1990s, ICH adopted guidance for the use of short- or medium-term bioassays in transgenic mice as an alternative carcinogenicity assay. The two most popular transgenic mouse models of carcinogenicity risk assessment are the P53+/− mouse and rasH2 mouse. While both models show an increase in tumor formation following carcinogen exposure, the rasH2 model is the most widely used, primarily due to rasH2 mice being responsive to compounds that exhibit both genotoxic and nongenotoxic mechanisms of action. In recent years, the historical data set for these models has expanded and there has been clear regulatory authority acceptance of the models demonstrated, leading to 75% of all mouse carcinogenicity studies submitted to the FDA using the rasH2 for assessing carcinogenicity hazard identification (Jacobs and Brown, 2015).

As previously mentioned, a potential complication in the nonclinical development of some biologics is the lack of therapeutic target in conventional animals, and consequently no pharmacologically relevant species. This was the case with keliximab, an anti-CD4 monoclonal antibody in development for the treatment of rheumatoid arthritis that had specificity for human and chimpanzee CD4 only. To avoid the ethical and experimental limitations associated with chimpanzee studies and the limited ability to evaluate host defense and reproductive effects, a transgenic mouse expressing CD4 (murine CD4 knock-out, human CD4 knock-in) was developed as a surrogate animal model of disease for safety testing (Bugelski et al., 2000). A full safety assessment program was conducted using the HuCD4 transgenic mice, to include 3-dose, 14-day, 6-month toxicity studies, a micronucleus study for genotoxicity, and fertility and embryonic development studies. In addition, immune function studies using pathogen and tumor cells to assess for host resistance to infection and immunosurveillance to neoplasia were also conducted. This approach had the advantage over an attempt to use an antibody surrogate in that the assessment of pharmacology-related toxicity, nonspecific toxicity, and local tolerance could all be assessed simultaneously.

In summary, although toxicology studies should always be performed in a pharmacologically relevant species, this can be difficult with the specificity observed with many of our current and emerging treatment modalities and specific biotherapeutics. In some cases it may not be possible to evaluate the toxicity in a traditional toxicology species. Animal models of disease are continuing to be refined in parallel with our ongoing implementation of conventional and innovative therapeutic modalities, potentially leading to increased use. However, no animal model is perfect. A tiered approach to using animal models of disease should be considered, and it cannot be overstated that the advantages and limitations of any animal model should be well understood before using it.

Digital Pathology in a Regulated Environment

Digital images are commonly used in the practice of toxicologic pathology. The statement "a picture is worth a thousand words" is never truer than when a digital photomicrograph is shared with colleagues to illustrate features of a histologic change or immunohistochemical assay. With digital cameras and whole-slide imaging (WSI) systems now routinely available, digital images can easily be made during gross, histologic, and ultrastructural evaluations. Because digital images may be used in several ways, it is important to understand where regulatory guidance may influence the use of digital pathology and how to remain compliant. To help guide toxicologic pathologists, the Society of Toxicologic Pathology developed recommendations in 2007 for the use of pathology image data in a regulated environment. Although the technology has rapidly progressed and the regulatory landscape has evolved somewhat since then, these recommendations still serve as a sound foundation to work from. This section highlights the STP recommendations on the use of pathology images, including considerations emanating from the FDA medical device classification of WSI systems.

The STP recommendations include:

1. Pathology images (printed, electronic, or digital) that are used for the purposes of data generation (e.g., to make a diagnosis or for morphometric analysis) are considered raw data, and therefore must be authenticated and archived.
2. Methods for authentication of images used to generate data include initialing and dating a print of the image or annotation of the electronic image file in compliance with Part 21 CFR11.
3. Images used as raw data are subject to GLP procedures and controls in order to ensure data integrity. In support of this there should be written standard operating procedures (SOPs), testing/validation of equipment, training of personnel, etc.

4. Imaging systems and software used to support GLP studies must be validated. The GLP Compliance Statement for the study should include any exceptions to full validation.
5. Images that are not used for data generation are illustrative images and are therefore not considered as raw data and are not subject to GLP requirements.
6. Illustrative images should not be used to reassess or replace the study pathologist's written diagnosis.

In the United States, guidance influencing digital pathology originates primarily from the Code of Federal Regulations (CFR), Volume 21, Part 58 (Good Laboratory Practices [GLP]) and Part 11 (Electronic Records/Signatures). Relevant guidance focused on medical devices includes Parts 860 (Biomedical Device Classification Procedures), 862.9 (Limitations of Exemptions from Section 510(k) of the Federal Food, Drug, and Cosmetic Act), and 864.3600 (Microscopes and Accessories). Fundamental to operating in a compliant fashion is knowing whether a digital image will be used for illustrative purposes or in the generation of data. Digital pathology images can be used to generate data if a study pathologist reviews WSIs or digital electron micrographs to make original diagnoses or by applying image analysis to measure a feature(s) of the digital image or print (e.g., size, width, number). In contrast, a digital image for illustrative purposes is used only to highlight for others specific characteristics of a lesion or staining features. Illustrative images are not used to generate data, as the original diagnosis or morphologic assessment was made during necropsy (gross image) or during review of the glass slide. Study-related illustrative images are used in a variety of ways such as in pathology reports to convey specific aspects of a lesion, in responses to regulatory authorities to clarify questions regarding a finding(s), and shared with colleagues for consultation. When illustrative images are included in a GLP pathology report, the images will be archived as part of any GLP final report even though they were not used to generate data. Therefore, in this instance, these images must be properly labeled to enable auditing of the final report and archiving of the images a part of the final report.

The GLP regulations, 21 CFR Part 58, Section 58.3 (k), state that raw data: "may include photographs, microfilm or microfiche copies, computer printouts, magnetic media, including dictated observations and recorded data from automated instruments." Therefore, once an image is used for data generation in a GLP study, it should be considered raw data. Similar to other types of GLP study−associated data, digital images need to have processes for appropriate management as well to insure the integrity of the data. What image information is recorded and how it is transcribed onto the image raw data prints or captured in the image raw data metadata can be articulated in an image capture SOP. As a general rule, unless the details are provided in the study plan, SOPs should be in place for aspects such as personnel training, equipment testing and calibration, image capture and labeling, and image archiving methods.

Images produced from a non-GLP study are not required to be generated and managed using a validated digital pathology system. However, those images used to create data in a GLP setting are required to be generated using a validated digital pathology system. In regard to the validation of digital pathology systems, regulatory guidance in the United Sates is primarily linked to U.S. FDA GLP regulations (U.S. FDA 1978) (21 CFR Section 58.61, 58.63(a)) that state that equipment used in the generation, measurement, or assessment of data shall be of appropriate design and capacity. It also states that it should be adequately tested, calibrated, and/or standardized. Furthermore, U.S. FDA regulations for electronic records: electronic signatures (U.S. FDA 1997) (21 CFR Section 11.10(a)) state that it is necessary to validate a system to ensure accuracy, reliability, consistent intended performance, and the ability to discern an invalid or altered record. Therefore, when used in a GLP setting, computer imaging systems should be validated to the full extent, when possible. Any gaps in validation should be described as an exception in the GLP Compliance Statement for the study. Several other guidance documents exist globally that direct the validation of digital pathology systems. It is beyond the scope of this section to discuss the validation of digital pathology systems in detail. More information on validation is covered in other literature citations.

Within toxicologic pathology, review of WSIs rather than glass slide specimens for the primary evaluation of a study and/or peer review has been limited. Part of this is due to technical limitations such as slow image refresh speed versus the quick movement of a glass slide on a microscope stage with refocusing as needed. Also, likely contributing to this hesitancy is the challenge of WSI systems being assigned a demanding medical device classification. This classification is influenced by concerns over the use of WSIs in the field of human diagnostic surgical pathology, where the potential hazard of misdiagnosis due to inferior image quality could pose a serious public health risk. In the United States, medical devices are classified by the Food and Drug Administration (FDA) as Class I–III, with the greatest regulation associated with Class III. The three classes are based on the degree of control necessary to assure the various types of devices are safe and effective. Microscopes are considered Class I medical devices and have the minimal regulatory control. WSI systems are classified as Class III medical devices. Class III devices usually sustain or support life, are implanted, or present potential unreasonable risk of illness or injury. Most of these devices require premarket approval because general and special controls alone cannot reasonably assure their safety and effectiveness. Examples of Class III devices include noninvasive glucose testing devices, implantable pacemakers, human immunodeficiency virus diagnostic tests, cochlear implants, and medical imaging analyzers. It is expected that WSI system manufacturers, users, and the FDA will continue to work together to bring systems forward that have full approval.

When a digital image is used for image analysis, the image may be used as it originally appeared or transformed through

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the use of altered contrast or pseudo-color to enhance the image's utility for measurement. Validated pathology data systems should be able to automatically track all the modifications to the image. If not, then the final transformed image can be printed and then authenticated and archived as data. When image analysis is completed using a digital image of a slide-base specimen, it is important to remember the original slide-based specimen is also archived.

A few comments regarding electron microscopy (EM) are pertinent. Even when digital electron photomicrographs are not used to make the diagnosis, it is customary to archive some images. This is due to the fact that EM specimens are not perceived as durable as glass slides, and those archived images serve to document that an ultrastructure evaluation was conducted as part of the study. As with illustrative images of histopathology findings, images of ultrastructure findings that are used to illustrate specific features are not considered raw data but would be archived if included in a GLP study pathology report.

Whole-slide images may occasionally be used during the peer review process. The most common scenario is where the study pathologist views the glass slide and the peer review pathologist reviews WSIs. When discrepancies are found during the peer review process, then these should be resolved using the glass slide. The WSIs are considered the peer review pathologist's interim notes and can be discarded once the peer review is completed. However, if the study pathologist used WSIs as the basis for their primary read, then these images must be authenticated and archived along with glass slides.

Finally, since illustrative images are not used to make diagnoses, they cannot be used to supersede the pathologist's written diagnosis. Most digital illustrations only capture a part of the overall slide specimen examined by the pathologist. The study pathologist has reviewed the full slide and likely taken into account additional study information such as clinical pathology data and organ weight data as well as changes observed in other treated and control animals. Therefore, the review of selected illustrative images cannot be used to supersede the study pathologist's interpretation(s).

In summary, the use of digital pathology continues to increase as digital technology evolves. Following the highlighted STP recommendations should provide pathologists a framework to utilize digital images and remain compliant in a regulated environment.

Digital Image Analysis and Stereology in Toxicologic Pathology

The Basics of Image Analysis/Morphometry

Two-dimensional (2D) morphometrics (e.g., cell profile counts, linear dimension measurements) enhance the qualitative histologic diagnosis traditionally provided by a pathologist by adding quantitative and objective support to the observations. The recent addition of whole-slide imaging and digital image analysis (often considered together as "digital pathology") greatly increases the amount of information that can be obtained from histology sections. More importantly, digital pathology allows a more consistent (i.e., objective) and quantitative evaluation than is possible by manual observation utilizing the human eye alone.

Digital tissue image analysis (tIA) solutions have been used to provide/corroborate data from nonclinical toxicity studies as well as quantify differences in biomarker expression in clinical samples. Within the field of toxicologic pathology, digital image analysis solutions have been developed to aid in a number of situations, for example to characterize test article-related effects in rats by counting corpora lutea in ovaries, to characterize the disposition and toxicity in rats of PEGylated linkers for biopharmaceuticals, and to quantify mitotic forms as a pharmacologic and toxicodynamic endpoint in rats following drug treatment. Numerous additional solutions are in use in investigational pathology, with novel applications currently being published in rapid succession.

The majority of digital image analysis solutions can be classified as area-based (quantification of individual pixel color/intensity), cell-based, and/or object-based measurements. Cell-based measurements (quantification of pixels grouped by similar defined structure profiles) can be used to identify specific structures (e.g., follicles, glomeruli), define biologically separate tissue compartments (e.g., tumor vs tumor microenvironment [TME; stroma]), or interrogate certain tissue regions (e.g., tumor-TME interface). Examples of object-based applications (quantification of specific objects or events) include counting chromogenic in situ hybridization (CISH) dots per cell, assessing the size and distribution of intracellular vacuoles, and identifying and quantifying blood vessels or myofibers of various sizes. Solutions of varying levels of complexity and quality can be built using software packages that include ImageJ and FARSIGHT (both free) as well as commercial packages (e.g., Aperio toolbox), or by fee-for-service providers.

High-throughput digital pathology is performed most efficiently using a team approach. Teams include individuals with expertise in:

- Systems/algorithm engineering to create the analytical algorithms
- Disease process biology (e.g., cancer biology, immunology) to ensure output accordance with current biological understanding
- Biostatistics to aid in study design and data set analysis
- Anatomic pathology to evaluate algorithm performance

A pathologist's expertise is required for development of meaningful analysis algorithms, regardless of algorithm development knowledge. Pathology review/input is central to all major steps of the workflow, including influencing study design, confirming sample suitability (e.g., disease diagnosis and tissue quality), assessing sample staining (e.g., sensitivity, specificity, dynamic range), guiding image preparation (e.g., section annotation and algorithm approval), and preparing

reports (e.g., data interpretation and photomicrographic selection).

Multiple key points should be considered during pathology review. First, an evaluation of appropriate staining in the sample should be conducted, such as staining in the correct compartment and relevant dynamic range. Overstaining of slides obscures hematoxylin/nuclear detection used to find cells and limits the software's ability to identify subtle, meaningful differences in staining. Second, exclusion annotations (e.g., exclude necrosis, non-target tissue, and artifacts of staining or scanning) should be used to refine the sample to improve the quality of data. Third, a pathologist should evaluate if the algorithm correctly identifies and enumerates cells, adequately and correctly separates the tumor/TME compartments, correctly classifies cell staining for scoring, and, for CISH, correctly identifies and enumerates dots.

The Paradox of Image Analysis

Modern digital pathology techniques, particularly tIA, simultaneously overcome pitfalls of manual observer scoring and take advantage of an anatomic pathologist's ability to guide the tIA process, including using the output to make clinical decisions and testing hypotheses in the translational environment. These types of innovations in modern pathology practice challenge the status quo on selection of an optimal "reference standard" for biomarker scoring (i.e., tIA vs a manual approach). When questioning which data set should define ground truth, the inherent differences between manual and tIA-based scoring approaches should be considered. While using conventional manual scores as a reference standard for a novel tIA-based assay is the most one-to-one evaluation, manual pathology scores are inherently qualitative (or at best semiquantitative), subjective, and prone to bias. Image analysis-based approaches are designed to overcome the pitfalls of manual evaluation, which makes the use of manual biomarker scoring somewhat questionable for defining ground truth for tIA.

Several well-known visual and cognitive traps affect manual pathology assessments, which can be avoided through use of tIA as a scoring aid. Visual traps occur when the perceived image is different from objective reality (i.e., optical illusions) and include the illusion of size (Ebbinghaus illusion), the Craik-O'Brien-Cornsweet illusion, the Hermann grid illusion. Cognitive traps represent tendencies for biased thinking that lead to systematic errors or deviation from rational thinking, including number preference, avoidance of extreme ranges, confirmation bias, and inattentional blindness (reviewed in Aeffner et al., 2017).

The Basics of Stereology

Although previously considered cumbersome and time-intensive, recent advances in computer software have made stereology more practical and time-efficient. Stereology uses 2D sections to render 3-dimensional (3D) interpretation and quantification of the volume, surface, length, and enumeration of objects. To achieve this goal, stochastic geometry knowledge and statistics, such as systematic uniform random sampling (SURS), is applied to generate unbiased data. Sampling is randomized by starting tissue sectioning at a random point. This randomization renders extrapolation to 3D data valid. In addition to randomizing the location of sectioning, the orientation of sections, referred to as isotropy, needs to be randomized.

The stereological approach is particularly useful when interrogating nonhomogeneous tissues/disease processes. For example, in lung, kidney and central nervous tissue, stereology is commonly used to determine the number of certain structural elements (e.g., podocytes present in glomeruli) and is considered to be the gold standard for quantitative assessment. In specific situations, sub-sampling techniques such as the smooth fractionator can increase efficiency. Measurements at the final sampling level are conducted using geometric probes. These probes consist of test points, test lines, test planes, or a volumetric probe known as the Disector. When these probes interact with events on a microscopic section, these interactions can be tagged. However, the 3D structure of the reference space (organ or tissue) also needs to be taken into consideration. This is accomplished by keeping track of the distance between sections and the section thickness (utilized for enumerating objects by the fractionator method) or by estimating the volume of the entire reference space (to convert densities into absolute values).

CROs and Sponsored Company Interactions

Contract research organizations (CROs, also called CSOs—contract service organizations, or PDOs—pharmaceutical development organizations) span an amazing range of areas of expertise. Though there are some organizations that present themselves as turnkey "we do it all" (none truly do, at least at a single site), and many present themselves as "full service CROs," many offer distinct niche services and at best can readily subcontract other needed services. These include the following:

- For our purposes here, we are focused on those which perform toxicology/biocompatibility.
- Start by considering the history of such commercial labs. The oldest in the United States (Food and Drug Research Laboratories [FDRL]) opened in 1934, moved from suburban New Jersey to rural upstate New York, and went out of operation (under the FDRL name) in the late 1980s, though the facilities are still utilized (with some of the same staff) by Liberty Laboratories, which specializes in felines (domestic cats) for and in research.
- As the regulatory and legal requirements for toxicity testing increased, there were substantial increases in the number of both commercial and internal company labs.
- From the second half of the 1970s a number of toxicology laboratories (Industrial Biotest [IBT], the University of Miami–operated lab, Cannon Laboratories, Biassay Systems, Lilton Biometrics, Tegaris Labs, Bushy Run [in earlier years called the

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Chemical Hygiene Fellowship of Carnegie Mellon Institute—and perhaps the second oldest contract toxicology laboratory], Borriston/Midatlantic Laboratories, Primate Research Institute [PRI], Utah Biomedical Testing Laboratory [UBTL], HTI, and Oread Laboratories—to name a few) of significant size thrived but subsequently have gone out of existence. Additionally, just as in the industries they serve, there has been a continued series of acquisitions, mergers (the current Charles River Laboratories includes what were once Sierra Biomedical, BioResearch, Pathology Associates Incorporated, Argus Research, Redfield Laboratory [site now closed], Springborn Laboratories, WIL Research Laboratories, and TSI Mason [also until site closed] among its parts), and renaming (Hazleton becoming Corning, changing to Covance to A subsidiary of LabCorp, for example). These same trends and forces have been active in other types of CROs. There have been noticeable trends where protracted periods of acquisition would be followed by fragmentation into separate laboratories. As has continued shifting (and generally) expansion of scope of services in the evolution of some organizations (such as Quintiles and Covance) which offer to "do it all" for the pharmaceutical industry. Periodic economic changes also have served to reshape the "population" of CROs.

- Contributing to growth of this industry have been the extensive reductions and closings of internal company laboratories. There are now more than 200 such organizations providing services under GLP companies globally. Figure 2 provides a snapshot of example labs.

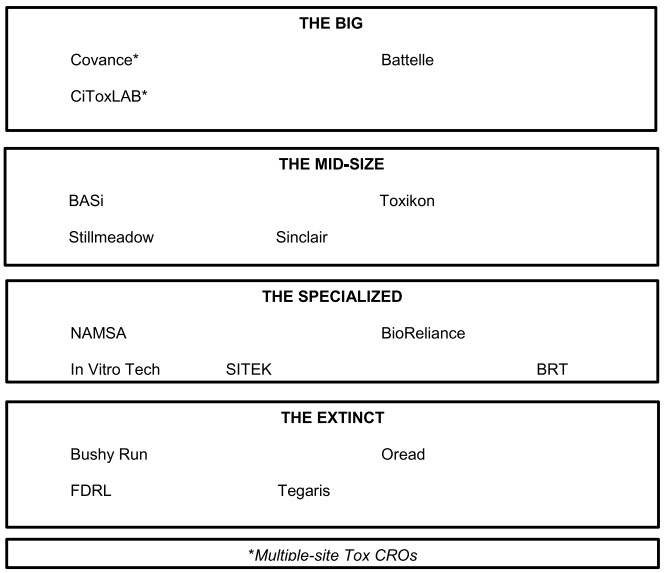


FIGURE 2 Examples of different types of toxicology CROs.

The relationship between client companies ("sponsors") and CROs is always contractual but should always function as a technical and scientific partnership. Because of pressures for CROs to compete on price (at least somewhat) while also meeting expectations of timeliness and quality, direct involvement in oversight by the sponsor or an agent (a consultant) is essential. Furthermore, the majority of CROs do not have their own pathologists, but rather subcontract this (and perhaps other) aspects of study conduct.

Selection of a CRO

Sponsor selection of one or more CRO(s), with or without guidance from a consultant, is based on a combination of factors that reflect the needs and preferences of the sponsor. Among these are (or should be) a balance of:

- Timeliness (when can the work be performed and by when can a final report be generated?)
- Technical capabilities of the CRO
- Dependability (the CRO doing what is required and on the promised timeline)
- Communication (advising sponsor of programs and any problems encountered in a timely manner)
- Quality
- Compliance (with regulatory guidelines, protocols, and SOPs)
- Location (Most CROs are not in the most convenient locations—an issue if monitoring/auditing of study conduct is required or desired. CROs in India and China offer significantly lower prices but not as extensive a range of services and are even more difficult—and expensive—to monitor.)

Good Laboratory Practice

In the United States, being a GLP laboratory is by self-proclamation. Once FDA or EPA receives one or more reports from the CRO as part of a submission, then they will (if there is an issue) make an inspection trip to the CRO or put such an inspection on a schedule for the appropriate regional office to perform periodic inspections.

Elsewhere in the world, CROs are granted GLP status after inspection and audit by either a regulatory authority or an authorized body. If successful, a facility GLP registration certificate and number are provided.

Vaccines

Vaccination was one of the earliest mass success stories for therapeutics, and also one of the earliest areas of regulation of therapeutics in the United States (Table 6).

Vaccination against viral and bacterial diseases has been one of the success stories of human and veterinary medicine. Probably the most outstanding examples of the effectiveness of vaccination are the eradication of smallpox and near eradication of polio. In 1967 between 10 and 15 million cases of smallpox occurred annually in some 33 countries. By 1977 the last naturally occurring case was reported in Somalia. Polio too has been controlled in developed countries; for example, the number of cases in the United States was reduced from over 40,000 per

TABLE 6
Historical Perspectives of Biologic Therapeutics Regulation

1902	Federal Virus, Serum and Toxin Act/PHS (after tetanus contaminated diphtheria antitoxin led to deaths of ten children). Intent was to ensure safety, purity, and potency.
1937	Division of Biologics Control/NIH
1955	Division of Biological Standards established (polio vaccine)
1972	Bureau of Biologics/FDA
1982	Bureau of Biologics merged with Bureau of Drugs ⇒ National Center for Drugs and Biologics
2002	Responsibility for regulation of biological substances divided between CDER and CBER. FDA Center for Biologics Evaluation and Research (CBER).

year in the early 1950s, before a vaccine was available, to only a handful of cases in the 1980s. Diphtheria is now almost unheard of, yet over 45,000 cases in 1940 led to 2480 deaths from diphtheria in the UK (similar numbers to those who died from AIDS in the UK in the entire 1980s). This has been reduced in the UK to only 13 cases and no deaths from the bacterium between 1986 and 1991. The scale of the problem is enormous—over 10 million deaths worldwide per year are due to infectious disease. World Health Organization (WHO) figures suggest that cancers, circulatory problems, and injuries cause fewer deaths in developing countries than infectious diseases.

The process of developing vaccines is becoming increasingly complex due to the nature of the infections being protected against, the nature of the cultures in which the effected individuals live, and societal concerns as to vaccine safety (Plotkin et al., 2008). Kaufmann (1996) provided an excellent addressal of this process and the inherent problems.

Approaches to Vaccination

There are two classical strategies for vaccination. One involves vaccination with either killed pathogenic organisms or subunits of the pathogenic organism. The other utilizes live attenuated viruses or bacteria that do not cause disease but have been derived from the pathogenic parent organism.

Inactivated vaccines are made from virulent pathogens by destroying their infectivity, usually with β-propiolactone or formalin, to ensure the retention of full immunogenicity. Vaccines prepared in this way are relatively safe and stimulate circulating antibody against the pathogen's surface proteins, thereby conferring resistance to disease. Two or three vaccinations are usually required to give strong protection, and booster doses are often required a number of years later to top up flagging immunity.

Subunit vaccines can be seen as a subcategory of inactivated vaccines because similar considerations apply to subunits and whole organisms. Doses, routes, duration of immunity, and efficacy of these vaccines are all comparable. In this case a part of the pathogen, such as a surface protein, is used to elicit antibodies that will neutralize the infectivity of the pathogenic agent. The widespread use of hepatitis B virus surface antigen purified from the blood of carriers (or more recently from recombinant yeast) shows that this can be a very effective way to immunize. Hepatitis B virus surface antigen, the product of a single gene, assembles into a highly antigenic 22 nm particle which if used in three 40 μg doses at 0, 1, and 6 months gives virtually complete protection against infection with hepatitis B virus.

About half of all vaccines have traditionally been from live attenuated mutants of parent pathogenic organisms (Walker and Gingold, 1993). In effect, live vaccines mimic natural infection yet produce subclinical symptoms and elicit long-lasting immunity often giving rise to resistance at the portal of entry. Most of today's attenuated vaccine strains have been derived by a tortuous, often empirical route involving passage in culture until the pathogen is found to lose its virulence. This loss of virulence is tested in animal model systems before being tested in human volunteers. For example, the vaccine used to immunize against tuberculosis was derived after 13 years' passage in bile-containing medium by Calmette and Guerin (hence the name BCG—bacille Calmette–Guerin).

Genetic Engineering and Vaccine Development

Since 1986, the USFDA has approved 22 vaccines (Table 7), half of them from a genetic engineering (and all, of course, from a biotechnology) source. The cells used for such genetic engineering production of vaccine can be mammalian, insect, or bacterial.

The WHO guidelines on nonclinical evaluation of vaccines, WHO Technical Report Series No. 927, Annex 1 (2005), which is very similar to but more detailed than U.S. regulations, is the default regulation. The following sections are based on this guidance. Table 8 summarizes the nonclinical safety assessment process.

The first issue in the study design is vaccine selection of an appropriate animal model. The issue of what constitutes a relevant animal species is one that deserves careful consideration prior to any safety assessment. A primary consideration should be that the species chosen should be "responsive" to the vaccine; that is, the animal should develop an immune response following vaccination. Ideally, the animal should be sensitive to the pathogenic organism or toxin against which the vaccine is being developed. In general, the FDA and EMA has required only one relevant animal species, although exceptions may occur on a case-by-case basis. Generally, the relevant model tends to be a small animal (rodents or rabbits), with nonhuman primates not being used unless the vaccine candidate characteristics dictate this model.

The route of administration, dose, and dosing regimen chosen for toxicity studies should duplicate the intended route of clinical administration as closely as possible. This can

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TABLE 7
Vaccines Approved by the FDA Since 1986

Vaccine	Indication	Date Approved	Company
Recombivax HB	Hepatitis B	June 23, 1986	Merck, Chiron
ProHIBIT	Haemophilus influenza B	1988	Connaught
Pedvax	HIB	1989	Merck
Engerix-B	Hepatitis B	1989	SmithKlineBeecham
Tetramune, Hib TITR Haemophilis b, diphtheria CRM 197 protein conjugate	Bacterial meningitus	Jan. 1991	Lederle-Praxis Biologics/American Cyanamid
IPOL	Poliovirus vaccine inactivated-injected	1991	Inst. Merieux
Acel-Imune	Diphtheria, tetanus toxoids acellular pertussis vaccine	Jan. 6, 1992	Takeda Chemical Industries / Amercan Cyanamid
Tripedia	Diphtheria, tetanus toxoids and acellular pertussis	Aug. 20, 1992	Connaught Laboratories Inc.
JE-VAX	Japanese encephalitis	Dec. 18, 1992	Connaught/Biken
Enzon	Bubonic plague	1994	Green Labs
Typhim Vi	Typhoid	1994	Laboratories Inc.
Havrix	HAV	Mar. 1995	SmithKlineBeecham
Varivax, Varicella Virus Vaccine Live	Chicken pox	Apr. 10, 1995	Merck
VAQTA	Hepatitis A	Mar. 29, 1996	Merck
COMVAX	Haeomophilis B and hepatitis B	Oct. 2, 1996	Merck
Infanivir	Diphtheria, tetanus, and pertussis (DTP)	Jan. 27, 1997	SmithKlineBeecham
Rabovert	Rabies (pre- and post-exposure)	Oct. 27, 1997	Chiron/Behring
Certina	DTP	Jul. 29, 1998	North Amercan Vaccine
RotaShield[a]	Rotavirus	Aug. 31, 1998	Wyeth
LYMEriv	Lyme disease	Dec. 21, 1998	SmithKlineBeecham
Prevnar	Pneumococcal disease	Feb. 17, 2000	Lederle
TWINRIX	Hepatitis A & B	May 11, 2001	SmithKlineBeecham

[a] Subsequently withdrawn.

TABLE 8
Vaccine Test Matrics

Test Requirement	Species
Initial Clinical Trial/IND Requirement	
1. Acute toxicity in rodents (intended route and IV[a])	R/M
2. Acute toxicity in non-rodents (intended route)	D/S/P
3. Pivotal/repeat-dose in rodents (14–28 day intended route)	R/M
4. Pivotal/repeat-dose in non-rodents (14–28 day intended route)	D/P/S
To Support Continued Clinical Development and to Support Marketing Approval	
5. Immunotoxicity[b]	TBD

Note: All studies described above must be performed GLP.
Abbreviations: R = Rat, M = Mouse, D = Dog, S = Pig, P = Primate, B = Rabbit, TBD = To be determined.
[a] Recommended.
[b] May be required.

be difficult when using small animal models, particularly if novel administration devices are employed. Generally, a full human-equivalent dose is preferred by regulators. However, many vaccines are administered in a dose of 500 μL; while this volume can be given intramuscularly in humans, it is impractical for rodents. Dividing this volume into multiple dose sites is one strategy, although admittedly less than ideal. Route of administration can also become a problem with mucosal administration, particularly with nasal vaccines where the human nasal environment is not easily replicated in animals. Finally, dose frequency (for vaccines that require multiple vaccinations, such as recombinant vaccines) might not be practical in animals with a short lifespan, such as rodents. In these cases, an abbreviated or compressed schedule is usually acceptable. Although dose is an important concept in toxicology, it is probably less important for safety assessment of vaccines as long as the amount administered to animals is demonstrably immunogenic.

Vaccine toxicology studies can be conducted using either single-dose or repeated-dose paradigms, depending on existing knowledge about the vaccine candidate. For repeated-dose studies the number of doses should generally be N + 1 (N = number of doses to be given to humans) in an effort to gain a margin of safety, and it is preferable to utilize a range of dose concentrations. Each study should include a concurrent control group (the formulation matrix lacking only the relevant antigen is generally used), and if an adjuvant is employed, an adjuvant-only formulation can be used.

Parameters Monitored

End-point assessment for vaccine studies is very similar to any other biopharmaceutical product, with some minor exceptions. First, immunogenicity of the vaccine should always be assessed concurrent with toxicologic endpoints; this serves to demonstrate that the vaccine is having its intended effect in conjunction with assessment of any adverse effects. Second, the local toxicity of vaccines should be assessed; this local reaction is generally termed "reactogenicity" and can routinely be measured using a standard or modified Draize scoring system. Local reactogenicity must be determined following administration of a full human dose (same volume to be used clinically), so the animal model must be able to accommodate an injection of this volume.

Routine toxicological endpoints are integral to vaccine safety assessment. These include clinical observations, serum chemistries, hematologic analysis, body and organ weights, and histopathology. Histopathology is generally done on the full standard battery of tissues, with particular emphasis on "pivotal" organs such as the liver, brain, kidneys, and so forth. In addition, special emphasis should be placed on histopathology of immune system organs and tissues (spleen, thymus, bone marrow, and lymph nodes, both distant and those draining the site of injection).

Another way in which vaccines differ from most other medicines is in the use of adjuvants, which act to improve or "boost" immunogenicity, possibly through engagement of the innate immune response (Leroux-Roels, 2010). In general, adjuvants have limited, if any, function exclusive of their role in improving vaccines, and as such are not licensed separately; rather, adjuvants are licensed in conjunction with the vaccine to which they are added (Sesardic, 2006). In general, regulatory agencies will expect to see data substantiating the need for an adjuvant, particularly in clinical trials; if there is no compelling reason to include an adjuvant, it should not be included. Before a consideration is made to include an adjuvant in a new vaccine candidate, the adjuvant should be tested separately as a new chemical entity, and the toxicology studies employed should be appropriate to the class of compound that the adjuvant represents. Recommended testing approaches for adjuvants are given in Guideline on Adjuvants in Vaccines for Human Use, EMA/CHMP/VEG/134716/2004 (EMA, 2005). While not strictly mandated by regulations, immunotoxicology assessment is a good idea given that the function of an adjuvant is often to "prime" the immune response (Brennan and Dougan, 2005). An explanatory note for Guideline on Adjuvants in Vaccines for Human Use was issued by EMA (EMA, 2006).

CBER has provided broad guidelines on the evaluation and production of vaccines (CBER, 1997, 2000). In general, the Center's requirements have paralleled those for other biotechnology products. Beyond establishing sterility, lack of pyrogenicity and of viral contaminants, a single GLP toxicity study in an appropriate species (one that has been established, if possible, to be immune-responsive to the vaccine) is required. If the vaccine is to be used in pregnant women or women of childbearing potential, a male and female fertility and early embryonic development (Segment I) style reproductive study should be performed in an appropriate animal species. A common concern that may require specific evaluation is dose site reactions (local site responses). It must be remembered that it is not possible to evaluate the safety of a vaccine uncoupled with its intended adjuvant (Brennan and Dougan, 2005).

Regulatory guidance for the conduct of clinical trials on vaccines is specific. Traditional Phase I trials in normal volunteers are not conducted. Rather, all trials assess not only safety but also efficacy (or at least immunogenicity). Trials may well be challenge trials—that is, after immunization subjects are purposely challenged with exposure to the infective agent of concern.

In any case, injection site responses (erythema, edema, pain, and tenderness) and systemic responses are both evaluated in subjects (Mathieu, 1997).

USFDA also has specific guidance on the tracking and reporting of adverse clinical responses to vaccines.

The Unique Challenges of Developing Specialty Biologics

The issues complicating the utilization of a classical toxicological approach for evaluating an rDNA product or species-specific protein is that standard protocols are probably inappropriate and nonrelevant in most cases. In the traditional approach to toxicology, a standard protocol or battery of tests is performed, followed by an estimation of the types of and degree of hazard or risk to humans. For example, conventional toxicity testing of a new rDNA product might lead to evaluation at excessively high doses in two species (a rodent and a non-rodent). The production of antibody in the test species during preclinical toxicology testing may inactivate the test compound and thus invalidate the toxicity evaluation. The potential risk to patients from these products may be categorized as shown in Table 9.

This approach appears somewhat irrational and without much scientific merit, since many of these new molecules are minimally toxic or nontoxic by this sort of acute evaluation. As in the case of interferons or monoclonal antibodies, the toxic effects observed in humans might not be predicted from safety assessments in rodents. An appropriate test species should be selected. Is the rat or mouse the appropriate species to evaluate a species-specific rDNA protein such as human growth hormone or interferons, or would nonhuman primates be more suitable? Does the nonhuman primate really offer any advantages? There is some consensus that the nonhuman primate may be a more appropriate species for testing some rDNA human proteins, but this is not a universal truth.

In contrast, in the "pharmacological approach" to toxicology, the potential targets of toxicity are first identified (Zbinden, 1986) and usually "off target hits." The criteria for relevant effects are established, usually based on experience with reference substances, and appropriate in vivo or in vitro

TABLE 9
Classification of Biological Drug Products into Distinct Safety Risk Categories

Lower Risk

Origin: Nonhuman
Target: Nonhuman protein
Structure: Not identical to an endogenous protein
Function: Any

Examples: Streptokinase, asparaginase, diptheria toxoid, L-asparaginase, botulinum toxin, and passive vaccines for infectious diseases such as chicken pox

Origin: Human or humanized
Target: Nonhuman protein
Structure: Not identical to an endogenous protein
Function: Any

Examples: Antibody drugs designed to bind and inhibit infectious agents such as RSV

Origin: Any
Target: Human protein
Structure: Not identical to an endogenous protein
Function: Not agonistic

Examples: Antibody drugs designed to bind and inhibit proteins such as TNF, CD20, CD25, CD52, α_4 integrin, VEGF

Potential Consequences of Immunogenicity

- Infusion reaction
- Injection site reaction
- Loss of efficacy
- Immune-complex disease

Medium Risk

Origin: Human or humanized
Target: Human protein
Structure: Identical, partially or completely, to endogenous protein
Function: Any
Other: Administered to subjects with gene deletion or defect

Examples: Human growth hormone

Origin: Any
Target: Human protein
Structure: Identical, partially or completely, to endogenous protein (includes truncated, mutated and fusion proteins)
Function: Any
Other: Administered to subjects with redundant endogenous counterparts

Examples: Interferon β1a/1b
Peginterferon α2a/2b

Origin: Any
Target: Human protein
Structure: Not identical to endogenous protein
Function: Agonistic

Examples: Peptidomimics, agonistic anti-CD28 antibodies, anti-CD3 antibodies, etc.

Potential Consequences of Immunogenicity

- Infusion reaction
- Injection site reaction
- Loss of efficacy
- Immune-complex disease
- Possible overstimulation of endogenous mechanisms by product molecules cross-linked by ADA (“superagonist”)

Higher Risk

Origin: Any
Target: Human protein
Structure: Identical, partially or completely, to endogenous protein
Function: Any
Other: Administered to subjects with a unique endogenous counterpart

Examples: Anti-hemophilic factor, laronidase, insulin, erythropoietin, GM-CSF, thrombopoietin, etc.

Potential Consequences of Immunogenicity:

- Infusion reaction
- Injection-site reaction
- Loss of efficacy
- Immune-complex disease
- Possible overstimulation of endogenous molecules cross-linked by ADA (“superagonist”)
- Neutralization of the endogenous counterpart by autoantibodies, leading to a deficiency syndrome

experimental models are selected to assess the pertinent toxicological responses.

Doses should be selected that are reasonable multiples of the proposed therapeutic dose to be employed, especially since in many cases the amount of material available for testing may be limited and not available in Kg amounts. Preclinical rodent and primate studies should merely provide the flags to monitor during Phase I clinical trials. Reason should prevail, not only in the selection of methods and models for assessing the potential toxicity of the new agents but also in the use of these data for extrapolation to humans. The pathologist and toxicologist must work as a thoughtful team in these assessments.

Purity and Homology

Major concerns in the production of a species-specific protein by rDNA technology are the purity of the product, the amount and type of contaminants present, and the homology of the product compared to the native molecule. The toxicologist should be concerned about the acceptability and toxicity of intentional or inadvertent contaminants introduced during fermentation or isolation of the product (e.g., DNA, chemicals, *Escherichia coli* proteins). Other issues concern the introduction of amino acid residues that might alter the three-dimensional structure or antigenicity of the molecule, partial denaturation of the product during isolation and recovery, genetic stability of the rDNA clone during production (mutation could result in altered amino acid sequence), and the level of foreign DNA present. Although these are issues of analytical biochemistry, their impact on the potential toxicity and overall safety of the finished product is of some toxicological concern.

Immunogenicity

The problem of the immunogenic nature of many human recombinant DNA proteins and the potential to generate antibodies to a normal human protein is of special interest to the immunotoxicologist. For example, 3 of 16 patients administered the rDNA-derived interferon-α (clone A) developed antibodies of the IgG class that were undetectable prior to or during therapy (Gutterman et al., 1982). These antibodies were capable of in vitro neutralization of interferon activity, although in vivo neutralization of interferon was not documented. Similarly, two patients treated with interferon-β for many months developed high-titered antibody, which in one case was correlated with an inability of the patient's fibroblasts to produce interferon (Vallbracht et al., 1982).

Virtually all patients treated with conventional porcine insulin develop circulating anti-insulin antibodies (Klaff et al., 1978) that are less frequent and in lower titer in individuals treated with more highly purified porcine (Falholt, 1982) or rDNA human insulin (Fineberg et al., 1983). In the study by Fineberg and associates, 44% of the patients developed antibodies to rDNA human insulin over a 12-month period compared to a 60% antibody frequency with porcine insulin. Human growth hormone (HGH; Genentech, Inc.) prepared by rDNA technology was observed to produce a frequency of immunogenicity similar to that seen with human insulin (approximately 40% of the children developed antibody, according to the product insert). The ultimate goal is to develop rDNA products that will be less immunogenic than purified animal sources of these therapeutic agents.

The exact mechanism of the immunogenicity of species-specific rDNA proteins is unknown but is believed to be attributable to (1) the addition of extra amino acid residues during synthesis, which the host reads as foreign, (2) denaturing of the native molecules, or (3) contamination by *E. coli* polypeptides or lipopolysaccharides.

A second unanswered concern is whether the antibody induced by the recombinant protein has any discernible health effect. Other than some reports of neutralization of biological activity, little pathology has been attributed to the presence of antibodies in patients given recombinant protein therapy. It should also be noted that the question of antibody specificity has not been well studied, so it is entirely conceivable that autoimmune pathology or even an anaphylaxis response could be induced. Equally important is the concern that induced antibody might neutralize the endogenous hormone or protein that it is intended to replace or supplement.

A third consideration is that certain routes of administration may favor immunogenicity of recombinant proteins. In early trials, rDNA proteins introduced by subcutaneous or intramuscular injections (procedures known to improve the immunogenicity of proteins) resulted in a higher frequency of antibody responses than in the intravenous route.

In summary, these are the clinically relevant questions about the immunogenicity of rDNA species-specific proteins: Will antibody be induced in the recipient that will neutralize the therapeutic effect or lead to immune complex disease? What is the class (e.g., IgG or IgE) and specificity (i.e., reactivity against specific protein or contaminant) of the antibody induced? The former antibody type could potentially neutralize the product and produce immune complex disease, while the latter could result in an anaphylaxis response.

Biology of Bioengineered Products

Though not necessarily a useful concept scientifically, the rapid pace of drug development often forces an acceleration of processes that help identify an interesting biological property of a molecule when only very small amounts are available (e.g., tumor necrosis factor or erythropoietin), resulting in large scale production, in some instances even before the full chemical structure is known. The clinical interest in administering the therapeutic substance to man for investigative or therapeutic purposes must be balanced against the total lack of knowledge of its general effects on the body and of the consequences of prolonged high-level exposure to it on the function of interest.

For example, there is the history of interferon: discovered through its antiviral actions, subsequently found to modulate mitosis and certain immune functions, capable of producing fever and probably ECG and EEG changes as evidence of membrane effects in excitable tissues. If an interferon were a novel discover, now being produced for the first time, then investigation of its general biological effects on repeated administration to responsive animals would be important prior to study in man. The same

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arguments apply to other lymphokines, for example, α-IFN, IL-2, and so sorth.

The planning of this type of investigation as an empirical, open study of responses must be carefully related to the nature and what is known of the product concerned.

- It is necessary to work in a species capable of responding to the principal activity. Interferons are notorious for their species specificity, but most other lymphokines at least are more generally active. Work in a primate may be required, but it depends on the substance to be tested. There may be no point in using more than one species in pivotal studies.
- Any test should be as broad and as general as possible, that is, monitor many variables clinically, in the laboratory and by pathology, until enough is known for there to be confidence in a focused approach.
- Relate any testing to the clinical circumstances of probable use.

  Thus, if a new synthetic antigen or engineered antigen is intended for testing, for administration only a few times to man, there would be no point in a multidose experiment. It should suffice to show that it was antigenic in the intended preparation. Unless there were a prior reason to do so, a special search for, say, autoimmune reactions, seems unnecessary. Similarly, testing a monoclonal antibody for activity is likely to be difficult if not impossible because of species specificity and the antigenicity of the preparation.
- The toxicologist/pathologist team should be prepared to do nothing if the material is well known, its properties are understood, and there is adequate characterization of the nature of the preparation supplied; for example, human insulin or growth hormone produced by genetic engineering should not be submitted to prolonged safety tests in animals provided that the molecular forms present are sufficiently well understood.

It may be useful, however, to consider limited animal studies to examine the pharmacokinetics and duration of action even of a well-known material made by a new route, unless physiochemical analyses show that to be pointless.

Animal Models

Species selection is probably one of the most important considerations when designing a preclinical safety program; for a biotechnologically derived pharmaceutical, an understanding of the biology of the product is required. Since most of these either are human proteins or target human receptors, they tend to be species-specific. Studies in rodents and dogs, the species commonly used in traditional toxicity studies, may not provide scientifically meaningful data. However, nonhuman primates are not necessarily the most appropriate species either, despite their phylogenetic similarity to human beings.

Some approaches that offer guidance in selecting relevant species include a literature review, determining the extent of homology between the endogenous animal protein and the human recombinant protein, determining the activity of the protein in pharmacological models, and in vivo assays of the receptor/tissue binding.

A literature review may provide useful information about the physiological properties of the protein in animals and how they compare with those of the human protein in man. For example, prior to recombinant DNA technology, growth factors and/or hormones were purified from biological fluids. Although the quantities obtained were limited, they were nevertheless sufficient to allow investigation of the physiological properties of these proteins. Computer programs are now available for on-line searching of databases that hold information not only on the sequences of various animal and human proteins, but also the extent of homology between an animal protein and its human equivalent, including common amino acid sequences. It should be remembered, however, that a protein showing a high degree of homology to the human protein may not necessarily share similar pharmacological activities. Evaluation of activity or lack of activity in pharmacological animal models, if available, certainly would aid species selection. Finally, in vitro assays that analyze receptor and/or tissue binding are commonly used to determine the appropriate species for preclinical safety evaluation.

Some biotechnologically derived pharmaceuticals will cross-react with species that can be evaluated toxicologically, while others cross-react only with nonhuman primates such as the chimpanzee—a protected species. In this case, a well-designed "safety," or "Phase 0" study at doses higher than the proposed clinical dose may provide valuable safety information. However, a lack of cross-reactivity with any nonhuman species does not necessarily make preclinical safety evaluation impossible, nor does it limit toxicity testing to species in which the protein lacks relevant pharmacological activity. Some alternative possibilities are summarized in Table 10.

Toxicity studies traditionally are conducted using "normal" animals. However, studies in animal disease models may provide additional safety information regarding the possibility of disease exacerbation. For example, the administration of human recombinant erythropoietin was associated with hypertension in patients with chronic renal failure, and also in uremic dogs, but not in normal dogs. See Nonclinical Safety in In Vivo Testing: Use of Conventional Animals Versus Alternative Toxicology Models section above.

Species differences must be considered when choosing a model, and in particular, species-specific immunological differences between the human and the test animal. For example, in man, an anti-CD4 monoclonal antibody (MAb) will bind to CD4 expressed on monocytes with subsequent fixing of complement and destruction of antigen-presenting cells. However, since CD4 molecules are not expressed on murine monocytes, these effects would not be evident in a murine model.

TABLE 10
Alternative Models for Toxicity Assessment

Model	Example	Caveat
Nontraditional animal model	Transgenic mice carrying appropriate human receptor.	Antibody formation would need to be monitored, as it is probable that a large human protein would produce an immune response.
Homologous proteins and/or systems	Testing purified animal protein in the same species or, for monoclonal antibodies, testing an antibody directed against the receptor in the animal.	Data should be interpreted with caution as the biological properties of the animal protein may differ from those of the human protein.
In vitro methods	Tissue binding assays.	If no in vivo models are available, in vitro; methods combined with in vivo testing in a pharmacologically nonreactive may suffice.

For highly humanized proteins, the approach to proper safety evaluation starts with identification of an appropriate nonclinical safety model.

First, evaluate for comparative tissue binding then if no appropriate species is identified then one can either:

- Prepare and test a homologue, or
- Test the molecule itself in a humanized mouse model.

A tissue cross-reactivity study is required by the FDA "points to consider" document for monoclonal antibodies prior to the first clinical trial. Its usefulness is debated, but its purpose is to evaluate the potential for binding to non-target tissues. Positive and negative controls are important for interpreting results. Tissues from humans and all nonclinical species used in safety studies should be evaluated. At minimum, the evaluation should include the 32 tissues recommended by the FDA "Points to Consider in the Manufacturing and Testing of Monoclonal Antibody Products for Human Use."

"Humanizing" Mice:

- Isolate CD34+ stem cells (hHPCs) from human cord blood
- Breed NOD. Cg-Prkdc^{scid}//2rg^{tmWjl}
- PND1 pup irradiated 1 cGy
- hHPCs (10^5) injected in 25 μL PBS into liver
- Assay tail blood for reconstitution of human immune cells

Humanized mice can be used to:

- Assess the in vivo influence of stressors and drugs on the development of immune cells
- Evaluate how toxicants can modify in vivo human immune responses
- Investigate whether hematopoietic stem cells from cord blood can be induced to develop into non-immune cell types
- Determine the influence of mouse effects on human immune cells' longevity and human immune cells on mouse longevity

Study Design

It is questionable whether traditional toxicological paradigms and small molecule pathology approaches are applicable to biological or protein agents. If they are not, then how can the clinician gain reassurance to administer the first dose to man, to move into multidose trials, and even assess the agent in combination with other established medicines or biological agents? Monoclonal antibodies, soluble cytokine receptors, and growth factors all have been used in patients for nearly a decade, providing a wealth of experience in this area from which to learn. One of the most striking lessons is that pharmacodynamic effects may appear long after dosing of the agent has been discontinued.

As a class, biotechnologically derived pharmaceuticals share certain characteristics that have influenced their preclinical development. They are proteins, and therefore toxicity was expected to be minimal and limited to an exaggeration of their desired pharmacological effects—a myth that was ultimately exploded. These agents are designed to perturb specific molecular or cell-to-cell interactions, sometimes with minimal effect on the pathophysiology of the target disease. Owing to the species-specific nature of these agents, preclinical toxicology is usually limited. For example, if a primatized anti-CD4 MAb cross-reacts only with chimpanzee and human CD4, the species of choice for toxicity tests is the chimpanzee, the use of which is restricted by its limited availability and ethical concerns.

These characteristics of protein agents give rise to problems in clinical development such that the traditional paradigm for preclinical testing may not be appropriate. The dose in animals may not be predictive of an appropriate starting dose for man. A surrogate marker—for example, CD4 cell counts in the preclinical chimpanzee model—may be useful in setting the initial human dose but may only serve to indicate a no-effect dose. Once in the clinic, trials conducted early in development are usually not sufficiently powered to distinguish effects due to the toxicity of the test agent from those due to, for example, the underlying disease, and concomitant or previous medications. Finally, short-term (3–6 months) preclinical studies do not necessarily predict the long-term effects of these agents.

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The long-term toxicities of concern are opportunistic infections, lymphoproliferative disorders, and immunogenicity, manifesting as tachyphylaxis and/or allergic reactions. Preclinical approaches that serve to identify these as potential hazards to man of a biologic drug moiety are thus needed.

The choice of toxicity studies and the design of individual studies will depend on the planned clinical program. Important issues to consider are:

- The frequency and route of administration, including the use of novel delivery systems
- The duration of dosing
- Special toxicity testing

Regimen and Route of Administration

Clinical trials (and therefore nonclinical safety evaluations) for biotechnologically derived pharmaceuticals may be more complex than those for conventional pharmaceuticals and so the route and frequency of test drug administration should, if possible, mirror the proposed clinical use, even if that route employs a novel delivery system.

Duration

Traditionally, the duration of a toxicity study depends on the intended clinical use and disease duration. The potential immunogenicity of the human protein is a significant issue since antibody binding can partially or completely inhibit the biological activity of that protein, affect is catabolism, or alter its distribution and clearance. Any multiple-dose study therefore should include evaluation of the impact of antibody formation, including their neutralizing capacity. However, antibody formation in itself should not be a reason for termination of a toxicity study, particularly if the antibodies are not neutralizing or do not alter the pharmacodynamics of the protein.

Multiple-dose safety assessment studies are usually conducted before single-dose administration to volunteers. Many of the clinical trials for biological agents target life-threatening illnesses, and it has therefore been suggested that single-dose toxicity studies are sufficient to support single-dose "proof-of-concept" clinical studies. While this approach promotes faster introduction into the clinic, it may be of limited use since, once in man, there is a tendency to overlook the preclinical data. Clinical development may not progress without interruption if relevant preclinical data are missing.

Special Toxicity Testing

In addition to multiple-dose studies, information on potential functional changes—as obtained from safety pharmacology studies—and the potential for genotoxicity, reproductive toxicity, and carcinogenicity may be required for registration. Once again, the species specificity of recombinant proteins may preclude the use of traditional animal species such as rodents and/or rabbits for safety pharmacology, reproductive toxicity, and carcinogenicity studies. Functional evaluations of cardiovascular and pulmonary systems could be incorporated into a nonhuman primate multidose toxicity study. If appropriate, potential reproductive toxicity can be evaluated in a nonhuman primate.

There may be situations that warrant an assessment of carcinogenic potential, but immunogenicity and species specificity may preclude a 2-year rodent bioassay. It may be necessary to develop in vitro assays to address a particular concern. For example, growth factors that may have the potential to support or stimulate the growth of transformed cells should be assessed for their ability to promote growth of either malignant or normal cells.

Large-molecular-weight compounds are unlikely to react with DNA or other chromosomal material and therefore a genotoxicity evaluation may be of little value. However, genotoxicity studies may provide useful information about the safety of products containing organic linkers.

Program Design Challenges

The standard safety assessment data package for any new drug entity typically evaluates:

- Potential toxicity following single and multiple dosing
- Genotoxic potential
- Functional changes—that is, safety pharmacology studies

In addition, depending on the proposed clinical plan, the following may need evaluation:

- Toxicity following chronic dosing
- Carcinogenic potential
- Possible reproductive toxicity

Although biotechnologically derived pharmaceuticals often need customized preclinical development programs, certain issues are common to all. These include species specificity, potential immunogenicity and its impact on the duration of dosing, and the need for special toxicity testing.

Challenges: Biosimilars/"Biolikes"

For small molecules, the availability of generic versions after patent expiration has significantly contributed to keeping the cost of many (particularly chronic use) medications down. Such generics have identical chemical structures to those of the marketed active molecules, demonstrating that structural equivalence is readily done by available analytical techniques.

For biologics, however, where the drug entity is produced by modified cellular processes and the precise complex molecular structure cannot precisely be defined and therefore an identical structure cannot be either achieved or proven. Accordingly, it is not possible to produce "generic" biologic drugs, even after patent expiry. Though guidelines and laws have been enacted in the EU and U.S. (the Biologics Price Competition

and Innovation [BPCI] Act, enacted in 2009) to provide a path to production (biologically sourced therapeutics that are equivalent in terms of efficacy and safety, "biosimilars"), and a specific guidance was enacted by FDA in 2012, progress has been slow. As of the end of 2015, only one drug (Zarxio, a biosimilar for Amgen's Neopogen which was first approved in 1991) has been so approved in the United States. The process of approval requires:

- Analytical studies demonstrating that the biologic product is highly similar to the marketed ("reference") product.
- Animal studies showing equivalence of safety and therapeutic activity.
- One or more clinical studies to demonstrate safety, purity, and potency under reference drug label conditions of use. Such studies must access and show equivalence for immunogenicity and either pharmacokinetics or pharmacodynamics.

The animal toxicity studies should be designed to provide a comparative evaluation of the reference and biosimilar product in a relevant animal species. As such, either pharmacokinetic (PK) or pharmacodynamic (PD) measures should be obtained to support a determination of equivalence (Baldrick and Donninger, 2012).

Examples of such nonclinical studies used to support marketing approval of biosimilars in Europe are presented in Table 11. The biosimilar approval process in the EU has moved along very quickly.

Bioengineered Infectious Agents as a Treatment Modality

Gene therapy (GT) holds great promise as a therapeutic approach for countless diseases. As a treatment modality, GT involves the introduction into the human body of genes or cells containing corrective genes to treat a disease. Delivery of the corrective gene to the target cells is a critical step in the therapy. Viral vectors for GT are currently considered to be the most effective way to achieve high expression of therapeutic transgenes. Most of these viruses are bioengineered to enhance transfection, decrease replication, and avoid immune response. Bioengineered viruses are also used in oncology based on the premise that the virus will target tumor cells over healthy cells and destroy them via tumor lysis. These viruses may also be engineered to carry transgenes to enhance their oncolytic activity. Therefore, they are also considered a segment of GT and are considered in this section.

Although much work has been done, only recently have treatments for specific diseases using GT been fully approved by regulatory authorities. Regulatory guidance for the nonclinical assessment of GT products is provided in the FDA's Guidance for Industry, Preclinical Assessment of Investigational Cellular and Gene Therapy Products (2013) and the European Medicines Agency's Guideline on the Non-Clinical Studies Required Before First Clinical Use of Gene Therapy Medicinal Products (2008). This section outlines the major nonclinical considerations associated with bioengineered infectious agents (focus on viruses) and highlights the nonclinical safety programs of the two approved treatments.

TABLE 11
Nonclinical Studies with Marketed Biosimilars

Biosimilar *vs* Innovator Name/Identity/ Action/Authorization Date/Reference[a]	Biological Activity/ Pharmacology	Kinetics	Toxicology
Growth Factor			
Omnitrope *vs* Genotropin/recombinant human growth somatropin/growth disorders/2006	Yes (in vivo)	TK from toxicology work	Repeat-dose rat toxicology + rabbit local tolerance studies
Valtropin *vs* humatrope/recombinant human growth somatropin/growth disorders/2006	Yes (in vivo)	PK in rabbit + TK from toxicology work	Repeat-dose rat toxicology study
Epoetin			
Retacrit and Silapo *vs* Eprex-Erypo/Epoetin alfa/Anaemia/2007	Yes (in vitro and in vivo)	TK from toxicology work	Repeat-dose rat and dog toxicology + rabbit local tolerance studies
Brinocrit, Epoetin alfa Hexal and Abseamed *vs* Eprex-Erypo/Epoetin alfa/Anaemia/2007	Yes (in vitro and in vivo)	PK in dog + TK from toxicology work	Repeat-dose dog toxicology + rabbit local tolerance studies
Granulocyte Colony-Stimulating Factor			
Biograstim, Ratiograstim, Tevagrastim and Filgrastim ratiopharm *vs* Nutrogen/Human G-CSF/Neutropenia/2008	Yes (in vitro and in vivo)	PK in rat and monkey + TK from toxicology work	Repeat-dose rat and dog toxicology + rabbit local tolerance studies
Filgrastim Hexal and Zarzio *vs* Neupogen/ Human G-CSF/ Neutropenis/2009	Yes (in vitro and in vivo)	TK from toxicology work	Repeat-dose rat toxicology + rabbit local tolerance studies
Nivestim *vs* Neupogen/Human G-CSF/ Neutropenia/2010	Yes (in vitro and in vivo)	TK from toxicology work	Repeat-dose rat toxicology + rabbit local tolerance studies

[a] Data extracted from European Public Assessment Report for each biosimilar (EPAR, 2011).

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Primary Considerations during Nonclinical Safety Assessment

Pharmacodynamic "Proof-of-Concept" Studies in Nonclinical Models

In vitro and/or in vivo studies should be conducted to generate the nonclinical evidence supporting the potential clinical effect or at least the related biological effect/molecular mechanism of action.

Biodistribution

This characterizes the spread of the vector after administration and its localization and persistence of vector and expressed transgene in tissues, body fluids, or organs. Studies should provide data on all organs, whether considered a target organ or not. Additional studies confirming the specificity and duration of gene expression and activity in target tissues are required if a GT is designed to have selective or restricted targeting and expression (tropism).

Shedding

Dissemination of the vector DNA via body secretions, including excreta, should be evaluated. Data collected from these studies may also contribute to the environmental risk assessment.

Viral Replication

Viruses and viral vectors may range from fully replicative, to conditionally replicative, to replication incompetent. It is important to characterize the level of viral replication and persistence (to include non-target tissues) and investigations should be completed to verify the vectors behave as expected.

Gene Integration/Insertional Effects

Engineered viruses can be used to insert almost any genetic information into cells. However, the insertion of genetic information into a host cell must be carefully monitored for random integration into the host genome. The gene therapy vector can potentially modify the activity of neighboring genes (positively or negatively) in close proximity to the insertion site or even inactivate host genes by integrating into them. These phenomena are referred to as "insertional mutagenesis." This can result in mutations leading to tumor formation or dysfunction of the gene. Using the newer technique of gene targeting by homologous recombination, it is possible to avoid positional effects and gene silencing and introduce the gene of interest specifically into a defined region of the genome. These issues and the concern over unregulated transgene expression therefore require the level and persistence of transgene expression in tissues should be characterized.

Carcinogenicity

As mentioned previously, insertional mutagenesis or a transgene product could potentially lead to tumor formation. In-silico evaluation should be conducted for the presence of oncogenic activity such as presence of oncogene protein sequences. If oncogenic potential is determined, the relevant in vitro/in vivo tumorigenicity studies should be conducted to assess parameters such as proliferative capacity, dependence on exogenous stimuli, response to apoptosis stimuli, and genomic modification. Standard lifetime rodent carcinogenicity studies are generally not required.

Immune Response

Antibody response may be observed against the viral vector and the expressed transgene product, and/or the transgene product's endogenous counterpart. Immunogenicity and immunotoxicity studies are generally required for GTs that encode for growth factors, cytokines, or other macromolecules that may impact the immune system. Effect of pre-existing immunity to transgene product and anti-vector antibody response should be investigated. In some cases, animal studies might not provide interpretable data and the use of homologous animal models may have to be considered.

Local Tolerance and General Toxicity

These studies should include the same route and method of administration planned for the clinical use unless otherwise justified. If only one species is used, then it should be the most relevant species for the anticipated toxicological effects. Singe-dose toxicity studies will generally be required before a single-dose clinical trial, and multiple-dose studies required before a multiple-dose clinical trial. The whole gene therapy (viral vector + expression vector including cassette + transgene) should be assessed for toxicity. Consequences related to overexpression of the transgene product and immunogenicity should also be assessed. The in vivo effect of vector-related expression of non-therapeutic proteins such as antibiotic resistance genes and viral proteins expressed from the constructs should be evaluated.

Reproductive Toxicology and Genotoxicity Studies

Standard studies as highlighted in ICH M3 are generally not required before first use in man but may be required later, depending on the clinical indication. Biodistribution studies and germline transmission studies may provide early recognition of potential risks for reproduction. Standard genotoxicity studies are not generally required.

Approved Gene Therapy Products: Nonclinical Approach

Much progress has been made in the clinical application of gene therapy, and both of the currently approved products utilize bioengineered viral vectors. Based on available literature, the nonclinical safety framework for each followed closely the fundamental requirements listed above.

Alipogene Tiparvovec (Glybera®)

Alipogene tiparvovec was approved in 2012 by European regulators for the treatment of lipoprotein lipase deficiency (LPLD). This is a rare genetic disorder that causes fat to build up in the blood leading to life-threatening, recurrent bouts of pancreatitis. Alipogene tiparvovec utilizes an adeno-associated virus serotype 1 (AAV1) viral vector to deliver the transgene LPL^{S447X} (a nonintegrating copy of the human lipoprotein lipase [LPL] gene) to the nucleus of muscle cells

resulting in the production of biologically active LPL production and the subsequent lowering of plasma triglycerides.

Nonclinical efficacy was shown using $LPL^{-/-}$ mice (Ross et al., 2004) and cats (Ross et al., 2006). A multiple-dose GLP toxicity study was conducted in C57BL/6 mice (Rip et al., 2005). Mice were treated intramuscularly with three dose levels of AAV1-LPL^{S447X} or formulation buffer and animals were killed 7, 28, and 90 days after dosing. Routine methods were used for clinical observation, food consumption, body weights, necropsy, and tissue macroscopic and microscopic examination. Terminal blood samples were taken for hematology and clinical chemistry. To characterize the biodistribution, whole blood and plasma, major organs, gonads (to assess for germ line vector transfer), and injected muscles were examined for viral DNA. The low-dose and high-dose groups were also examined for vector expression at 7, 28, and 90 days after treatment. To confirm transgene expression, human LPL expression was measured in plasma on days 7 and 28 and in muscle homogenates on day 90. Blood samples were also analyzed for antibodies against AAV1 capsid protein or against the transgenic product. Maternal-fetal biodistribution and toxicity were examined in a breeding study by treating males 6 days prior to pairing with untreated females and females were treated 4 weeks prior to mating with untreated males (Salmon et al., 2014). Postmortem examination included evidence for maternal and fetal toxicity as well as vector DNA in male and female reproductive tissues and the fetuses. Shedding was reportedly assessed in clinical studies by collecting saliva, urine and semen (Salmon et al., 2014).

Talimogene Laherparepvec (T-VEC [IMLYGIC®])

T-VEC was approved in 2015 by both the European Commission and the FDA for the treatment of melanoma. It is a herpes simplex virus 1 (HSV-1) bioengineered to replicate in tumor tissues and express human granulocyte macrophage colony-stimulating factor (hGM-CSF). It is injected directly into cutaneous, subcutaneous, or nodal melanomas, where it replicates and causes lysis of tumor cells. The release of tumor-associated antigens in concert with the local transgenic expression of GM-CSF promotes an antitumor immune response.

The nonclinical program focused on T-VEC's recombination risk, biodistribution and clearance, tumor selectivity, viral shedding and replication, immunogenicity, and general toxicity in normal and tumor-bearing mice (Amgen, 2015). The pharmacology program examined direct lysis of a variety of tumors in vitro. In vivo studies were conducted to evaluated selective tumor lysis and development of a systemic antitumor immune response following intratumoral injection. A surrogate HSV-1 molecule encoding the murine version of GM-CSF was used in certain nonclinical safety and pharmacology studies because human GM-CSF has no activity in the mouse. In regarding to nonclinical safety studies, T-VEC biodistribution to tissue, blood, and excreta were examined in normal and tumor-bearing mice. Repeat-dose, subcutaneous general toxicology studies up to 12 weeks in duration were conducted that also included repeated intratumoral injections. A repeat-dose IV study evaluating embryo and fetal development toxicity was conducted in the BALB/c mouse. This included evaluation of maternal-to-fetal viral transfer. Because of the neurovirulence associated with wild type HSV-1 virus, exploratory studies evaluated the neurovirulence of T-VEC following intracerebral or intranasal injection in the BALB/c mouse, the in vitro susceptibility of T-VEC to acyclovir as a standard of care antiviral treatment, and tolerability or histopathology in tumor bearing genetically immunodeficient mice (SCID and nude strains). Clinical safety evaluation included the monitoring of adverse and serious adverse events, biodistribution, and viral shedding. Biodistribution was evaluated in blood and urine samples and viral shedding was evaluated using samples taken from the surface of injected tumors and noninjected lesions, and a viral surveillance program was conducted looking at T-VEC exposure of family members and healthcare providers.

SUGGESTED READING

Drug Development Overview

None.

Toxicologic Pathology

None.

Important/Special Topics in Nonclinical Safety and Toxicity

Adversity/NOAEL in Toxicity Studies

None.

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European Union Link:

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ICH Links:

- Quality Risk Management http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q9/Step4/Q9_Guideline.pdf (last accessed November 12, 2016).
- Pharmaceutical Quality System http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q10/Step4/Q10_Guideline.pdf (last accessed November 12, 2016).

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Appendix 2: Diagnostic Criteria of Proliferative Lesions in Rodents (Rat and Mouse) and Selected Non-Rodent Laboratory Species[1]

Dan Patrick, John Curtis Seely, Russ Cattley, Tom Steinbach, Daher Ibrahim Aibo, Charlotte M. Keenan*

BONE, MUSCLE, AND TOOTH

Adipose tissue hyperplasia is an increase in the number of adipocytes or fat cells. Hyperplasia may cause an increase in organ volume, and results from physiologic or pathologic mechanisms. Reduced temperature may cause brown fat adipocyte hyperplasia (the adipocytes display microvesiculation), and the increase is often seen in the interstitial and preadipocyte cells. Hyperglycemia and obesity may cause white fat adipose tissue hyperplasia (these adipocytes display macrovesiculation). See **Lipid accumulation** for further detail.

Differential diagnoses: **Lipoma**; **Liposarcoma**.

Synonym(s): **Adipose tissue, polymorphic**.

Reference

Greaves, P. et al. 2013. Proliferative and non-proliferative lesions of the rat and mouse soft tissue, skeletal muscle and mesothelium. *J Toxicol Pathol* 26:1S–26S.

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Adipose tissue, polymorphic, see the preferred term **Adipose tissue hyperplasia**.

Ameloblastic fibro-odontoma, see **Ameloblastic odontoma**.

Ameloblastic odontoma is a rare, slow growing, benign, mixed tumor of odontogenic (dental) origin that has characteristics of both odontoma and ameloblastoma. This neoplasm typically has defined borders but is locally aggressive and contains a variety of dental components (e.g., enamel, dentin, osteodentin, pulp) with the hard tissue (odontoma component) centrally located. Neoplastic ameloblasts (soft tissue/ameloblastic component) are found at the tumor edges. Other features may include multinucleated and keratinized cells. *

These tumors are rarely reported spontaneously in rats and mice but have been reported in a snow monkey. Derivatives of *N*-nitrosourea compounds can produce these tumors in rodents. Ameloblastic odontomas differ from ameloblastomas in that ameloblastic odontomas contain hard dental tissues (odontoma component). Ameloblastic fibro-odontomas are a variant of this tumor that have fibroblastic proliferation with these dental features.

Differential diagnoses: **Ameloblastoma**; **Odontoma**; **Dental dysplasia**; **Fibroma, odontogenic**.

Synonym(s): **Odontoameloblastoma**.

References

Fossey, S. et al. 2016. Nonproliferative and proliferative lesions of the rat and mouse skeletal tissues (bones, joints, and teeth). *J Toxicol Pathol* 29:49S–103S.

Long, P. et al. 1993. Proliferative lesions of bone, cartilage, tooth, and synovium in rats, MST-2. In: *Guides for Toxicologic Pathology*. Washington, DC: STP/ARP/AFIP.

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Ameloblastoma is a benign tumor of dental epithelial cells originating from dentigerous cysts, dental lamina, enamel epithelium, and the oral mucosa. This neoplasm is an expansile, often infiltrative mass in the gingiva with neoplastic epithelium arranged in a variety of patterns (e.g., follicular, plexiform) surrounding stellate cells. No dental hard tissues are present. Ameloblastomas rarely occur spontaneously in rodents and dogs. They are the most commonly reported dental tumor in nonhuman primates (e.g., cynomolgus, rhesus, cebus, and spider monkeys). Derivatives of *N*-nitrosourea compounds can produce these tumors in rats.

Differential diagnoses: **Ameloblastic odontoma**; **Ameloblastic fibro-odontoma**; **Odontoma**; **Fibroma, odontogenic**.

[1] Major contributions to Appendix 2 provided by the Organ System teams were reviewed and edited by the Appendix 2 team.
* Indicates Lead Contributor.

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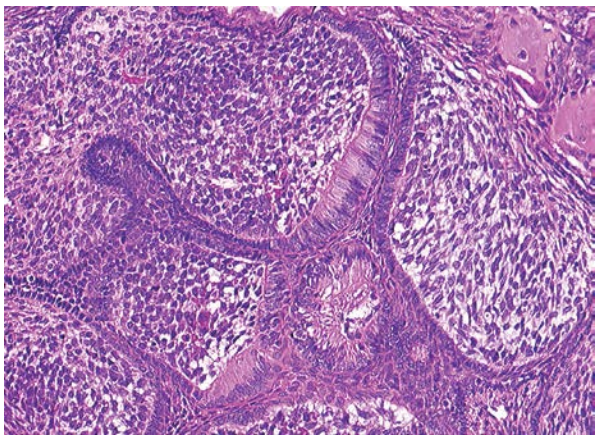


FIGURE 1 Ameloblastoma, rat. This locally expansile neoplasm consists of intersecting columns of mildly pleomorphic epithelial cells resembling the inner enamel epithelium encompassing aggregates of loosely arranged central cells similar to stellate reticulum. Decalcified tooth, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Fossey, S. et al. 2016. *J Toxicol Pathol* 29:49S–103S.)

References

Fossey, S. et al. 2016. Nonproliferative and proliferative lesions of the rat and mouse skeletal tissues (bones, joints, and teeth). *J Toxicol Pathol* 29:49S–103S.

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Miller, A.D. 2012. Neoplasia and proliferative disorders of nonhuman primates. In: Abee, C.R. et al. (eds.) *Nonhuman Primates in Biomedical Research*. London: Academic Press, pp. 325–356.

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http://www.sciencedirect.com/science/article/pii/B9780123813664000067

Ameloblastoma, acanthomatous is a locally invasive, often aggressive oral tumor of dogs. Appearing grossly as an exophytic verrucous gingival mass, commonly in the mandible, this neoplasm is composed of nonkeratinizing, polygonal, odontogenic epithelium arranged in wide sheets and cords. The sheets are bordered by a row of tall columnar cells and central acantholytic cells with intercellular bridges. Mesenchyme typical of periodontal ligament tends to be highly cellular with stellate fibroblasts surrounded by dense collagen.

Differential diagnoses: Gingival epithelial hyperplasia; Gingival squamous cell carcinoma.

Synonym(s): **Canine ameloblastoma, acanthomatous**; **epulis, acanthomatous**; **ameloblastoma, peripheral**.

References

Arzi, B. et al. 2011. Expression of cytokeratins in the epithelium of canine odontogenic tumours. *J Comp Pathol* 145:345–351.

Brown, C., Baker, D., and Barker, I. 2007. Alimentary system. In: Maxie, M.G. (ed.) *Jubb, Kennedy, and Palmer's Pathology of Domestic Animals*, Vol. 2. Philadelphia: Elsevier, pp. 25–26.

Fiani, N. et al. 2011. Clinicopathologic characterization of odontogenic tumors and focal fibrous hyperplasia in dogs: 152 cases (1995–2005). *J Am Vet Med Assoc* 238:495–500.

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Angioma, intramuscular is a mass of variable size that develops within skeletal muscle. These masses are composed of numerous profiles of small capillaries or cavernous blood vessels filled with red blood cells, separated by collagenous stroma. In a majority of cases, these vascular proliferations are associated with the accumulation of mature white adipose cells and are referred to as an infiltrative angiolipoma. Less frequently, other tissue types or tissue features can be observed in association with these vascular/lipovascular proliferations, including calcification, ossification, and fibrin clots. Cellular atypia and mitoses are rare. They seem more prevalent in humans compared to other mammalian species and are frequently located within thigh muscles in the human. No unique locations have been determined in other mammalian species. There is still debate regarding the true neoplastic nature of these proliferations, but at least in the subcutaneous localization in humans, cytogenetic studies have shown the absence of clonal chromosomal aberrations. While rare, in veterinary pathology these proliferations have been reported in dogs, sometimes under different names (e.g., mixed intramuscular hemangioma, infiltrative angiolipoma). In patas and rhesus monkeys, intramuscular angiolipomas have been induced in offspring of mothers treated with *N*-nitrosoethylurea during weeks 6–19 of gestation, with a latency period of 4–76 months in the affected offspring.

Differential diagnoses: **Hemangioma**; **Hemangiosarcoma**; **Lipoma**; **Liposarcoma**.

Synonym(s): **Hemangioma, mixed intramuscular**; **hemangioma, intramuscular**; **angiolipoma, intramuscular**; **angiolipoma, infiltrative**.

References

Greaves, P. et al. 2013. Proliferative and non-proliferative lesions of the rat and mouse soft tissue, skeletal muscle and mesothelium. *J Toxicol Pathol* 26:1S–26S.

Liggett, A., Frazier, K., and Styer, E. 2002. Angiolipomatous tumors in dogs and a cat. *Vet Pathol* 39:286–289.

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Brown adipose tissue tumor, see the preferred term **Hibernoma**.

Brown fat tumor, see the preferred term **Hibernoma**.

Cartilage hyperplasia, see the preferred term **Chondrocyte hyperplasia**.

Chondrocyte hyperplasia is an increase in the number of chondrocytes and/or cartilage resembling an expansile growth, but it is nonneoplastic. Proliferating chondrocytes are well differentiated, often hypertrophied, and observed in irregular clusters. This change often occurs focally in response to inflammation, cartilage injury, and in association with chondromucinous degeneration in rodents.

Differential diagnosis: **Chondroma**.
Synonym(s): **Cartilage hyperplasia**.

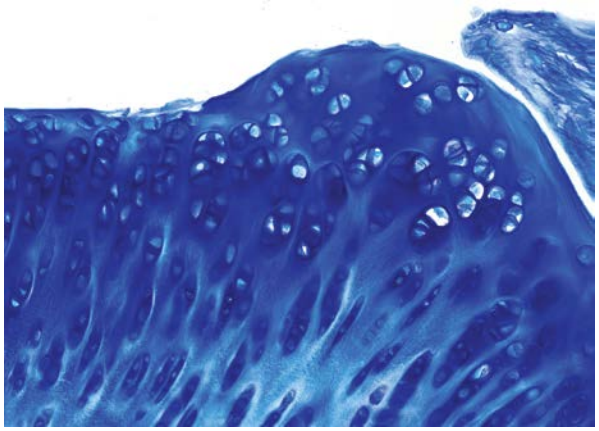


FIGURE 2 Chondrocyte hyperplasia in the tibia of a mouse. Note the increased number of chondrocytes that appear hypertrophied and arranged in irregular clusters. Decalcified bone, toluidine blue stain.

References

Fossey, S. et al. 2016. Nonproliferative and proliferative lesions of the rat and mouse skeletal tissues (bones, joints, and teeth). *J Toxicol Pathol* 29:49S–103S.

Long, P. et al. 1993. Proliferative lesions of bone, cartilage, tooth, and synovium in rats, MST-2. In: *Guides for Toxicologic Pathology*. Washington, DC: STP/ARP/AFIP.

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https://www.toxpath.org/ssdnc/BoneJointToothPro.pdf

Chondroma is a benign tumor composed primarily of cartilage-forming cells (e.g., chondrocytes, chondroblasts) occurring most commonly in the skeleton, but also in extraskeletal sites. It is a well-circumscribed, expansile tumor with neoplastic chondrocytes lacking orderly arrangement, with minimal pleomorphism and rare mitotic figures. Neoplastic chondrocytes are surrounded by abundant, lightly basophilic matrix. Chondromas typically do not metastasize or invade the surrounding tissues. Chondroma is rare in dogs, mice, and hamsters but can occasionally be observed in the nasal turbinates of rats. Although osseous metaplasia can be observed in these tumors, this should not be confused with neoplastic osteoblastic bone formation.

Differential diagnosis: **Chondrocyte hyperplasia**.

References

Fossey, S. et al. 2016. Nonproliferative and proliferative lesions of the rat and mouse skeletal tissues (bones, joints, and teeth). *J Toxicol Pathol* 29:49S–103S.

Long, P. et al. 1993. Proliferative lesions of bone, cartilage, tooth, and synovium in rats, MST-2. In: *Guides for Toxicologic Pathology*. Washington, DC: STP/ARP/AFIP.

McInnes, E.F., Ernst, H., and Germann, P. 2013. Spontaneous neoplastic lesions in control Syrian hamsters in 6-, 12-, and 24-month short-term and carcinogenicity studies. *Toxicol Pathol* 41:86–97.

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Chondrosarcoma is a malignant tumor of cartilage-forming cells (e.g., chondrocytes, chondroblasts). These neoplasms arise in the skeleton but can occur in other locations such as the eyelid, larynx, and ear. Tumors typically consist of highly cellular lobules composed of large basophilic neoplastic cells in lacunae with adjacent cartilage matrix. These tumors are usually well differentiated, but neoplastic cells can show variation in size (e.g., larger, multinucleated) and shape (e.g., spindle-shaped). Metastasis to the lung is common. These tumors rarely occur in mice but can occur spontaneously in rats or be induced by carcinogens. Chondrosarcoma has been reported in a squirrel monkey, and in older dogs.

Differential diagnoses: **Osteosarcoma**; **Chondroma**; **Osteochondroma**; **Chordoma**.

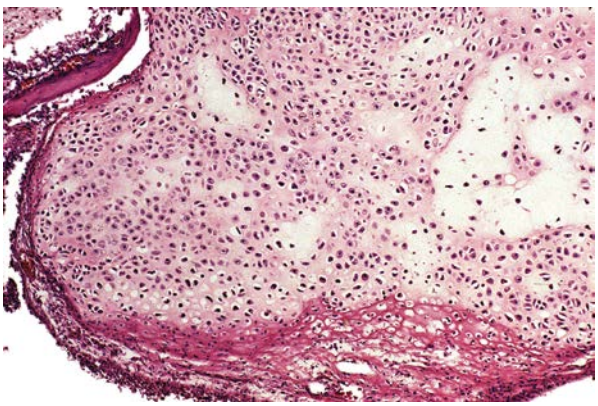


FIGURE 3 Chondrosarcoma in a rat, H&E. The unencapsulated tumor displays well-differentiated, large, basophilic cells within lacunae surrounded by occasional areas of cartilaginous matrix. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

References

Fossey, S. et al. 2016. Nonproliferative and proliferative lesions of the rat and mouse skeletal tissues (bones, joints, and teeth). *J Toxicol Pathol* 29:49S–103S.

Long, P. et al. 1993. Proliferative lesions of bone, cartilage, tooth, and synovium in rats, MST-2. In: *Guides for Toxicologic Pathology*. Washington, DC: STP/ARP/AFIP.

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Chordoma is a malignant tumor of primitive notochord remnants. Neoplastic mesenchymal cells are arranged in lobules and contain abundant cytoplasmic vacuolation ("physaliphorous cells"). This invasive tumor has been reported in humans, rats, mice, ferrets, dogs, and zebrafish. Chordomas are frequently observed in the axial skeleton and at the base of the skull, with or without metastasis to the lungs. Immunohistochemical stains aid in confirming the diagnosis of chordoma from similar-appearing tumors. Chordomas are positive for biomarkers such as glycogen, keratin, neuron-specific enolase, S-100 protein, and vimentin but are negative for lipid. Mucin has been described in these tumors.

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Differential diagnoses: **Chondroma**; **Chondrosarcoma**; **Liposarcoma**; **Hibernoma** (see below for differentiating biomarkers).

Differential Diagnosis	Histochemical and Immunohistochemical Stain
Chondromas, chondrosarcoma	Keratin negative
Liposarcoma	Lipid (oil red O and Sudan IV) positive; glycogen (periodic acid-Schiff) negative
Hibernoma	Oil red O and Sudan IV positive

References

Cho, E. et al. 2011. Chordoma in the tail of a ferret. *Lab Anim Res* 27:53–57.

Fossey, S. et al. 2016. Nonproliferative and proliferative lesions of the rat and mouse skeletal tissues (bones, joints, and teeth). *J Toxicol Pathol* 29:49S–103S.

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Epulis, fibromatous of periodontal ligament origin is a benign oral neoplasm in dogs. This stromal neoplasm appears grossly as a gray mass adjacent to teeth, commonly in the maxilla. It is composed of stellate to spindle-shaped fibroblasts, and collagen resembling the periodontal ligament. Islands or cords of epithelial cells are commonly seen in these tumors but are considered a secondary feature derived from the cell rests of Malassez. Cementum-like material is often observed in the stroma. Modifiers of "fibromatous" and "ossifying" have been applied to these tumors.

Differential diagnosis: **Fibrous hyperplasia**.

Synonym(s): **Odontogenic fibroma, peripheral**.

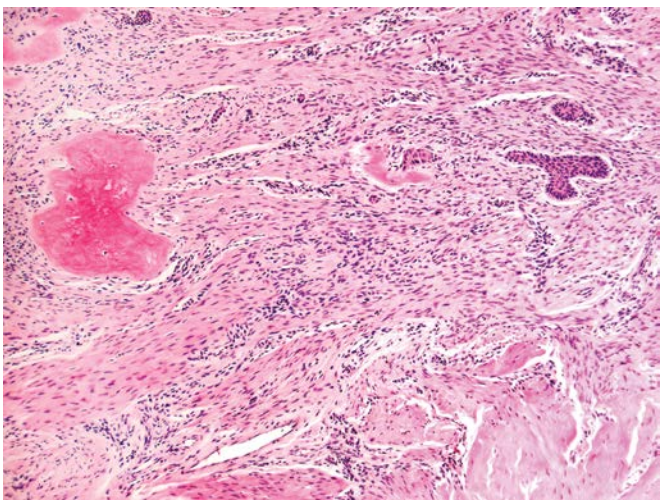


FIGURE 4 Epulis, fibromatous of periodontal ligament origin in the oral cavity of a dog. Abundant spindle-shaped fibroblasts and collagen comprise the mass with occasional islands of epithelial cells and cementum-like material. Decalcified tissue, H&E.

References

Arzi, B. et al. 2011. Expression of cytokeratins in the epithelium of canine odontogenic tumours. *J Comp Pathol* 145:345–351.

Brown, C., Baker, D., and Barker, I. 2007. Alimentary system. In: Maxie, M.G. (ed.) *Jubb, Kennedy, and Palmer's Pathology of Domestic Animals*, Vol. 2. Philadelphia: Elsevier, pp. 27–28.

Fiani, N. et al. 2011. Clinicopathologic characterization of odontogenic tumors and focal fibrous hyperplasia in dogs: 152 cases (1995–2005). *J Am Vet Med Assoc* 238:495–500.

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http://avmajournals.avma.org/doi/abs/10.2460/javma.238.4.495?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed

Fibroma is a benign neoplasm of fibroblasts. Neoplasms are dense, space occupying, and typically contain abundant, mature, dense collagen matrix with low cellularity. Neoplastic fibroblasts are spindle-shaped and well-differentiated without mitotic figures or pleomorphism. Neoplastic cells often form interlacing bundles; however, storiform or cartwheel-shaped patterns have been described. Nuclei are oval-shaped and vesicular to hyperchromatic. Myxomatous areas and stellate cells can be observed in these tumors. Fibromas have been described in rats, mice, hamsters, ferrets, and dogs spontaneously in skin, and in rats with iron dextran injections.

Differential diagnoses: **Fibrosarcoma**; **Fibrosis**; **Mammary gland fibroadenoma**; **Fibrous hyperplasia**.

Synonym(s): **Histiocytoma fibrous, benign**.

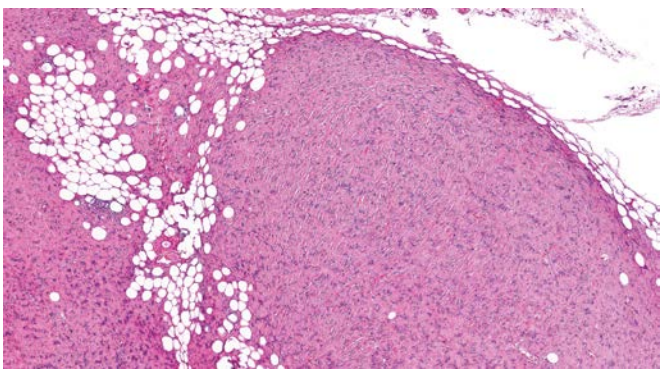


FIGURE 5 Fibroma in the subcutaneous tissues of a rat, H&E. Spindled fibrocytes are arranged into streaming bundles and whorls with interspersed bands of collagen. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

References

Greaves, P. et al. 2013. Proliferative and non-proliferative lesions of the rat and mouse soft tissue, skeletal muscle and mesothelium. *J Toxicol Pathol* 26:1S–26S.

McInnes, E.F., Ernst, H., Germann, P. 2013. Spontaneous neoplastic lesions in control Syrian hamsters in 6-, 12-, and 24-month short-term and carcinogenicity studies. *Toxicol Pathol* 41:86–97.

Parker, G.A. and C.A. Picut. 1993. Histopathologic features and post-surgical sequelae of 57 cutaneous neoplasms in ferrets (*Mustela putorius furo* L.). *Vet Pathol* 30:499–504.

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http://vet.sagepub.com/content/30/6/499.long

Fibroma, cementifying/ossifying is a benign, well-demarcated neoplasm composed of spindle-shaped cells arising in the jaw, often adjacent to the incisors. Neoplastic cells surround islands of woven bone or cementum creating islands that can produce shapes reminiscent of the letters "Y" or "C." Neoplastic cells can transform into osteoblasts and cementoblasts forming these islands. Cementifying/ossifying fibromas have rarely been reported in mice and dogs.

Differential diagnoses: **Fibro-osseous lesion**; **Osteoma**; **Osteofibroma**; **Osteosarcoma**.

References

Fossey, S. et al. 2016. Nonproliferative and proliferative lesions of the rat and mouse skeletal tissues (bones, joints, and teeth). *J Toxicol Pathol* 29:49S–103S.

Soltero-Rivera, M. et al. 2015. Benign and malignant proliferative fibro-osseous and osseous lesions of the oral cavity of dogs. *Vet Pathol* 52:894–902.

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Fibroma, odontogenic is a benign dental tumor arising from the periodontal ligament or dental papilla. These expansile, well-circumscribed masses have primitive mesenchymal cells admixed with collagen, undifferentiated dental epithelium, and cementum-like material. Nests of squamous epithelial cells have been observed. Odontogenic fibromas have been described as arising spontaneously in rats and mice.

Differential diagnoses: **Ameloblastoma**; **Ameloblastic odontoma**; **Ameloblastic fibro-odontoma**; **Odontoma**.

References

Fossey, S. et al. 2016. Nonproliferative and proliferative lesions of the rat and mouse skeletal tissues (bones, joints, and teeth). *J Toxicol Pathol* 29:49S–103S.

Long, P. et al. 1993. Proliferative lesions of bone, cartilage, tooth, and synovium in rats, MST-2. In: *Guides for Toxicologic Pathology*. Washington, DC: STP/ARP/AFIP.

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https://www.toxpath.org/ssdnc/BoneJointToothPro.pdf

Fibromatosis, retroperitoneal is a proliferation of fibrous tissue localized in the mesentery, and in monkeys, frequently at the junction of the ileum and cecum. The proliferation usually exhibits areas of florid fibroblastic proliferation organized in bundles and whorls associated with abundant blood vessels and inflammatory cells, and/or less cellular areas rich in sclerotic fibrous tissue. The neoplastic masses can strangle and/or invade various portions of the gastrointestinal tract. This proliferation bears similarities with human Kaposi sarcomas. The disease is usually associated with latent gamma herpesviruses (rhadinoviruses and retroperitoneal fibromatosis herpesvirus) reactivated during periods of immunosuppression. It was also recently observed in immunodeficient simian immunodeficiency virus–positive monkeys coinfected with simian polyomavirus and rhesus cytomegalovirus.

Differential diagnoses: **Sarcoma NOS**; **Fibrosarcoma, pleomorphic**.

Reference

White, J. et al. 2011. Longitudinal patterns of viremia and oral shedding of rhesus rhadinovirus and retroperitoneal fibromatosis herpesviruses in age-structured captive breeding populations of rhesus Macaques (Macaca mulatta). *Comp Med* 61:60–70.

Link

https://www.ncbi.nlm.nih.gov/pubmed/21819683

Fibrosarcoma is a malignant neoplasm of fibroblasts. Tumors are invasive and contain variable amounts of collagen matrix, with or without necrosis and hemorrhage. Spindle-shaped neoplastic fibroblasts are arranged in interlacing bundles. There can be many mitotic figures and pleomorphism observed in these tumors. Fibrosarcomas have been described in rats, mice, ferrets, and dogs. Connective tissue neoplasms are uncommon in nonhuman primates; however, fibrosarcomas have been reported in association with viruses. These tumors have been observed in rats administered peroxisome proliferator–activated receptor agonists and are often induced by implant materials or chemical injection. Pleomorphic fibrosarcomas contain more neoplastic cellular heterogeneity and can feature giant cells.

Differential diagnoses: **Fibroma**; **Fibrosis**; **Fibrous hyperplasia**.

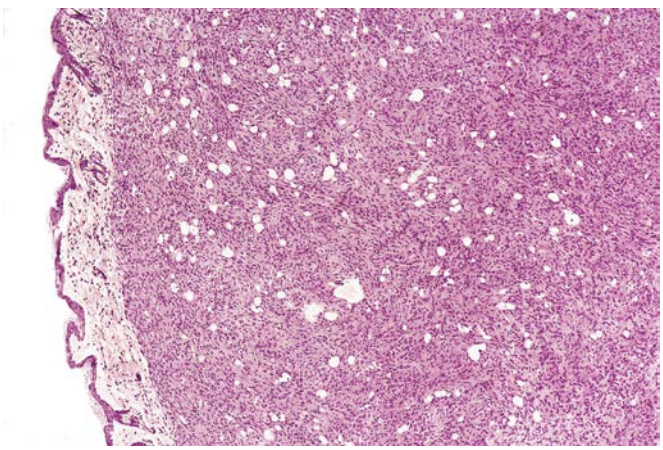


FIGURE 6 Fibrosarcoma in the subcutaneous tissues of a mouse, H&E. The unencapsulated, pleomorphic tumor displays spindled cells arranged into streaming bundles and whorls with occasional mitotic figures observed. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

References

Greaves, P. et al. 2013. Proliferative and non-proliferative lesions of the rat and mouse soft tissue, skeletal muscle and mesothelium. *J Toxicol Pathol* 26:1S–26S.

Miller, A.D. 2012. Neoplasia and proliferative disorders of nonhuman primates. In: Abee, C.R. et al. (eds.) *Nonhuman Primates in Biomedical Research*. London: Academic Press, pp. 325–356.

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Fibrosarcoma, pleomorphic is a malignant neoplasm in which the cell of origin is unknown. The two most widely accepted hypotheses are that this tumor arises from undifferentiated, early (stem) mesenchymal cells, or a collection of undifferentiated sarcomas that have morphological similarities. The subcutaneous tissue is a site where this tumor is frequently observed in mammalian species used in toxicology studies (mice, rats, dogs, and monkey). Two neoplastic cell populations in variable numbers are usually distinguished: cells that are fusiform, organized in storiform or cartwheel patterns, and presumably of (myo)fibroblastic origin, and round or polygonal cells that are assumed to be of histiocytic lineage. Neoplastic multinucleated giant cells, a myxoid background, florid angiogenesis, and/or variable numbers of inflammatory cells can be associated with these cells. In rodents, this tumor can be induced by various implanted materials such as polymers (3 polyvinyl chlorides, 1 polyhydroxyethyl methacrylate, and 1 dimethyl polysiloxane), silicone, zirconia, and nickel alloys or by the administration of chemicals such as 7,12-dimethylbenz[a]anthracene (DMBA) or *N*-methyl-*N*-nitrosourea (MNU), 4-(hydroxyamino)-quinoline 1-oxide (4-HAQO). This neoplasm has also been associated recently with the subcutaneous injection of a pegylated protein.

Differential diagnosis: **Sarcoma NOS**.

Synonym(s): **Sarcoma, pleomorphic undifferentiated**; **histiocytoma fibrous malignant**.

References

Greaves, P. et al. 2013. Proliferative and non-proliferative lesions of the rat and mouse soft tissue, skeletal muscle and mesothelium. *J Toxicol Pathol* 26:1S–26S.

Kirkpatrick, C. et al. 2000. Biomaterial-induced sarcoma: A novel model to study preneoplastic change. *Am J Pathol* 156:1455–1467.

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https://www.ncbi.nlm.nih.gov/pubmed/10751369

Fibrous hyperplasia is expansion of the gingiva in dogs appearing grossly as localized or widespread thickening. This nonneoplastic lesion is composed of dense stromal tissue and inflammatory cells with overlying hyperplastic epithelial cells. Hard tissue and nests of epithelial cells can be a feature. The mature fibroblastic stroma in this lesion has lower cellularity as compared to that in the tumor fibromatous epulis of periodontal ligament origin. Fibrous hyperplasia is thought to form in response to irritation and inflammation.

Differential diagnosis: **Epulis, fibromatous of periodontal ligament origin**.

References

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Hibernoma is a neoplastic growth arising from brown adipose cells (a type of fat cell found in specific locations, i.e., packed with mitochondria and responsible for nonshivering thermogenesis in cold environment). In animals, these tumors are usually multilobulated, the lobules being separated by a delicate collagenous stroma. Neoplastic cells resemble the normal brown adipose cell counterpart with a round to polygonal morphology and an eosinophilic, finely vacuolated cytoplasm with small, variably sized vacuoles and a round, usually central to paracentral nucleus containing a small round nucleolus (typical hibernoma cell). Cellular polymorphism and mitoses are typically low. The cytoplasmic fat content is positive with oil red O or other fat stains. By immunohistochemistry, these tumors are positive for uncoupling protein 1, and ultrastructurally they exhibit lipid vacuoles and abundant mitochondria. Hibernomas usually arise from the sites of brown adipose tissue depots in the thoracic or abdominal cavities or subcutaneous tissue. They are rare in all species and seem slightly more prevalent in males than in females. Their occurrence within muscle has not been reported in the literature. In rodents, contrary to other mammalian species (humans, dogs, or monkeys), brown adipose tissue continues to develop after birth, and plays a more significant role in nonshivering thermogenesis, which could explain the slightly higher prevalence and occurrence of the malignant variant of this tumor in these species. In rats, hibernomas seem more frequently localized in the mediastinum or abdominal cavity and can be malignant in older animals, contrary to humans and dogs where they seem mostly benign. In the dog, they have been observed in the ocular orbit or in the omentum. Human pathologists distinguish four variants, called typical, myxoid, spindle cell type, and lipoma-like subtype, but no such categorization has been recognized in the veterinary literature. In toxicologic pathology, hibernomas have been observed in rats after prolonged exposure to cold, prolonged sympathetic activation, prolonged hypoxemia, peroxisome proliferator–activated receptor (PPAR)-alpha or gamma agonists, or inhibitors of the Janus kinase/signal transducer and activator of transcription administration. Cynomolgus monkeys and rats given a PPAR-gamma agonist for a few months both exhibited brown adipose tissue hyperplasia/hypertrophy.

Differential diagnoses: **Lipoma**; **Liposarcoma**.

Synonym(s): **Brown adipose tissue tumor**; **brown fat tumor**.

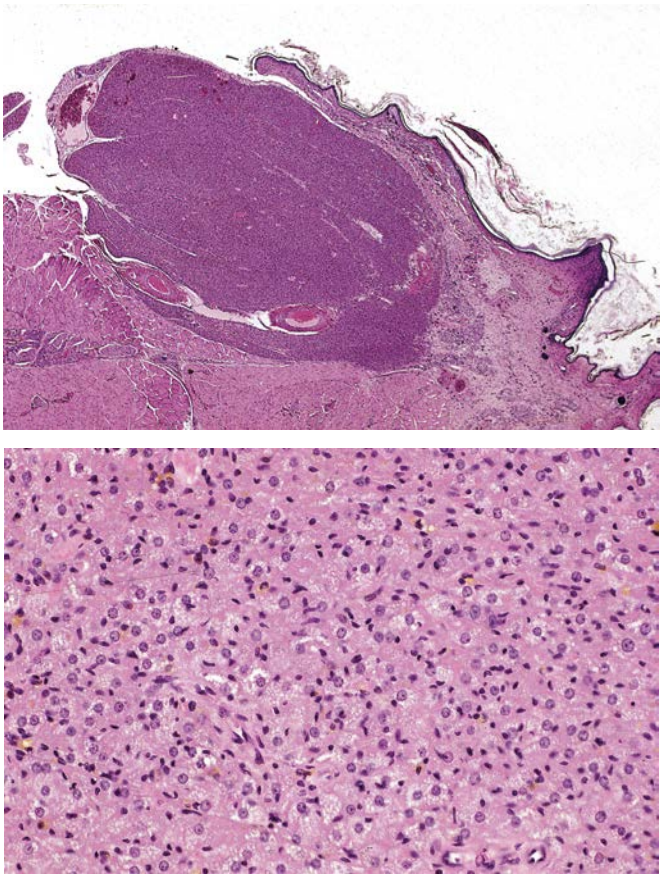


FIGURE 7 Hibernoma in the subcutaneous tissues of a rat, H&E. The well-circumscribed mass at low magnification displays eosinophilic adipocytes with cytoplasmic microvesiculation. On higher magnification, neoplastic cells are arranged into dense sheets. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

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Histiocytoma, fibrous benign, see the preferred term **Fibroma**.

Histiocytoma, fibrous malignant, see the preferred term **Fibrosarcoma, pleomorphic**.

Leiomyoma is a benign neoplasm arising from smooth muscle cells. Leiomyomas are usually well-circumscribed, nodular tumors. Cytological, histochemical, and immunohistochemical characteristics (immunoreactive for desmin and smooth muscle actin) and ultrastructural features are similar to those described for leiomyosarcomas except for the presence of minimal cell polymorphism, a minimal number of mitoses, and the absence of local invasion and metastases. These tumors are uncommon in rodents, with a relatively greater frequency in the uterus compared to other visceral organs. The tumor is also generally uncommon in dogs but is the most common tumor of the uterus, and is hormone(s)-dependent at this location. The stomach also seems to be a site of predilection of leiomyoma in dogs, particularly at the junction with the esophagus. In cynomolgus monkeys, leiomyomas have been reported in the uterus.

Differential diagnoses: **Leiomyosarcoma**; **Fibrosarcoma**.

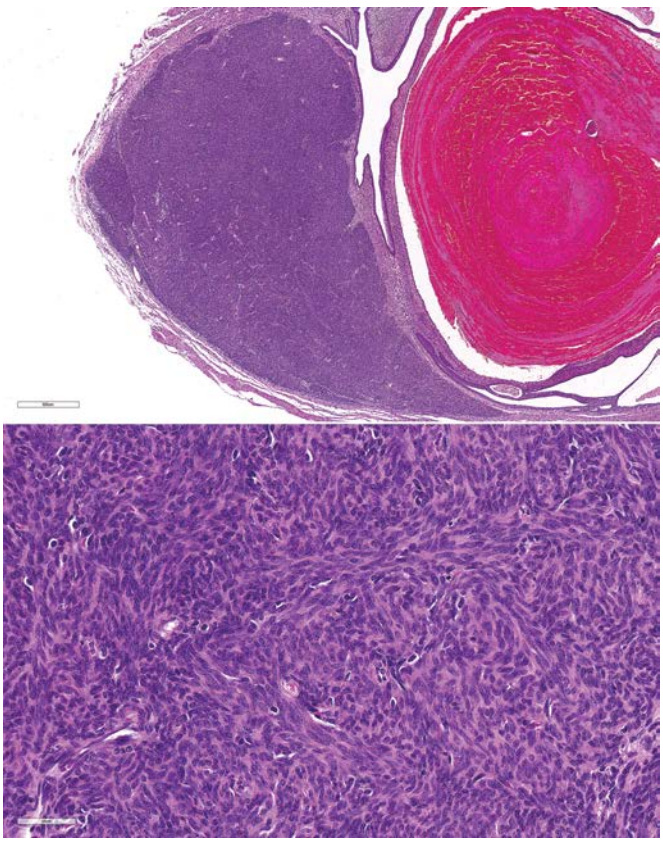


FIGURE 8 Leiomyoma in the uterus of a mouse, H&E. Lower magnification image of the well-circumscribed tumor on the top. Note the elongated cigar-shaped appearance of the neoplastic cells in the higher magnification image.

References

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Leiomyosarcoma is a malignant neoplasm arising from smooth muscle cells. They are characterized by interlacing whorls and bundles of spindle-shaped cells forming criss-cross patterns. Cells with bizarre polygonal shapes with multiple nuclei can also be observed, particularly in the urinary bladder of dogs. Characteristic neoplastic cell features include blunt-ended or oval, elongated (cigar-shaped) nuclei, eosinophilic cytoplasm containing longitudinal myofilaments that stain with phosphotungstic acid hematoxylin, and the presence of perinuclear clear spaces. Cellular polymorphism is usually high with a moderate to high mitotic index. Areas of degeneration, necrosis, and mineralization can be observed. Leiomyosarcomas show immunoreactivity for desmin and smooth muscle actin. Ultrastructurally, characteristic features include the presence of bundles of myofilaments with dense bodies, and dense plaques at the points of attachment of myofilaments to the cell membranes, the presence of vesicles, and a basal lamina. In toxicologic pathology, leiomyosarcomas have been associated following the implantation of various biomaterials, or administration of nickel sulfide or *N*-methyl-*N*′-nitro-nitrosoguanidine in rodents or dogs.

Differential diagnoses: **Leiomyoma**; **Fibrosarcoma**.

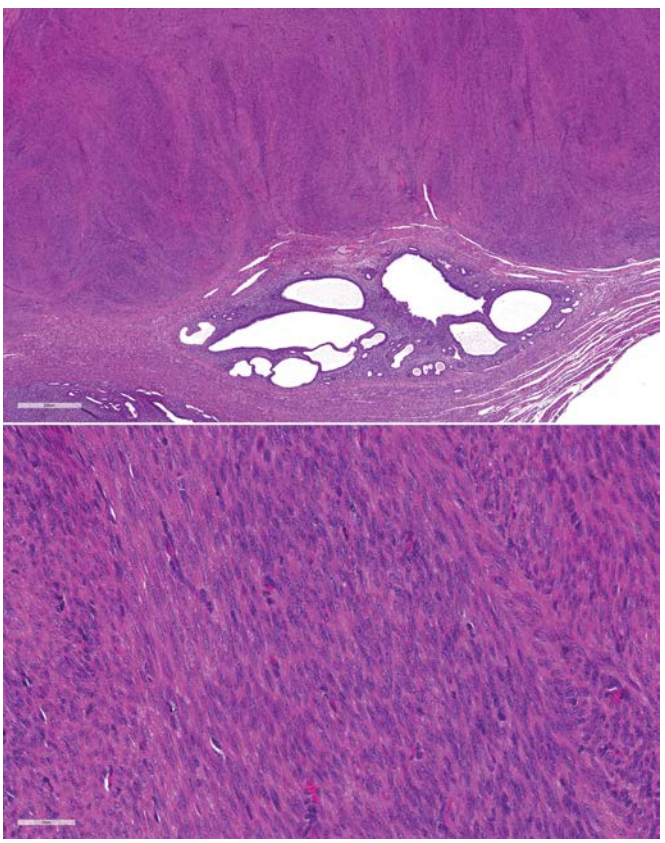


FIGURE 9 Leiomyosarcoma in the uterus of a mouse, H&E. Lower magnification image of the highly cellular malignant tumor. Note the elongated, cigar-shaped appearance of the neoplastic cells in the higher magnification image.

References

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Lipoma is a benign neoplasm arising from white adipose (fat) cells. The tumor is usually identified macroscopically as a white mass. The neoplastic cells resemble mature adipocytes with one or a few large vacuoles in the cytoplasm that push the nucleus to one side of the cell. There is very little stroma in lipomas, usually limited to fine collagenous strands separating tumor lobules. Similar to liposarcomas, lipomas are more often reported in dogs, and seem to be one of the most frequent mesenchymal tumors in this species. In dogs, a rare subtype called "spindle cell lipoma" has been reported in the subcutis of the head. In laboratory monkeys, lipomas have been reported in the abdominal cavity or subcutis as single or multiple (lipomatosis) masses. Intracranial lipomas have been reported in mice, rats, and baboons. In all laboratory species, intramuscular lipomas are rare. In toxicologic pathology, lipomas have been associated with the administration of peroxisome proliferator-activated receptor (PPAR)-alpha or gamma agonists.

Differential diagnoses: **Liposarcoma**; **Adipose tissue hyperplasia**; **Hibernoma**; **Angioma**.

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Kaspareit, J. et al. 2007. Spontaneous neoplasms observed in cynomolgus monkeys (Macaca fascicularis) during a 15-year period. *Exp Toxicol Pathol* 59:163–169.

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Liposarcoma is a malignant neoplasm arising from white adipose (fat) cells. The neoplastic adipocytes or lipoblasts are round or polygonal, have one or a few large or multiple small cytoplasmic vacuoles with a single, centrally placed

or eccentric nucleus with dense chromatin, and an irregular nuclear envelope compared to mature nonneoplastic adipocytes. Liposarcomas are divided into three subtypes. The well-differentiated subtype is characterized by neoplastic, lipid-filled adipocytes as demonstrated by fat histochemical stains (oil red O) positive cytoplasm. Mitotic activity and cellular pleomorphism are low. The myxoid subtype has cellular characteristics similar to well-differentiated tumors, but with the presence of small numbers of variously shaped neoplastic cells (fusiform or elongated cells, multinucleated cells) and bluish myxoid stromal deposits. The third subtype is called pleomorphic liposarcoma and has very few easily recognizable neoplastic adipocytes. There is usually high cytonuclear pleomorphism (elongated cells, star-shaped cells, giant cells) with an abundant eosinophilic cytoplasm, and sometimes multiple nuclei per cell. The observation of vacuoles in occasional cells and fat histochemical staining, as well as immunohistochemical positivity for vimentin and S100, usually lead to a strong suspicion of pleomorphic liposarcoma. The usefulness of mouse double minute 2 homolog (MDM2) immunostaining in poorly differentiated liposarcoma is not well established in animals. Liposarcomas are more frequently reported in dogs compared to other species utilized in toxicology studies (rat or monkeys) and is rare within muscle. In fact, it has only been reported in the dog within the skeletal muscle of the thigh or tongue. Old Osborne-Mendel and Fisher 344 rats seem to be predisposed to kidney liposarcomas. In monkeys, there are very few reports of liposarcomas, and to our knowledge, only one article has been published arising from the peritoneum of a Japanese macaque. In toxicologic pathology, liposarcomas have been associated with persistent inert material (glass, microchip), or with systemic administration of peroxisome proliferators-activated receptor (PPAR)-alpha or gamma agonists. The PPAR and CCAAT enhancer-binding protein (C/EBP) pathways are both important for liposarcoma pathogenesis.

Differential diagnoses: Lipoma infiltrative; **Sarcoma NOS**; **Myxosarcoma**; **Fibrosarcoma, pleomorphic**.

References

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https://www.ncbi.nlm.nih.gov/pubmed/15945392

Mesenchymoma, malignant is a neoplasm composed of several types of mesenchymal cells. These tumors usually comprise an undifferentiated spindle-shaped mesenchymal cell population organized in bundles or whorls, and several populations of differentiated mesenchymal cells (e.g., skeletal muscle, cartilage, bone, white adipose). Variable numbers of inflammatory cells can be observed in the stroma. This tumor has been reported in dogs, rats, mice, and in a rhesus macaque. Some reports show that in dogs, these tumors have a tendency to grow locally and invade local tissues, but infrequently metastasize. In rodents, malignant mesenchymomas have been induced by 1,2-dimethylhydrazine dihydrochloride, associated with inoculation of viruses (Moloney murine sarcoma virus or adenovirus type 9) or ultraviolet irradiation.

Differential diagnosis: **Sarcoma NOS**.

Synonym(s): **Sarcoma, mixed**.

Reference

Greaves, P. et al. 2013. Proliferative and non-proliferative lesions of the rat and mouse soft tissue, skeletal muscle and mesothelium. *J Toxicol Pathol* 26:1S–26S.

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Mesothelial hyperplasia is characterized by dense sheets or villous-like, nonneoplastic thickenings of the mesothelium. Mesothelial cells in these thickenings are well differentiated, 1–2 layers thick, and appear as mature cuboidal cells. Cells in mesothelial hyperplasia do not exhibit mitotic figures or cellular atypia. In areas with villous-like growth patterns, the mesothelial cells are supported by a fine fibrovascular stroma. The stroma in mesothelial hyperplasia occasionally contains inflammatory cells, and usually has a variable amount of collagen support. In rats, reactive mesothelial hyperplasia has been observed after chronic intraperitoneal administration of 0.9% sodium chloride solution or fluid containing methylglyoxal a glucose degradation product contained in dialysis liquids. In the same species, mesothelial hyperplasia occurs in the acute phase of intrapleural deposition of asbestos fibers or fibrous glass.

Differential diagnosis: **Mesothelioma, malignant**.

Reference

Greaves, P. et al. 2013. Proliferative and non-proliferative lesions of the rat and mouse soft tissue, skeletal muscle and mesothelium. *J Toxicol Pathol* 26:1S–26S.

Link

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Mesothelioma, malignant is a neoplastic growth arising from the sheet of specialized cells lining the serosal cavities (pleural, peritoneal, and pericardial), and the surface of organs in these cavities. This tumor usually infiltrates adjacent tissues, has high cell polymorphism, many mitotic figures, and frequently exhibits areas of necrosis. Mesotheliomas can have one of the following three morphological presentations. In the epithelioid subtype, tumor cells are organized in papilla or tubes with the

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presence of poorly differentiated gland-like structures. Solid areas can be observed in epithelioid mesothelioma. The cells in these neoplasms are usually round and epithelioid, with round vesicular nuclei and a foamy or vacuolated cytoplasm. In the sarcomatoid subtype, cells are arranged in intersecting bundles or whorls. This presentation usually contains a variable amount of collagen in the stroma. Cells are fusiform, and often have a variable number of vacuoles in sarcomatoid tumors. The third presentation has mixed epithelioid and sarcomatoid structures. Each cytoarchitectural feature (sarcomatoid and epithelioid) must represent 10% of the tumor to be labeled mixed cell type. Fibrosarcomatous, osteosarcomatous, and/or chondrosarcomatous differentiations can be observed in sarcomatoid or mixed mesotheliomas. Malignant mesothelial cells are usually immunopositive for cytokeratins 5 and/or 6, cytokeratin 18, Wilm's tumor gene-1 (WT1), calretinin, and mesothelin, while they are negative or weakly positive for carcinoembryonic antigen (CEA) or MOC-31 antibody. Mesothelioma has been associated with various natural and synthetic persistent fibrous materials such as asbestos or with chemicals such as potassium bromate in rodents or dogs. Simian virus 40, a polyomavirus of macaques, has been shown to act as a cocarcinogen with asbestos in hamsters or mice, but its role in human mesothelium carcinogenesis (the question became relevant with SV40-contaminated polio vaccines) remains controversial.

Differential diagnoses: **Fibrosarcoma**; **Leiomyosarcoma**; **Histiocytoma, fibrous malignant**; **Mesothelial hyperplasia**; **Thymoma**; Lung adenocarcinoma.

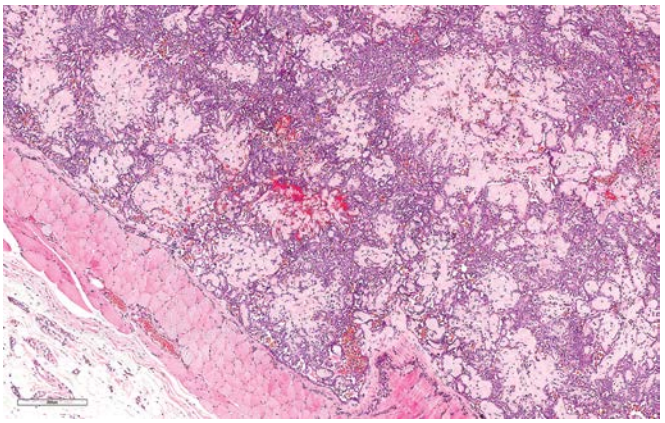


FIGURE 10 Malignant mesothelioma in the abdominal cavity of a rat, H&E. Note the papillary growth of neoplastic cells supported by dense collagenous stroma.

References

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Myxosarcoma is a malignant neoplasm of connective tissue arising from primitive fibroblasts. A characteristic feature of this tumor is the presence of copious amounts of stromal mucins. In laboratory animals (most frequently in dogs), it has been reported in various locations including but not limited to long and flat bones, subcutaneous connective tissues, heart, peritoneum, and joints. Because of the low prevalence of this tumor, there does not seem to be a predominant site of predilection. The heart and skeletal muscle seem relatively frequent locations in people. Grossly, the tumor usually has a gelatinous consistency and is sometimes cystic. Neoplastic cells are spindle to stellate shaped and are embedded in characteristic abundant mucinous stroma rich in acid mucopolysaccharides that stain with Alcian blue. In dog, a disease similar to human Carney syndrome has been described with the co-occurrence of heart myxosarcoma, bilateral adrenal adenomas, and pituitary hyperplasia. This tumor was reported to be induced in the subcutis of mice by administration of 4-(Methyl)benzenediazonium sulfate or with application of 12-0-tetradecanoylphorbol-13-acetate. In this same species, mutations of the tumor suppressor TP53 at serine 18 in the *N*-terminal region resulted in several tumors, including myxosarcomas.

Differential diagnoses: **Fibrosarcoma, pleomorphic**; **Liposarcoma**; **Sarcoma NOS**.

References

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Odontoameloblastoma, see the preferred term **Ameloblastic odontoma**.

Odontogenic tumor, benign is a benign neoplasm originating from components of the tooth germ. This diagnosis is often used when the neoplasm is of odontogenic origin but cannot be specified in one of the other odontogenic tumor categories. This tumor has been described in rodents.

Differential diagnoses: **Fibroma, odontogenic**; **Ameloblastic odontoma**.

References

Fossey, S. et al. 2016. Nonproliferative and proliferative lesions of the rat and mouse skeletal tissues (bones, joints, and teeth). *J Toxicol Pathol* 29:49S–103S.

Long, P. et al. 1993. Proliferative lesions of bone, cartilage, tooth, and synovium in rats, MST-2. In: *Guides for Toxicologic Pathology*. Washington, DC: STP/ARP/AFIP.

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https://www.toxpath.org/ssdnc/BoneJointToothPro.pdf

Odontogenic tumor, malignant is a malignant neoplasm originating from components of the tooth germ. This diagnosis is often used when the neoplasm is of odontogenic origin but cannot be specified in one of the other odontogenic tumor categories. This tumor has been described in rodents.

Differential diagnoses: **Fibroma, odontogenic**; **Ameloblastic odontoma**.

References

Fossey, S. et al. 2016. Nonproliferative and proliferative lesions of the rat and mouse skeletal tissues (bones, joints, and teeth). *J Toxicol Pathol* 29:49S–103S.

Long, P. et al. 1993. Proliferative lesions of bone, cartilage, tooth, and synovium in rats, MST-2. In: *Guides for Toxicologic Pathology*. Washington, DC: STP/ARP/AFIP.

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https://www.toxpath.org/ssdnc/BoneJointToothPro.pdf

Odontoma, complex is a malformation (hamartoma) of dental tissues. (See **Hamartoma** for further information.) These lesions are composed of normal mesenchymal and epithelial components such as odontoblasts, cementoblasts, pulp mesenchymal cells, dentin, cementum, and enamel. Tissues are irregularly arranged without resemblance to normal structures as compared to compound odontomas, where there is more differentiation producing toothlike structures (see **Odontoma, compound** for further information). Odontomas occur spontaneously, and following administration of nitrosourea compounds in rodents. They have also been reported in dogs.

Differential diagnoses: **Odontoma, compound**; **Dental dysplasia**; **Ameloblastoma**; **Ameloblastic odontoma**; **Fibroma, odontogenic**.

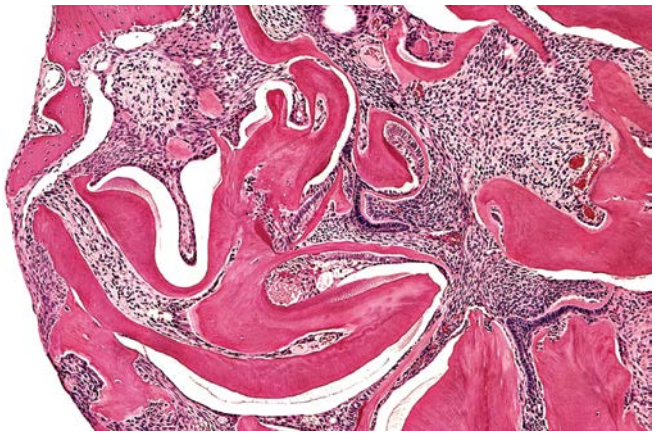


FIGURE 11 Odontoma, rat. This lesion represents a developmental malformation (not neoplasm) in which all dental hard tissues including enamel (appears as clear spaces due to its loss during decalcification), dentin, and cementum as well as odontoblasts, cementoblasts. and dental pulp mesenchymal cells are present within a disorganized mass. Decalcified tooth, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Fossey, S. et al. 2016. *J Toxicol Pathol* 29:49S–103S.)

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Arzi, B. et al. 2011. Expression of cytokeratins in the epithelium of canine odontogenic tumours. *J Comp Pathol* 145: 345–351.

Fossey, S. et al. 2016. Nonproliferative and proliferative lesions of the rat and mouse skeletal tissues (bones, joints, and teeth). *J Toxicol Pathol* 29:49S–103S.

Long, P. et al. 1993. Proliferative lesions of bone, cartilage, tooth, and synovium in rats, MST-2. In: *Guides for Toxicologic Pathology*. Washington, DC: STP/ARP/AFIP.

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https://www.toxpath.org/ssdnc/BoneJointToothPro.pdf

Odontoma, compound is a malformation (hamartoma) of dental tissues. (See **Hamartoma** for further information.) These lesions are composed of normal mesenchymal and epithelial components such as odontoblasts, cementoblasts, pulp mesenchymal cells, dentin, cementum, and enamel. Compound odontomas produce normal-appearing toothlike structures compared to complex odontomas which have irregularly arranged tissues (see **Odontoma complex** for further information). Odontomas occur spontaneously, and following administration of nitrosourea compounds in rodents. They have also been reported in dogs.

Differential diagnoses: **Odontoma, complex**; **Dental dysplasia**; **Ameloblastoma**; **Ameloblastic odontoma**; **Fibroma, odontogenic**.

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Arzi, B. et al. 2011. Expression of cytokeratins in the epithelium of canine odontogenic tumours. *J Comp Pathol* 145:345–351.

Fossey, S. et al. 2016. Nonproliferative and proliferative lesions of the rat and mouse skeletal tissues (bones, joints, and teeth). *J Toxicol Pathol* 29:49S–103S.

Long, P. et al. 1993. Proliferative lesions of bone, cartilage, tooth, and synovium in rats, MST-2. In: *Guides for Toxicologic Pathology*. Washington, DC: STP/ARP/AFIP.

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https://www.ncbi.nlm.nih.gov/pubmed/27621538
https://www.toxpath.org/ssdnc/BoneJointToothPro.pdf

Osteoblast hyperplasia is a proliferation of well-differentiated osteoblasts described in bones of rats administered parathyroid hormone or related peptides. This nonneoplastic finding is observed as single or multiple foci of increased osteoblast-like cells with minimal atypia. The lesion can be associated with an increase in osteoid and mineralized bone locally but does not alter the existing trabeculae.

Differential diagnoses: **Osteodystrophy fibrous**; **Osteoblastic surface increased**; **Bone marrow fibrosis**; **Osteoblastoma**.

References

Fossey, S. et al. 2016. Nonproliferative and proliferative lesions of the rat and mouse skeletal tissues (bones, joints, and teeth). *J Toxicol Pathol* 29:49S–103S.

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https://www.toxpath.org/ssdnc/BoneJointToothPro.pdf
https://www.ncbi.nlm.nih.gov/pubmed/12051548

Osteoblastoma is a benign, expansile neoplasm of bone forming cells (osteoblasts). There is an increase in intramedullary immature bone characterized by well-differentiated osteoblasts bordering irregular trabeculae. Often, fibrovascular stroma is observed between bone trabeculae. Osteoblasts have minimal cellular atypia, and occasionally, evidence of only minimal invasion. Multinucleated cells may be observed. Osteoblastomas have been observed in rats following parathyroid hormone administration.

Differential diagnoses: **Osteoblast hyperplasia**; **Osteosarcoma (osteoblastic)**; **Osteofibroma**.

References

Fossey, S. et al. 2016. Nonproliferative and proliferative lesions of the rat and mouse skeletal tissues (bones, joints, and teeth). *J Toxicol Pathol* 29:49S–103S.

Long, P. et al. 1993. Proliferative lesions of bone, cartilage, tooth, and synovium in rats, MST-2. In: *Guides for Toxicologic Pathology*. Washington, DC: STP/ARP/AFIP.

Vahle, J. et al. 2002. Skeletal changes in rats given daily subcutaneous injections of recombinant human parathyroid hormone (1–34) for 2 years and relevance to human safety. *Toxicol Pathol* 30:312–321.

Links

https://www.ncbi.nlm.nih.gov/pubmed/27621538
https://www.toxpath.org/ssdnc/BoneJointToothPro.pdf
https://www.ncbi.nlm.nih.gov/pubmed/12051548

Osteochondroma is a benign neoplasm composed of lamellar bone and cartilage. Extending from the periosteum, the neoplasm consists of a core of mature trabecular bone with intervening marrow, and an overlying cartilage cap resembling a growth plate. The chondrocytes in this cap are hypertrophic and irregularly arranged. Osteochondromas have been reported in humans, dogs, pigs, rhesus and cynomolgus macaques, and the ring-tailed lemur. These neoplasms have been observed in rats following exposure to chemicals

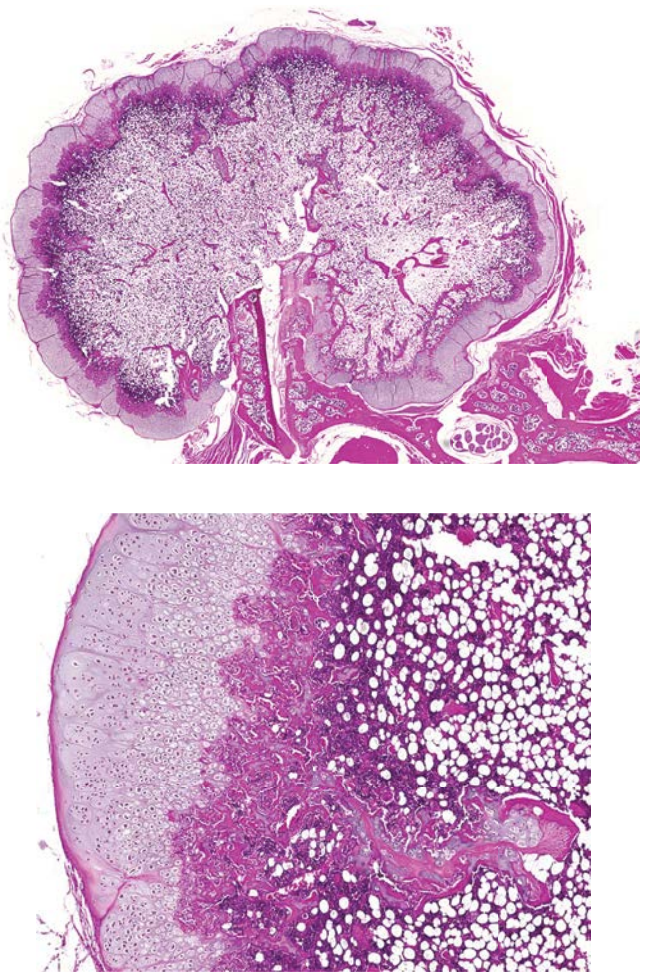


FIGURE 12 Osteochondroma, rat. Low magnification image on the top of the benign mixed mesenchymal neoplasm characterized by both cartilaginous and osseous components. The orderly cap of hyaline cartilage is a distinctive feature of this tumor in the higher magnification image on the bottom. Decalcified bone, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Fossey, S. et al. 2016. *J Toxicol Pathol* 29:49S–103S.)

(vinyl chloride), and radiation. Tumors develop early in life in some species and can undergo malignant transformation. Osteochondromas are not related to degenerative joint disease.

Differential diagnoses: **Osteophytes**; **Osteoma**; **Chondroma**; **Chondrosarcoma**; **Osteosarcoma**.

References

Fossey, S. et al. 2016. Nonproliferative and proliferative lesions of the rat and mouse skeletal tissues (bones, joints, and teeth). *J Toxicol Pathol* 29:49S–103S.

Hope, K. et al. 2015. Solitary osteochondroma in a ring-tailed lemur (*Lemur catta*). *Comp Med* 65:348–351.

Long, P. et al. 1993. Proliferative lesions of bone, cartilage, tooth, and synovium in rats, MST-2. In: *Guides for Toxicologic Pathology*. Washington, DC: STP/ARP/AFIP.

Links

https://www.ncbi.nlm.nih.gov/pubmed/27621538
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4549681/
https://www.toxpath.org/ssdnc/BoneJointToothPro.pdf

Osteofibroma is a benign, expansile neoplasm of bone. Arising from mesenchymal stem cells and osteoblasts, these neoplasms are found predominantly in the axial skeleton, specifically from the medullary cavity of bone. The neoplasm consists of trabecular bone with intervening connective tissue stroma. Given their location, these neoplasms may cause paralysis. These neoplasms have been reported in mice exposed to radioactive material.

Differential diagnoses: **Fibro-osseous lesion**; Bone, reactive; **Osteoma**; **Osteosarcoma**.

Reference

Fossey, S. et al. 2016. Nonproliferative and proliferative lesions of the rat and mouse skeletal tissues (bones, joints, and teeth). *J Toxicol Pathol* 29:49S–103S.

Link

https://www.ncbi.nlm.nih.gov/pubmed/27621538

Osteogenic fibrosarcoma is a malignant neoplasm of fibroblasts originating in bone. Interlacing neoplastic fibroblasts are pleomorphic, produce collagen, and invade the adjacent bone. This tumor has been reported in rodents in control and treated animals in 2-year carcinogenicity studies. Skeletal fibrosarcomas occur in older, medium to large breed dogs.

Differential diagnoses: **Fibrosis**; **Osteosarcoma**.

References

Fossey, S. et al. 2016. Nonproliferative and proliferative lesions of the rat and mouse skeletal tissues (bones, joints, and teeth). *J Toxicol Pathol* 29:49S–103S.

Long, P. et al. 1993. Proliferative lesions of bone, cartilage, tooth, and synovium in rats, MST-2. In: *Guides for Toxicologic Pathology*. Washington, DC: STP/ARP/AFIP.

Links

https://www.ncbi.nlm.nih.gov/pubmed/27621538
https://www.toxpath.org/ssdnc/BoneJointToothPro.pdf

Osteogenic sarcoma, see the preferred term **Osteosarcoma**.

Osteoma is a benign, expansile, well-circumscribed neoplasm of bone derived from osteoblasts and osteocytes arising from cortical bone (periosteal surface). These tumors have been frequently observed in the skull, but also arise from other bones. Although there are features specific to either rats or mice, osteomas typically are composed of dense, mature bone trabeculae, with or without osteoid, with fewer cells in the interior of the neoplasm. Neoplasms in mice contain mostly woven bone, while those in rats have largely lamellar bone. Spaces between trabeculae may contain fat or hematopoietic cells. Osteomas do not display the cellular features of malignancy often associated with osteosarcomas. These neoplasms are rare in rodents (rat, mice, and hamsters), but have been observed more frequently in female mice. Increased incidence of osteomas has been reported following administration

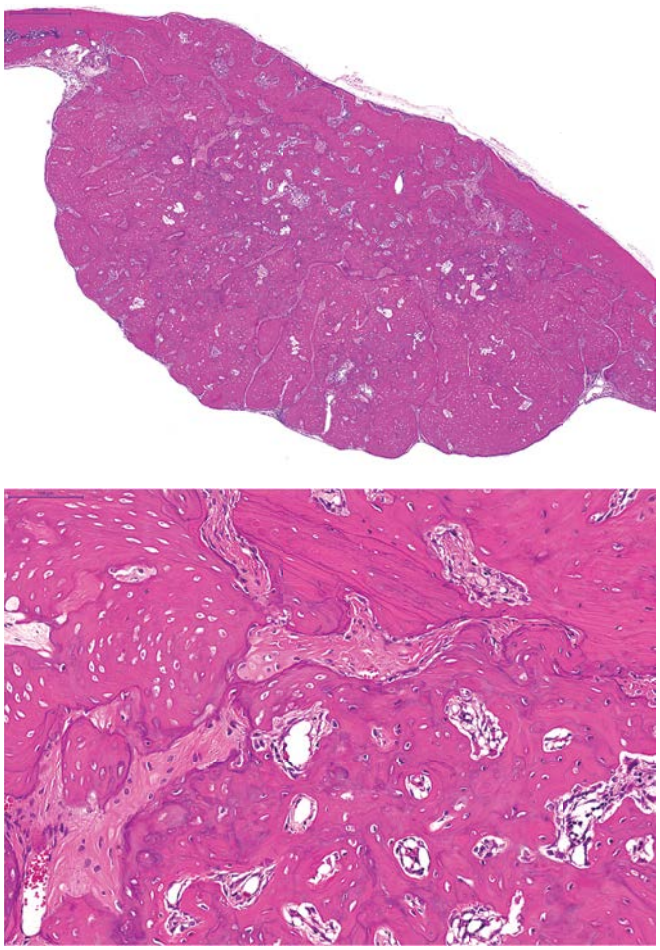


FIGURE 13 Osteoma, mouse. Low magnification image on the top of an expansile, well-demarcated, benign neoplasm of osteocytic or osteoblastic origin consisting of irregular lobules of well-differentiated bone separated by narrow bands of fibrous connective tissue. On higher magnification, the disorganized arrangement of lacunae in the woven bone of the well-differentiated benign neoplasm contrasts with the regular laminated architecture of the cortical bone (upper right quadrant of bottom image). Decalcified bone, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Fossey, S. et al. 2016. *J Toxicol Pathol* 29:49S–103S.)

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with either parathyroid hormone fragment or glucocorticoid. Retroviral particles may be found in these tumors in mice. Osteomas have been described in the oral cavity of dogs ranging from one to eleven years of age.

Differential diagnoses: Bone, reactive; **Osteosarcoma**; **Osteofibroma**; **Osteochondroma**.

Synonym(s): **Osteoma** (with various modifiers e.g., cancellous, medullary, compact, spongious, trabecular).

References

Fossey, S. et al. 2016. Nonproliferative and proliferative lesions of the rat and mouse skeletal tissues (bones, joints, and teeth). *J Toxicol Pathol* 29:49S–103S.

Long, P. et al. 1993. Proliferative lesions of bone, cartilage, tooth, and synovium in rats, MST-2. In: *Guides for Toxicologic Pathology*. Washington, DC: STP/ARP/AFIP.

McInnes, E.F., Ernst, H., and Germann, P. 2013. Spontaneous neoplastic lesions in control Syrian hamsters in 6-, 12-, and 24-month short-term and carcinogenicity studies. *Toxicol Pathol* 41: 86–97.

Soltero-Rivera, M. et al. 2015. Benign and malignant proliferative fibro-osseous and osseous lesions of the oral cavity of dogs. *Vet Pathol* 52:894–902.

Links

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https://www.toxpath.org/ssdnc/BoneJointToothPro.pdf
https://www.ncbi.nlm.nih.gov/pubmed/22707381
https://www.ncbi.nlm.nih.gov/pubmed/25957357

Osteosarcoma is a malignant neoplasm of bone-forming cells (osteoblasts). These highly invasive tumors arise in the skeleton but can occur in other locations (e.g., skin, gastrointestinal tract). Neoplastic cells can be variable in shape and size (polygonal to spindle-shaped to multinucleated), and form tumor osteoid, an important diagnostic feature. Bone lysis and necrosis are sometimes present. Osteosarcomas have been categorized as multiple subtypes such as fibroblastic, osteoblastic, and telangiectatic; however, subclassification is often not informative in toxicologic pathology. Osteosarcomas frequently metastasize to other skeletal sites and lung. Osteosarcomas are rare in mice, rats, rabbits, and hamsters but have been observed as the most common bone neoplasm in rodent carcinogenicity studies. These neoplasms can occur in dogs and occur with a bimodal age distribution, with peak incidences reached in middle- to older-aged dogs. Osteoblastic osteosarcomas are the most common bone tumor in rabbits, with half arising in the skull. Although bone tumors in nonhuman primates are rare, most of those reported are osteosarcomas in squirrel monkeys, rhesus macaques, ring-tailed lemurs, and baboons. These tumors have occurred with increased frequency in some rodent strains (mouse NMRI strain), and have been induced with ionizing radiation, parathyroid hormone, viruses, and carcinogens.

Differential diagnoses: **Osteofibroma**; **Osteochondroma**; **Osteoma**; **Chondrosarcoma**; **Fibrosarcoma**.

Synonym(s): **Osteogenic sarcoma**.

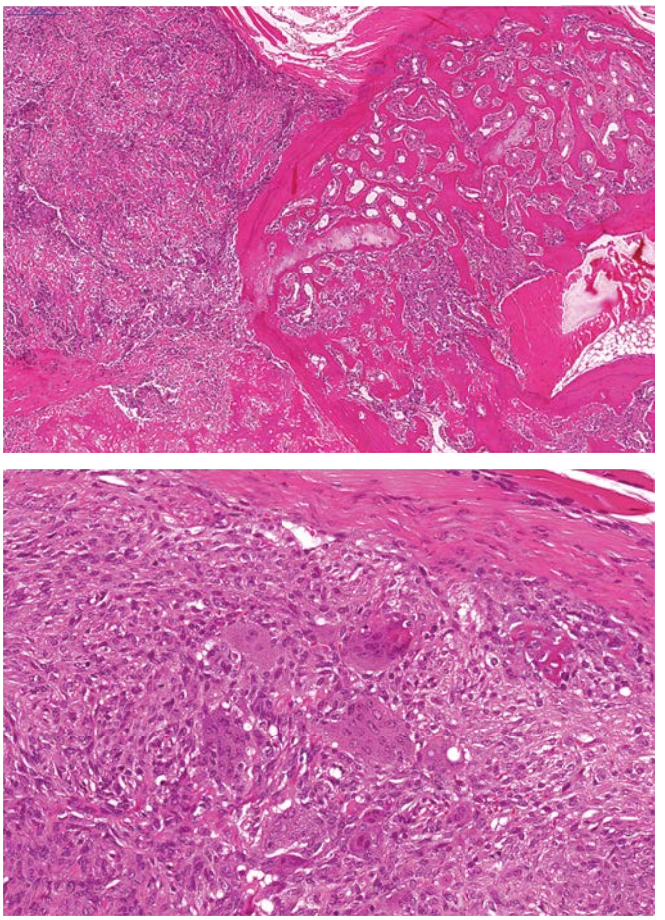


FIGURE 14 Osteosarcoma, mouse. (top) Low magnification; (bottom) higher magnification. An aggressively invasive, highly cellular, variably anaplastic malignant spindle-cell neoplasm of bone characterized by formation of osteoid by tumor cells. Decalcified bone, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Fossey, S. et al. 2016. *J Toxicol Pathol* 29:49S–103S.)

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Fenger, J., London, C., and Kisseberth, W. 2014. Canine osteosarcoma: A naturally occurring disease to inform pediatric oncology. *ILR* 55:69–85.

Fossey, S. et al. 2016. Nonproliferative and proliferative lesions of the rat and mouse skeletal tissues (bones, joints, and teeth). *J Toxicol Pathol* 29:49S–103S.

Heatley, J. and Smith, A. 2004. Spontaneous neoplasms of lagomorphs. *Vet Clin Exot Anim* 7:561–577.

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http://www.sciencedirect.com/science/article/pii/S1094919404000210
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Rhabdomyoma is a benign neoplasm of striated muscle cells. This tumor is usually a well-circumscribed,

encapsulated mass composed of closely packed rhabdomyoblasts and a delicate stroma. As in rhabdomyosarcoma, rhabdomyoma cells contain glycogen granules that are removed during processing and leave cytoplasmic vacuoles. Cells containing substantial glycogen vacuoles with radiating cytoplasmic strands are often referred as "spiderweb cells." Mitotic figures are usually rare. Histochemical, immunohistochemical, and ultrastructural characteristics described for rhabdomyosarcoma are valid for rhabdomyoma. Rhabdomyoma is also a rare tumor in laboratory animals, and to our knowledge, no spontaneous cases of skeletal muscle rhabdomyoma have been reported in rodents. In the young dog, rhabdomyoma occurs with some frequency in the larynx. Experimental activation of the Hedgehog/Patched-1/Smoothened pathway has been associated with the development of rhabdomyomas (and rhabdomyosarcomas) in mice.

Differential diagnosis: **Rhabdomyosarcoma**.

References

Greaves, P. et al. 2013. Proliferative and non-proliferative lesions of the rat and mouse soft tissue, skeletal muscle and mesothelium. *J Toxicol Pathol* 26:1S–26S.

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Links

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4091527/
https://www.ncbi.nlm.nih.gov/pubmed/23780909

Rhabdomyosarcoma is a malignant neoplasm arising from striated muscle cells. Skeletal muscle rhabdomyosarcomas are characterized by a high mitotic index with numerous abnormal mitoses and a high degree of polymorphism. The classical neoplastic cell is the rhabdomyoblast-fusiform, strap-like, polygonal or round cells with deeply eosinophilic fibrillary cytoplasm usually exhibiting cross-striations and glycogen granules that are often removed during processing, leaving fine vacuoles. Based on morphologic characteristics, three varieties of rhabdomyosarcomas are recognized in animals: embryonal, alveolar, and pleomorphic. Embryonal rhabdomyosarcomas are composed of round cells or primitive rhabdomyoblasts. Alveolar rhabdomyosarcomas form alveoli populated by round cells and separated by dense collagenous pillars. Pleomorphic rhabdomyosarcomas are usually composed of bundles of fusiform cells. Botryoid rhabdomyosarcoma is a subtype of the embryonal variety most frequently reported as grapelike masses within the wall of the urinary bladder in dogs. In rodents, rhabdomyosarcomas can comprise areas of necrosis and hemorrhage. Rhabdomyosarcoma is an uncommon tumor in laboratory animals. The presence of rhabdomyoblasts that are immunohistochemically positive for desmin, myoD1 and myogenin, and the presence of Z bands (ultrastructurally) are diagnostic. Cross-striations are usually demonstrated by staining with phosphotungstic acid hematoxylin (PTAH). In toxicologic pathology, rhabdomyosarcoma has been associated with the administration of nickel sulphide, monocrotaline, dehydroretronecine, or with tungsten alloy (tungsten, nickel, and cobalt), lead wire, and chronic injection of agents persistent at sites of injection (e.g., following iron dextran).

Differential diagnoses: **Rhabdomyoma**; **Sarcoma NOS**; **Fibrosarcoma, pleomorphic**; **Leiomyosarcoma**; **Histiocytoma, fibrous malignant**.

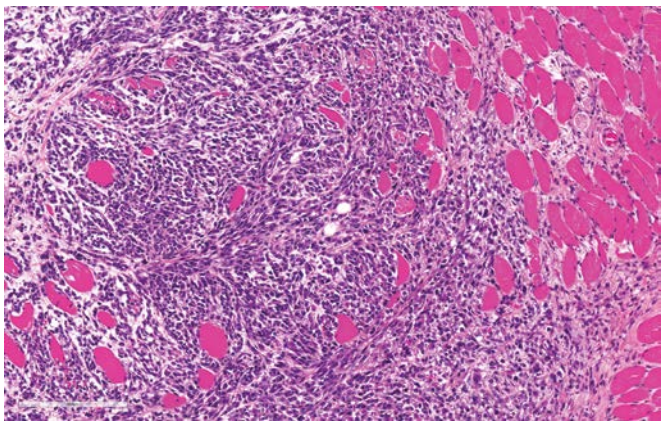


FIGURE 15 Rhabdomyosarcoma in the skeletal muscle of a mouse, H&E. Note extensive invasion of adjacent normal myofibers by spindle-shaped neoplastic cells.

Reference

Greaves, P. et al. 2013. Proliferative and non-proliferative lesions of the rat and mouse soft tissue, skeletal muscle and mesothelium. *J Toxicol Pathol* 26:1S–26S.

Link

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4091527/

Sarcoma, mixed, see the preferred term **Mesenchymoma, malignant**.

Sarcoma, NOS (not otherwise specified) is a category of malignant neoplasms created to group mesenchymal tumors with unclear histomorphological differentiation. The neoplastic cells are fusiform or spindle-shaped. Less frequently, neoplastic cells with various other shapes can be observed.

Differential diagnoses: **Fibrosarcoma**; **Rhabdomyosarcoma**; **Leiomyosarcoma**; **Liposarcoma** (i.e., sarcomas with localized differentiation).

Synonym(s): **Undifferentiated sarcoma**.

Reference

Greaves, P. et al. 2013. Proliferative and non-proliferative lesions of the rat and mouse soft tissue, skeletal muscle and mesothelium. *J Toxicol Pathol* 26:1S–26S.

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Sarcoma, pleomorphic undifferentiated, see the preferred term **Fibrosarcoma, pleomorphic**.

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Skeletal muscle hyperplasia is a rarely observed phenotype in toxicology studies, probably limited to regenerative hyperplasia of skeletal myofibers after local (injection sites), systemic drug administration (statins), or after prolonged decubitus in moribund conditions. Regenerating skeletal muscle hyperplasia is usually limited to specific regions of a muscle, and myofibers in these regions have reduced size, and their sarcoplasm is basophilic with multiple, centrally located nuclei arranged in a single row. Recently, some of the pathways controlling muscle growth or regeneration have been unraveled, and myostatin, peroxisome proliferator–activated receptor δ, and Notch-3 seem to play important roles in these processes. Spontaneous or experimental manipulation of these pathways can result in skeletal muscle hyperplasia. The increase in skeletal myofiber number in these instances (e.g., myostatin deficiency) is diffuse, and frequently associated with cell hypertrophy.

References

Greaves, P. et al. 2013. Proliferative and non-proliferative lesions of the rat and mouse soft tissue, skeletal muscle and mesothelium. *J Toxicol Pathol* 26:1S–26S.

Kitamoto, T. and Hanaoka, K. 2010. Notch3 null mutation in mice causes muscle hyperplasia by repetitive muscle regeneration. *Stem Cells* 28:2205–2216.

Matsakas, A. et al. 2012. Exercise training attenuates the hypermuscular phenotype and restores skeletal muscle function in the myostatin null mouse. *Exp Physiol* 97:125–240.

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https://www.ncbi.nlm.nih.gov/pubmed/20960513
https://www.ncbi.nlm.nih.gov/pubmed/22058168

Smooth muscle hyperplasia is a nonneoplastic proliferation of smooth muscle cells. These cells have cytological features comparable to normal cells (well-differentiated, elongated, fusiform cells with eosinophilic cytoplasm and nuclei with tapered ends often cigar-shaped) within muscle bundles that have conserved normal architecture, that is, intersecting fasciculi with parallel myofibers within each fasciculus. Smooth muscle hyperplasia, as with skeletal muscle hyperplasia, is a rare morphological finding in toxicology studies. Infravesical outflow obstruction in the urinary system or experimental gastrointestinal *Trichinella spiralis* infection causes smooth muscle cell hypertrophy, and hyperplasia in the urinary bladder or intestinal wall in rats.

Differential diagnosis: **Leiomyoma**.

Reference

Greaves, P. et al. 2013. Proliferative and non-proliferative lesions of the rat and mouse soft tissue, skeletal muscle and mesothelium. *J Toxicol Pathol* 26:1S–26S.

Link

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4091527/

Synovial cell hyperplasia is an increase in the number of cells lining the joint space (synovium). Grossly, this may appear as firm, pale nodules in the synovium. This nonneoplastic lesion manifests typically as larger cells (hypertrophy) composing multiple cell layers, with or without formation of folds and villi. These villi are of variable size and shape. This change often occurs in response to inflammation and/or injury to the synovium.

Synonym(s): **Synovial cell hyperplasia/hypertrophy**.

References

Fossey, S. et al. 2016. Nonproliferative and proliferative lesions of the rat and mouse skeletal tissues (bones, joints, and teeth). *J Toxicol Pathol* 29:49S–103S.

Long, P. et al. 1993. Proliferative lesions of bone, cartilage, tooth, and synovium in rats, MST-2. In: *Guides for Toxicologic Pathology*. Washington, DC: STP/ARP/AFIP.

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https://www.toxpath.org/ssdnc/BoneJointToothPro.pdf

Synovial cell hyperplasia/hypertrophy, see the preferred term **Synovial cell hyperplasia**.

Synovial sarcoma is a malignant neoplasm of the synovium. It is observed in association with the joint to include the capsule, bursae, and tendon sheath. This tumor is characterized by a mono- or biphasic morphologic appearance; however, the cell of origin is not known. Biphasic tumors contain a mix of neoplastic cells, some having an epithelioid appearance while others manifest mesenchymal characteristics (spindle-shaped). Neoplastic cells in monophasic tumors are of one differentiation pattern and mostly epithelial. Neoplasms have narrow spaces or pseudoglandular patterns as features. Synovial sarcomas are rarely reported in rats and mice. These tumors do occur in middle-aged dogs, with spindle-shaped neoplastic cells that are cytokeratin and vimentin positive. Although not available for rodents, diagnostic markers have been developed for human epithelial (high molecular weight cytokeratin [HMW-CK]) and mesenchymal (melanoma antigen recognized by T cells 1 [MART-1/MLANA]) lineage neoplastic cells.

Differential diagnosis: **Fibrosarcoma**.

References

Craig, L., Julian, M., and Ferracone, J. 2002. The diagnosis and prognosis of synovial tumors in dogs: 35 cases. *Vet Pathol* 39:66–73.

Fossey, S. et al. 2016. Nonproliferative and proliferative lesions of the rat and mouse skeletal tissues (bones, joints, and teeth). *J Toxicol Pathol* 29:49S–103S.

Long, P. et al. 1993. Proliferative lesions of bone, cartilage, tooth, and synovium in rats, MST-2. In: *Guides for Toxicologic Pathology*. Washington, DC: STP/ARP/AFIP.

Links

http://vet.sagepub.com/content/39/1/66.long
https://www.ncbi.nlm.nih.gov/pubmed/27621538
https://www.toxpath.org/ssdnc/BoneJointToothPro.pdf

CARDIOVASCULAR SYSTEM

Angiomatous hyperplasia is a focal, well-demarcated lesion consisting of increased numbers of capillaries and other vascular structures lined by normal-appearing, flattened endothelium. Findings suggestive of malignancy such as nuclear atypia and increased mitotic figures are not present in angiomatous hyperplasia. Angiomatous hyperplasia occurs in mice treated with peroxisome proliferator–activated receptor (PPAR) agonists, generally does not occur spontaneously, and occurs most frequently in subcutaneous adipose tissue.

Alternatively, in some older classification systems angiomatous hyperplasia may refer to a proliferation of capillary-sized vessels without compression of surrounding structures in various tissues, including the myocardium. Endothelial cells may be inconspicuous or hypertrophic. The lesion may occur spontaneously. Angiomatous hyperplasia by this definition seems to be synonymous with **hemangioendothelial hyperplasia**.

Differential diagnoses: **Hemangioendothelial hyperplasia**; **Hemangioma**; **Hemangiosarcoma**; **Angiectasis**.

Synonym(s): **Hemangiomatous hyperplasia**.

Anitschkow cell sarcoma, see the preferred terms **Intramural schwannoma** or **Endocardial schwannoma**.

Aortic body tumor, see the preferred term **Paraganglioma**.

Atriocaval mesothelioma is a proliferation of cells originating from the atriocaval node, which is located at the junction of the right atrium with the vena cava. These tumors expand into and infiltrate the right atrium and cranial vena cava, appearing as squamous to low cuboidal epithelioid cells forming tubular and acinar structures. Morphology is variable, with cells forming nests, clumps, and masses. Neoplastic cells can display variable levels of pleomorphism and mitotic activity. Larger neoplasms sometimes invade adjacent structures and may metastasize locally to the mediastinum and to distant sites including the lungs, thoracic lymph nodes, and liver. These spontaneous neoplasms are generally rare and occur more often in rats than in mice. In morphology and location they are very distinctive, and diagnosis is easily made.

Differential diagnosis: **Pericardial mesothelioma**.

Synonym(s): **Atriocaval node tumor**.

Links

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Atriocaval node tumor, see the preferred term **Atriocaval mesothelioma**.

Endocardial schwannoma occurs as a spontaneous malignant neoplasm in most rat strains and is the most common cardiac neoplasm. It originates from the subendocardial Schwann cells, always involving the left ventricle. Initially, neoplastic cells proliferate along the endocardium, but they can subsequently invade the underlying myocardium. Schwannomas can become very extensive and partially occlude the ventricular lumen or replace a significant proportion of the myocardium. Histologically, they often consist of two different cell types. The superficial cell layer consists of round to polygonal cells with ovoid nuclei and finely vacuolated cytoplasm. The deeper and thicker layer, which is characteristic of these tumors, comprises streams of fusiform cells with scant cytoplasm and long spindle-shaped hyperchromatic nuclei with prominent nucleoli. These cells are interspersed with collagen fibers. Antoni type A (Verocay) bodies, characterized by nuclear palisading, are a common feature. Less frequently, Antoni Type B bodies are observed, with loosely arranged cytoplasmic processes and increased ground substance. Neoplasms are usually immunohistochemically

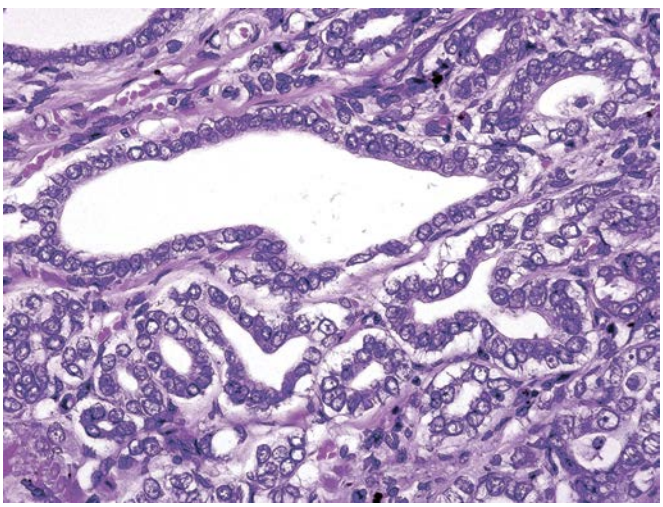


FIGURE 1 Atriocaval mesothelioma, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Berridge, B.R. et al. 2016. *J Toxicol Pathol* 29(3 Suppl):1S–47S.)

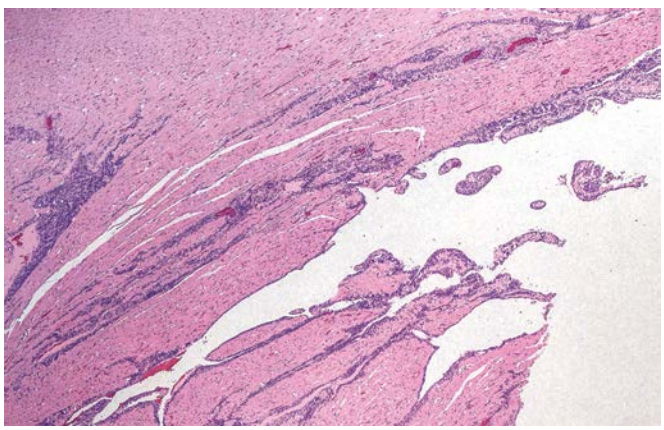


FIGURE 2 Endocardial schwannoma, Rat, H&E.

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positive for S-100 and neuron-specific enolase. Endocardial schwannomas have been induced in rats by administration of *N*-methyl-*N*-nitrosourea.

Differential diagnoses: Endocardial fibrosis; **Subendocardial hyperplasia**.

Synonym(s): **Neurofibroma**; **neurosarcoma**.

Links

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https://www.goreni.org/

Endothelial hyperplasia, see the preferred term **Hemangioendothelial hyperplasia**.

Hemangioendothelial hyperplasia describes endothelial cell proliferation lining dilated capillaries that may also be increased in number. Endothelial cells can be normal to hypertrophied, and vascular spaces variably contain proteinaceous fluid, red blood cells, and/or lymphoid cells. This change is typically diffuse and poorly circumscribed but is not associated with compression of adjacent tissue. It occurs in mice and has most often been described in the heart as a spontaneous finding or following chronic exposure to chemicals such as 1,3-butadiene. In the latter instance, this finding likely represented a preneoplastic change, as there was also a high incidence of cardiac hemangiosarcoma.

Differential diagnoses: **Angiectasis**; **Hemangioma**; **Lymphangioma**.

Synonym(s): **Endothelial hyperplasia**.

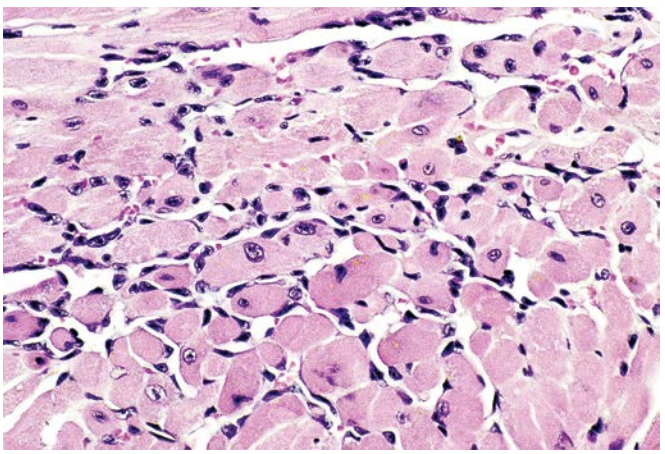


FIGURE 3 Hyperplasia, hemangioendothelial, 1,3-butadiene treated heart, mouse. (Image courtesy of the National Toxicology Program; Reproduced with permission of the Japanese Society of Toxicologic Pathology from Berridge, B.R. et al. 2016. *J Toxicol Pathol* 29(3 Suppl):1S–47S.)

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https://www.goreni.org/

Hemangioendothelioma, benign, see the preferred term **Hemangioma**.

Hemangioendothelioma, malignant, see the preferred term **Hemangiosarcoma**.

Hemangioma is a benign tumor of the vasculature originating from the vascular endothelial cells and thus can occur almost anywhere in the body. They are usually well defined and demarcated from the normal parenchyma. The liver and spleen are common sites for these tumors in mice. In Han Wistar rats, hemangiomas of the mesenteric lymph node are a strain-specific peculiarity. Morphologically, spaces or channels are lined by a single layer of well-differentiated endothelial cells which are often slightly hypertrophied with hyperchromatic nuclei. Based on the size of the blood-filled spaces, hemangiomas can be broadly divided into cavernous and capillary types based on the most predominant morphological pattern. Cavernous hemangiomas consist of large blood-filled spaces separated by variable amounts of fibrous stroma. Capillary hemangiomas consist of small blood vessels separated by reticular fibers. However, in safety studies they are not subclassified. Pigment-laden macrophages are a common feature within and around hemangiomas. Thrombi sometimes develop within larger cavities, especially in the murine ovary and uterus.

Differential diagnoses: **Angiomatous hyperplasia**; **Hemangiosarcoma**; **Lymphangioma**.

Synonym(s): **Hemangioendothelioma, benign**.

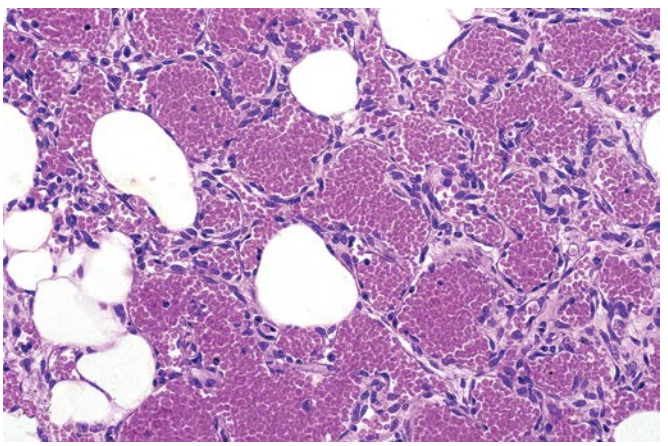


FIGURE 4 Hemangioma, 1,3-butadiene treated mouse, subcutaneous tissue. (Image courtesy of the National Toxicology Program; Reproduced with permission of the Japanese Society of Toxicologic Pathology from Berridge, B.R. et al. 2016. *J Toxicol Pathol* 29(3 Suppl):1S–47S.)

Links

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5013710/
https://www.goreni.org/

Hemangiomatous hyperplasia, see the preferred term **Angiomatous hyperplasia**.

Hemangiosarcoma is an invasive malignant tumor arising from the vascular endothelium or from pluripotential mesenchymal stem cells. Capillary- to cavernous-sized blood-filled

spaces are supported by varying amounts of fibrous stroma. Endothelial cells are large, poorly differentiated, and can be anaplastic in appearance. Mitoses are common, often with bizarre nuclear figures. Local invasion is common and distant metastases can occur (e.g., from the ovary to the lungs in mice). Areas of hemorrhage and pigmented macrophages frequently manifest within these tumors or in the surrounding tissue. In the liver, malignant endothelial cells often line the sinusoids and are unapparent, causing the tumors to resemble hepatocellular carcinomas.

Differential diagnoses: **Hemangioma**; **Lymphangiosarcoma**.

Synonym(s): **Hemangioendothelioma, malignant**.

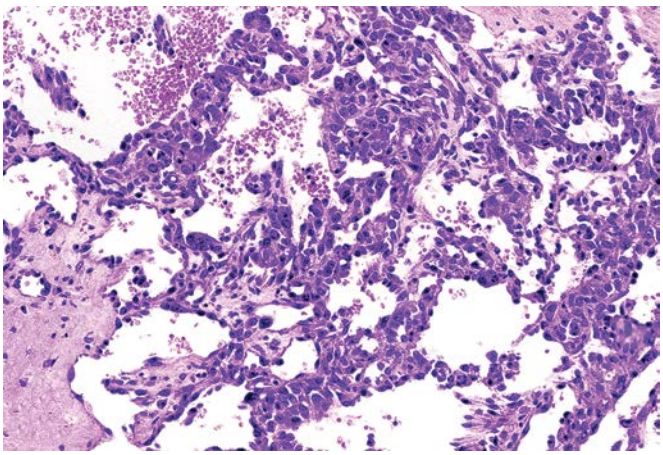


FIGURE 5 Hemangiosarcoma. 1,3-Butadiene, treated mouse, H&E. (Image courtesy of the National Toxicology Program; Reproduced with permission of the Japanese Society of Toxicologic Pathology from Berridge, B.R. et al. 2016. *J Toxicol Pathol* 29(3 Suppl):1S–47S.)

Links

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5013710/
https://www.goreni.org/

Intramural schwannoma is less common than endocardial schwannoma but is occasionally seen as a spontaneous finding in rats. These tumors develop due to proliferation of intramural Schwann cells, and appear as poorly defined bundles of polygonal or fusiform cells. Intramural schwannomas generally arise within the left ventricular wall or intraventricular septum, appearing as discrete nodular masses.

They are less well delineated and more invasive than endocardial schwannomas, sometimes interdigitating with the surrounding myocardial fibers. Some level of pleomorphism is usually present, and areas showing both Antoni type A and Antoni type B morphology can be present within the same tumor. As with endocardial schwannomas, intramural schwannomas can be induced in rats by administration of *N*-methyl-*N*-nitrosourea.

Differential diagnoses: **Myocardial fibrosis**; **Myocardial infarct**.

Synonym(s): **Neurosarcoma**.



FIGURE 6 Intramural schwannoma, heart, rat, H&E.

Links

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5013710/
https://www.goreni.org/

Lymphangioma is a rare, benign tumor originating from the lymphatic endothelial cells that may be associated with lymphedema. They are usually well-defined and demarcated from the normal parenchyma, but locally infiltrative lesions have been reported in the dog. Morphologically, spaces or channels that are devoid of blood are lined by a single layer of well-differentiated endothelial cells, which are often slightly hypertrophied with hyperchromatic nuclei. Lymphangioma is a rare diagnosis in all species and may be difficult to differentiate from hemangioma without immunohistochemistry. Antibodies that have been useful in the identification of neoplastic lymphatic vessels in humans include LYVE-1 and VEGFR-3, while markers of vascular endothelium such as PECAM, CD34, and basement membrane components are expected to be negative.

Differential diagnoses: **Hemangioma**; **Angiomatous hyperplasia**; **Lymphangiosarcoma**.

Link

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1481132/

Lymphangiosarcoma is a rare, invasive malignant tumor arising from the lymphatic endothelium that is generally associated with lymphedema. Neoplastic spindle-shaped cells surround slits or channels that are devoid of blood and invade surrounding tissue often following fascial planes. Moderate pleomorphism and/or atypia of the neoplastic cells may be present. Lymphangiosarcoma is rare in all species but is most frequently seen in the subcutis of dogs and has been reported as an intraabdominal mass in a Fischer-344 rat. Metastasis primarily to the thorax, but also to other organs may be noted. Antibodies that have been useful in the identification of neoplastic lymphatic vessels in humans include LYVE-1 and VEGFR-3, while markers of vascular endothelium such as PECAM, CD34, and basement membrane components are expected to be negative. Ultrastructural features include

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interdigitating cell junctions, variable presence of Weibel-Palade bodies, and lack of a continuous basement membrane.

Differential diagnoses: **Hemangiosarcoma**; **Lymphangioma**.

Links

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4488415/
https://pdfs.semanticscholar.org/100e/3fa5112f305a2142e56b4e5db467df73e336.pdf
http://journals.sagepub.com/doi/pdf/10.1177/019262339702500410

Masson's hemangioma, see the preferred term **Papillary endothelial hyperplasia**.

Neurofibroma, see the preferred term **Endocardial schwannoma**.

Neurosarcoma, see the preferred terms **Endocardial schwannoma** and **Intramural schwannoma**.

Papillary endothelial hyperplasia is a rare proliferative lesion primarily found in the subcutis of dogs. It is characterized by a benign papillary proliferation of endothelial cells in the lumen of a vessel typically associated with an organizing thrombus. The papillary projections are lined by a single layer of plump endothelial cells that have no evidence of pleomorphism, mitotic activity, necrosis, or invasion. In man, these lesions are thought to be secondary to trauma and may represent exuberant recanalization of a thrombus.

Synonym(s): **Masson's hemangioma**.

Links

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5013710/
https://www.goreni.org/

Paraganglioma develops from the aortic body paraganglion, which is comprised of neuroendocrine cells. They originate in the interventricular septum and are locally invasive, sometimes penetrating the myocardium and epicardium and occasionally the atria. Morphologically, they consist of round cells arranged in nests, separated by fine reticulin fibers and capillaries. Cells are typically neuroendocrine in appearance, with abundant faintly basophilic, finely granular cytoplasm and round nuclei. They occur spontaneously, albeit rarely, in rats and mice on long-term studies. Cells can stain positively for synaptophysin and chromogranin A, and granules are argyrophilic (have an affinity for silver stains).

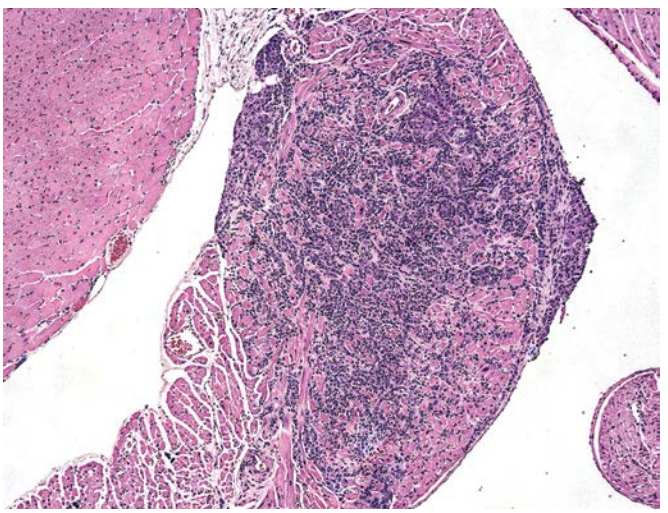


FIGURE 7 Paraganglioma, heart, rat, H&E.

Differential diagnosis: **Atriocaval mesothelioma**.

Synonym(s): **Aortic body tumor**.

Links

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5013710/
https://www.goreni.org/

Pericardial mesothelial hyperplasia describes multiple layers of mesothelial cells lining the pericardial sac, often associated with inflammation and/or effusions. The cells are typically cuboidal, have minimal supporting stroma, and exhibit no nuclear atypia or evidence of invasion. Typically, the cells do not protrude into pericardial cavity, but infrequent papillary projections can be noted.

Pericardial mesothelioma is a rare neoplasm arising from the mesothelial lining cells of the pericardial sac. Mesotheliomas may be pleomorphic and can be divided into three types: epithelioid (predominantly tubular or papillary epithelial morphology), sarcomatoid (predominantly spindle cell morphology with collagen bundles), and biphasic (a mix of epithelial and spindle cell morphology). Pericardial mesotheliomas may be exophytic or plaque-like and show evidence of increased mitotic rate and invasion but are typically less invasive than atriocaval mesotheliomas.

Differential diagnoses: **Atriocaval mesothelioma**; **Pericardial mesothelial hyperplasia**.

Links

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5013710/
https://www.goreni.org/

Subendocardial hyperplasia, see the preferred term **Endocardial Schwann cell hyperplasia**.

Subendocardial Schwann cell hyperplasia is a lesion of aged rats and to a lesser extent, mice. It is characterized by proliferation of spindle cells, up to 20 cells thick, immediately below an intact endocardium with no or minimal invasion of the myocardium. The lesion is most commonly seen in the left ventricle wall, but the atria and/or valve leaflets may rarely be affected. The proliferating spindle cells have pale cytoplasm and elongated or oval nuclei, minimal supporting stroma, and usually exhibit S100 immunoreactivity. This lesion may be a precursor to subendocardial schwannomas.

Differential diagnosis: Endocardial fibrosis.

Synonym(s): **Endocardial hyperplasia**.

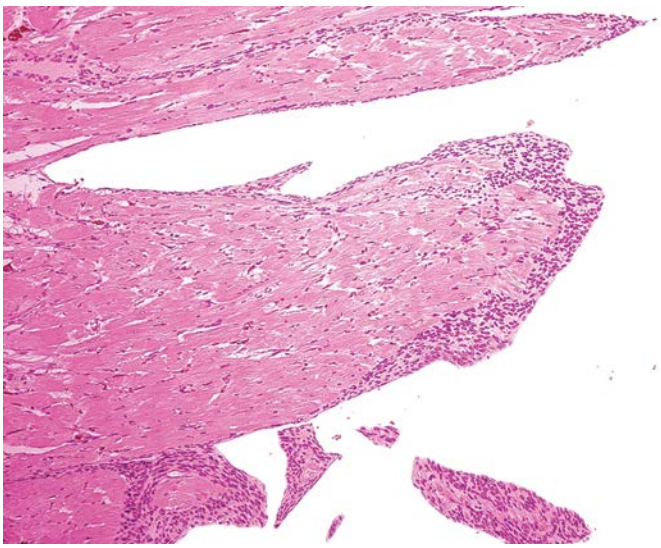


FIGURE 8 Subendocardial Schwann cell hyperplasia, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Berridge, B.R. et al. 2016. *J Toxicol Pathol* 29(3 Suppl):1S–47S.)

Links

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5013710/
https://www.goreni.org/

ENDOCRINE GLANDS

Acinar-islet cell tumor, benign is a mixed exocrine-endocrine neoplasm that is rare as a spontaneous background proliferative lesion. These tumors are composed of a mixed cell population of ductal, acinar, and islet cells in varying numbers. Benign tumors are characterized by an expansile, encapsulated mass of cells with variable cytological atypia, and do not metastasize as compared to the malignant counterpart, which is invasive and composed of cells with more cellular atypia and higher metastatic potential.

Synonym(s): **Islet-acinar tumor, benign**; **islet-acinar adenoma**.

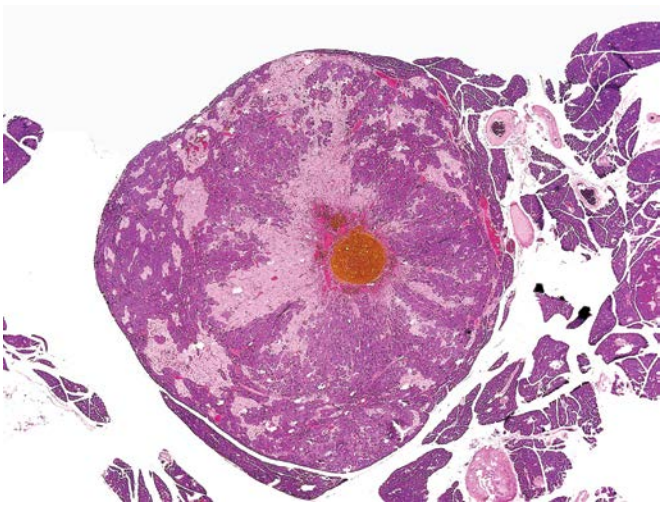


FIGURE 1 Pancreas, acinar-islet cell tumor, benign, F344/N rat, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Reference

Nolte, T. et al. 2016. Nonproliferative and proliferative lesions of the gastrointestinal tract, pancreas and salivary glands of the rat and mouse. *J Toxicol Pathol* 29(1 Suppl):1S–125S.

Acinar-islet cell tumor, malignant is a mixed exocrine-endocrine neoplasm that is rare as a spontaneous background proliferative lesion. These tumors are composed of a mixed cell population of ductal, acinar, and islet cells in varying numbers. Malignant tumors are invasive and composed of cells with more cellular atypia compared to the benign form, and may metastasize.

Synonym(s): **Islet-acinar tumor, malignant**; **islet-acinar carcinoma**.

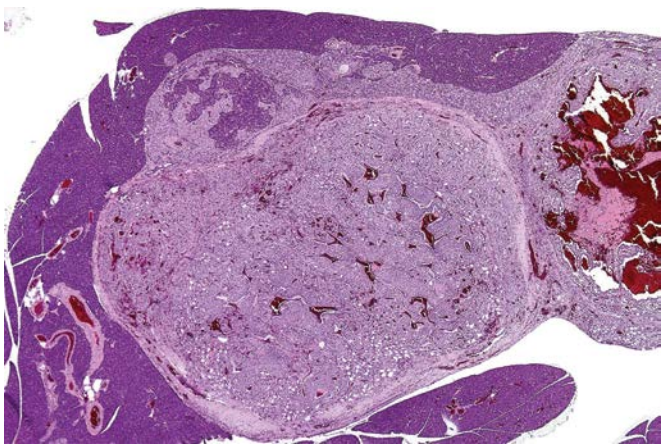


FIGURE 2 Acinar-islet cell tumor, malignant, F344 rat, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

References

Riley, M.G.I., Boorman, G.A., and Hayashi, Y. 1990. Endocrine pancreas. In: Boorman, G.A., Eustis, S.L., Elwell, M.R., Montgomery, C.A., Jr., MacKenzie, W.F. (eds.) *Pathology of the Fischer Rat*: Reference and Atlas. San Diego, New York, London: Academic Press, pp. 545–552.

Riley, M.G.I., Boorman, G.A., McDonald, M.M., Longnecker, D., Solleveld, H.A., and Giles, H.D. 1990. Proliferative and metaplastic lesions of the endocrine pancreas, E-1. In: *Guides for Toxicologic Pathology*. Washington: STP/ARP/AFIP, pp. 1–7.

Adrenal cortical adenoma, benign is a tumor composed of neoplastic adrenal cortical cells originating from the adrenal cortex. These tumors are nodular, well-defined, and compress adjacent cortical tissue. They are usually encapsulated and may contain a single or mixed population of cells.

Synonym(s): **Adrenal cortical tumor, benign**.

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FIGURE 3 Adrenal gland, cortical adenoma, benign, Sprague Dawley rat, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

References

Frith, C.H. and Ward, J.M. 2010. Endocrine system. In: *Color Atlas of Neoplastic and Non-Neoplastic Lesions in Aging Mice*. Elsevier 1988. Adapted for the Web by Mouse Genome Informatics. Bar Harbor, Maine: The Jackson Laboratory.

Laast, V.A., Larsen, T., Allison, N., Hoenerhoff, M., and Boorman, G. 2014. Distinguishing cystic degeneration from other aging lesions in the adrenal cortex of Sprague-Dawley rats. *Toxicol Pathol* 42:823–829.

Adrenal cortical carcinoma, malignant is a tumor composed of neoplastic adrenal cortical cells. These tumors usually contain bizarre, rapidly dividing cells and can grow quickly with significant local invasion. The tumors may have areas of hemorrhage and necrosis, and characteristically invade the capsule of the gland into adjacent blood or lymphatic vessels with metastasis to lymph nodes and lungs as common sequelae. Animal models of naturally occurring adrenal cortical carcinoma include the dog and ferret. Some inbred strains of mice are also used as models of this malignancy, including DBA/2J, C3H, BALB/c, and NU/J^{l} animals, and other mouse strains are genetically modified to produce animals with a high incidence of this malignant neoplasm.

Synonym(s): **Adrenal cortical adenocarcinoma**; **adrenal cortical tumor, malignant**.

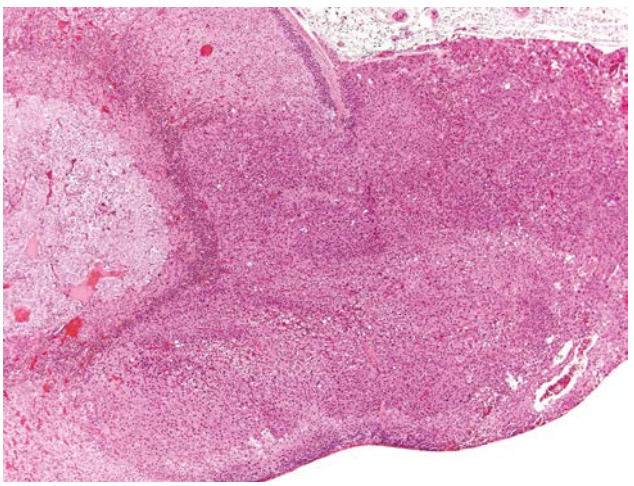


FIGURE 4 Adrenal gland cortical carcinoma, malignant, Sprague Dawley rat, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Reference

Frith, C.H. and Ward, J.M. 2010. Endocrine system. In: *Color Atlas of Neoplastic and Non-Neoplastic Lesions in Aging Mice*. Elsevier 1988. Adapted for the Web by Mouse Genome Informatics. Bar Harbor, Maine: The Jackson Laboratory.

Adrenal cortical hyperplasia refers to the increase in the number of cells involving any of the three zones of the cortex (zona fasciculata, zona reticularis, zona glomerulosa) resulting in the enlargement of adrenal cortex. It can be nodular or diffuse, congenital or late onset. Cells may exhibit tinctorial differences and vacuolation. Congenital adrenocortical hyperplasia usually results from a deficiency of 21-hydroxylase, an enzyme involved in mineralocorticoid and glucocorticoid synthesis. Decreased levels of cortisol cause a compensatory increase in ACTH secretion resulting in adrenal cortical hyperplasia. Nodular hyperplasia is common in older animals, while diffuse cortical hyperplasia is noted in response to autonomous hypersecretion of ACTH by a corticotroph adenoma of the pituitary gland or after prolonged periods of stress. Multinucleated cells and rare mitoses may be present, aiding in the differential diagnosis of hyperplasia from hypertrophy; however, hypertrophy is often present in conjunction with hyperplasia.

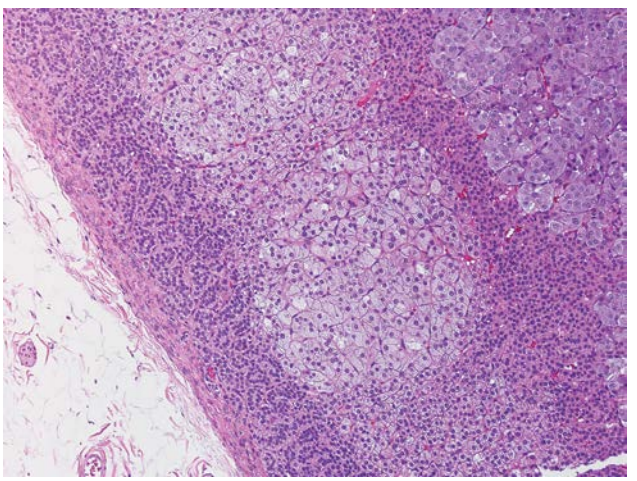


FIGURE 5 Adrenal gland, cortical hyperplasia, cynomolgus monkey, H&E.

References

Frith, C.H. and Ward, J.M. 2010. Endocrine system. In: *Color Atlas of Neoplastic and Non-Neoplastic Lesions in Aging Mice*. Elsevier 1988. Adapted for the Web by Mouse Genome Informatics. Bar Harbor, Maine: The Jackson Laboratory.

White, P.C. and Speiser, P.W. 2000. Congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *Endocr Rev* 21(3):245–291.

Adrenal cortical hypertrophy is an increase in size of the adrenal cortex, which may be focal or diffuse, resulting from individual cell enlargement. Focal hypertrophy is characterized by single or multiple focal clusters of enlarged cells, most often in the zona fasciculata or zona reticularis, that are well-delineated but not compressing adjacent tissue. Diffuse hypertrophy is characterized by an enlargement of all cells in the adrenal cortex, resulting in an increased cortical thickness. The changes may be unilateral or bilateral. Hypertrophic cells are larger than those of the quiescent gland, with increased cytoplasm and enlarged nuclei, but are not undergoing multiplication, hence are without multinucleation and mitoses noted in cortical hyperplasia; however, hypertrophy and hyperplasia often occur together. Hypertrophy of the adrenal cortex is commonly stress induced (i.e., stress-induced adrenocortical hypertrophy), with stimulation of the hypothalamic-pituitary-adrenal axis (HPA) resulting in increased adrenal corticotropic hormone (ACTH) release from the pituitary gland; however, toxicity to the renal cortex (adrenal cortical insufficiency) with failure of feedback inhibition to the pituitary gland must be considered when evaluating the change.

Synonym(s): **Adrenocortical hypertrophy**.

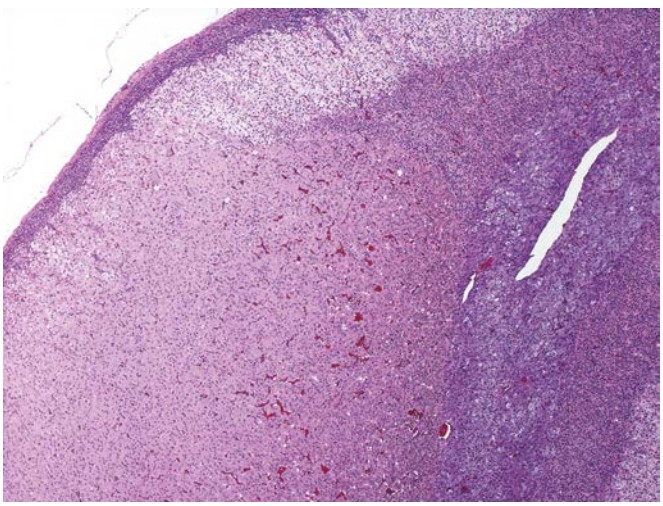


FIGURE 6 Adrenal gland, cortical hypertrophy, cynomolgus monkey, H&E.

Reference

Laast, V.A., Larsen, T., Allison, N., Hoenerhoff, M., and Boorman, G. 2014. Distinguishing cystic degeneration from other aging lesions in the adrenal cortex of Sprague-Dawley rats. *Toxicol Pathol* 42:823–829.

Adrenal cortical myelolipoma is a benign neoplasm composed of adipose tissue and hematopoietic cells and is thought to develop from metaplastic transformation of cells in the adrenal cortex. These masses are observed as spontaneous lesions in nonhuman primates, such as Cotton-top tamarins, and uncommonly in other species. Myelolipomas are well-demarcated, tan to white masses that may contain foci of mineralization or bone and areas of hemorrhage. They are composed of accumulations of well-differentiated adipose tissue with admixed hematopoietic cells including megakaryocytes, erythrocytes, and myeloid cells in progressive stages of maturation, as well as lymphocytes, plasma cells, and hemosiderin-laden macrophages. Microscopically, myelolipomas must be differentiated from other discrete cortical masses, such as nodular cortical hyperplasia and cortical adenomas.

References

Kakinuma, C., Harada, T., Watanabe, M., and Shibutani, Y. 1994. Spontaneous adrenal and hepatic myelolipomas in the common marmoset. *Toxicol Pathol* 22(4):440–446.

Neville, A.M. and O'Hare, M.J. 1982. *The Human Adrenal Cortex. Pathology and Biology – An Integrated Approach*. Chapter 23. Myelolipoma and related changes. Berlin, Heidelberg, New York: Springer, pp. 290–293.

Adrenal cortical tumor, see the preferred terms **Adrenal cortical adenoma, benign**; **Adrenal cortical carcinoma, malignant**.

Adrenal gland subcapsular cell adenoma, see the preferred term **Adrenal gland subcapsular cell tumor, benign**.

Adrenal gland subcapsular cell carcinoma, see the preferred term **Adrenal gland subcapsular cell tumor, malignant**.

Adrenal gland subcapsular cell hyperplasia is characterized by a subcapsular focus of small, basophilic cells that extend into the zona fasciculata. Subcapsular cells are considered the multipotential stem cells that replenish senescent cells within the adrenal cortices and can transdifferentiate

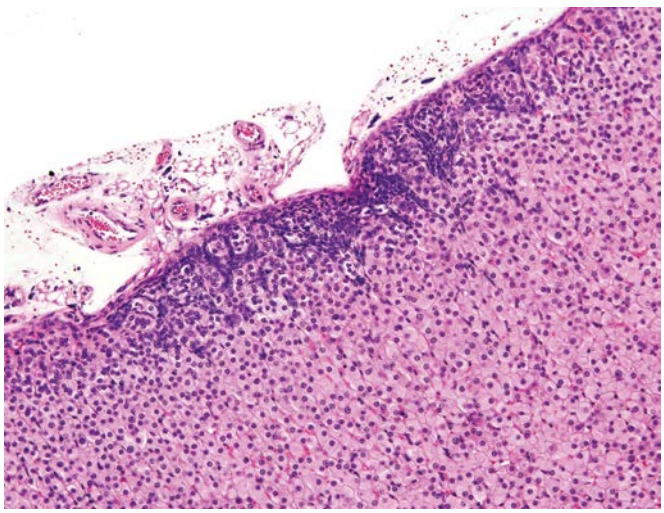


FIGURE 7 Adrenal gland, cortex, subcapsular cell hyperplasia, B6C3F1 mouse, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

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into sex steroid–producing cells. Typically, areas of hyperplasia start near the zona glomerulosa, and may impinge upon the subtending tissue depending on the extent of the lesion. Subcapsular cell hyperplasia is only seen in mice, particularly older mice, but not in rats. It can also be induced in certain mouse strains after a gonadectomy.

Reference

Goodman, D.G. 1996. Subcapsular-cell hyperplasia, adrenal, mouse. In: Jones, T.C., Capen, C.C., Mohr, U. (eds.) *Monographs on Pathology of Laboratory Animals. Endocrine System*, 2nd ed. Berlin, Heidelberg, New York, Tokyo: Springer, pp. 464–467.

Adrenal gland subcapsular cell tumor, benign is a well-demarcated, nodular neoplasm in mice that is composed of transformed subcapsular progenitor cells (type A—densely cellular, small, oval-spindle, with scant basophilic cytoplasm; type B—large, polygonal cells with clear cytoplasm and small lipid vacuoles; or mixed type A/B cells) within the subcapsular space of the adrenal gland.

Synonym(s): **Adrenal gland subcapsular cell adenoma**.

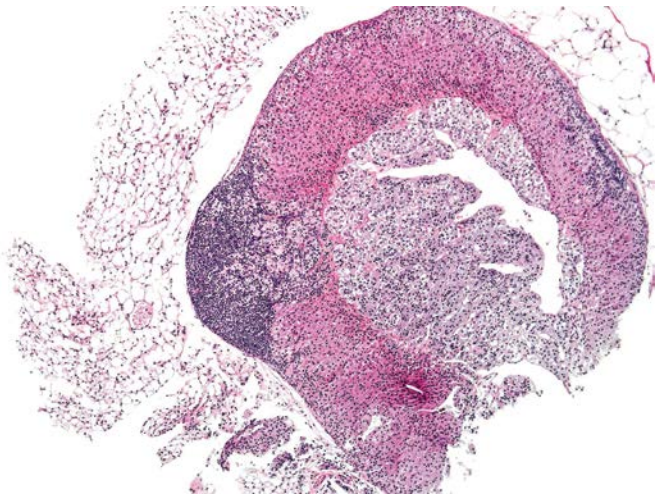


FIGURE 8 Adrenal gland, subcapsular cell adenoma, B6C3F1/N mouse, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Reference

Frith, C.H. and Ward, J.M. 2010. Endocrine system. In: *Color Atlas of Neoplastic and Non-Neoplastic Lesions in Aging Mice*. Elsevier 1988. Adapted for the Web by Mouse Genome Informatics. Bar Harbor, Maine: The Jackson Laboratory.

Adrenal gland subcapsular cell tumor, malignant is a neoplasm only observed in mice that arises from undifferentiated progenitor cells (type A—densely cellular, small, oval-spindle, with scant basophilic cytoplasm; type B—large, polygonal cells with clear cytoplasm and small lipid vacuoles; or mixed type A/B cells) in the subcapsular space of the adrenal cortex. Malignant subcapsular cell tumors have cytological atypia, are organized in nests, ribbons, or cords, and invade into the adjacent tissue and out of the capsule. Type A cell carcinomas have been documented to metastasize, most commonly to the lung.

Synonym(s): **Adrenal gland subcapsular cell carcinoma**.

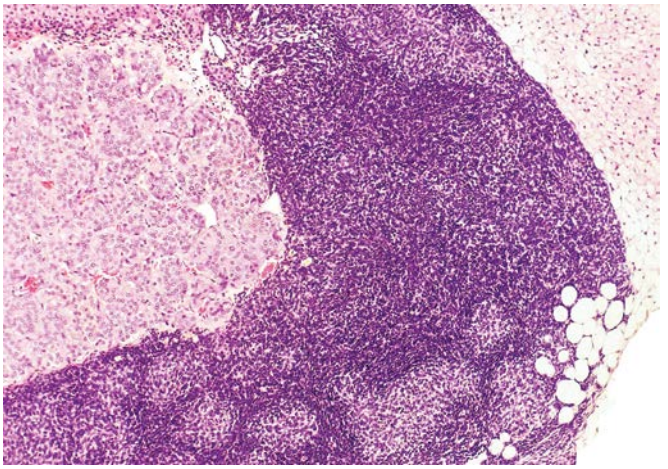


FIGURE 9 Adrenal gland, cortex, subcapsular cell tumor, malignant, B6C3F1/N mouse, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Reference

Frith, C.H. and Ward, J.M. 2010. Endocrine system. In: *Color Atlas of Neoplastic and Non-Neoplastic Lesions in Aging Mice*. Elsevier 1988. Adapted for the Web by Mouse Genome Informatics. Bar Harbor, Maine: The Jackson Laboratory.

Adrenal medulla tumor, see the preferred terms **Pheochromocytoma, Adrenal medullary ganglioneuroma**, or **Adrenal medullary neuroblastoma**.

Adrenal medullary ganglioneuroma is a rare tumor comprised of neoplastic ganglion cells and neurofibrillary matrix and supporting cells, such as stellate and Schwann cells, that have been

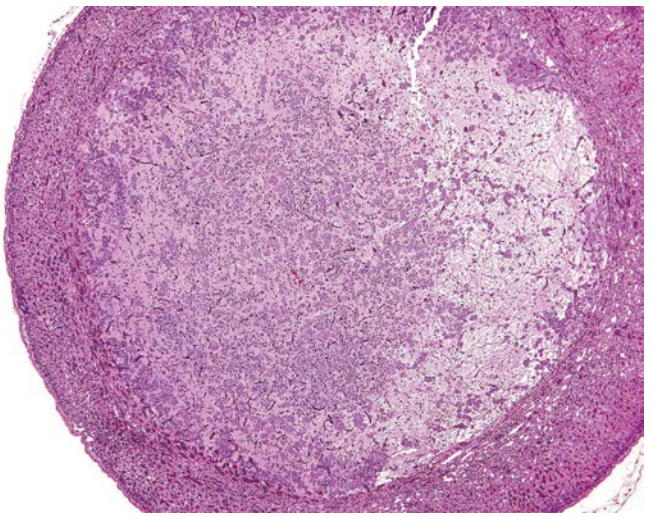


FIGURE 10 Adrenal gland, medulla, ganglioneuroma, F344/N rat, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

reported as spontaneous lesions in a variety of animals, including mice and rats. These tumors are typically unilateral, well-demarcated, nonencapsulated, and compressive neoplasms that can be locally invasive but typically do not metastasize. The ganglion cells have eosinophilic and often vacuolated cytoplasm and a large vesicular nucleus with eccentric and multiple nuclei. Mitotic figures are uncommon, and hemorrhage may be present. Due to a common neural crest precursor cell, the sympathoadrenal cell, there is histologic overlap with the complex pheochromocytoma, in which ganglion cells and neural components may also be present, but the neural component accounts for <80% of the mass. Ganglioneuromas have more mature and usually larger ganglionic cells as compared to the malignant counterpart—the **adrenal medullary neuroblastoma**.

Reference

Pace, V., Perentes, E., and Germann, P.G. 2002. Pheochromocytomas and ganglioneuromas in the aging rats: Morphological and immunohistochemical characterization. *Toxicol Pathol* 30:492–500.

Adrenal medullary neuroblastoma is a neoplasm originating from sympathetic neural crest cells and uncommonly occurring as spontaneous lesions in rodents and certain transgenic mouse models. Histologically, neoplastic cells are small and round with scant cytoplasm, elongated nuclei, and a high nuclear-to-cytoplasmic ratio. Binucleated cells, rosette-like formations, and mitoses may be present. Neoplastic cells show immunoreactivity for chromogranin A and neuron-specific enolase (NSE), and transmission electron microscopy reveals processes containing synaptic vesicles and neurosecretory granules. Neuroblastomas differ from the benign **neuroganglioma** in that they have less well-defined ganglionic cells and increased neurofibrillary matrix that invades surrounding tissue.

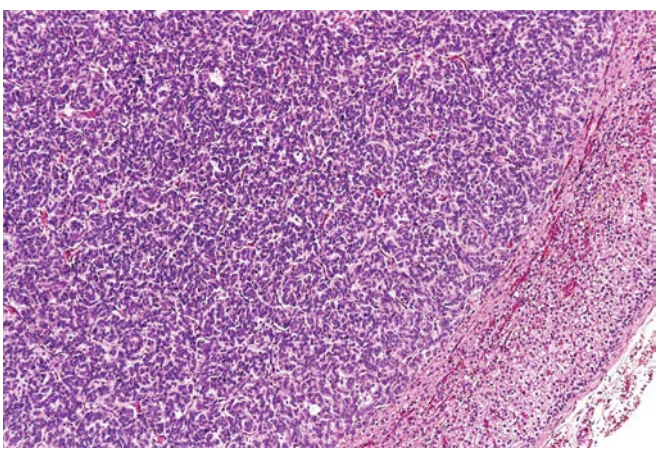


FIGURE 11 Adrenal gland, medulla, neuroblastoma, F344/N rat, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Reference

Reznik, G. and Germann, P.G. 1996. Neuroblastoma, adrenal, rat. In: Jones, T.C., Capen, C.C., Mohr, U. (eds.) *Monographs on Pathology of Laboratory Animals. Endocrine System*, 2nd ed. Berlin, Heidelberg, New York, Tokyo: Springer, pp. 433–435.

Adrenocortical hypertrophy, see the preferred term **Adrenal cortical hypertrophy**.

Apudoma is a tumor originating from cells derived from the embryological neural crest with amine precursor uptake and decarboxylation (APUD) properties when evaluated cytochemically. These tumors have been identified in many animal species and in humans, and produce multiple hormones and amines, neuron-specific enolase (NSE), synaptophysin, and chromogranin A or C. APUD cells are components of endocrine tumors, including pancreatic islet cell tumors, pituitary adenomas, paragangliomas (carotid body tumor), pinealocytomas, carcinoid tumors, thyroid carcinomas, melanomas, oat cell tumors of the lung, and pheochromocytomas.

Reference

Weber, K., Garman, R.H., Germann, P., Hardisty, J.F., Krinke, G., Millar, P., and Pardo, I.D. 2011. Classification of neural tumors in laboratory rodents, emphasizing the rat. *Toxicol Pathol* 39:129–151.

C cell adenoma, see the preferred term **Thyroid C cell tumor, benign**.

C cell carcinoma, see the preferred term **Thyroid C cell tumor, malignant**.

C cell hyperplasia, see the preferred term **Thyroid C cell hyperplasia**

C cell proliferation, see the preferred term **Thyroid C cell hyperplasia**.

Carcinoid is a type of apudoma that occurs primarily in the intestinal tract but has been reported in the pancreas of humans. See images under neuroendocrine tumor, benign and neuroendocrine tumor, malignant.

Clear cell hyperplasia, see the preferred term **Thyroid C cell hyperplasia**.

Cortical tumor, see the preferred terms **Adrenal cortical adenoma, benign**; **Adrenal cortical carcinoma, malignant**.

Endocrine pancreas cell hyperplasia refers to an increase in islet size with increased islet cell numbers that may occur multifocally through the pancreas of rats and mice. Affected islets are composed of islet cells that generally resemble those of normal islets but have differing proportions and distribution of α- and β-cells throughout the islet. There is low mitotic activity and no cellular atypia, and there may be dilated/cystic vascular spaces within the centers of the hyperplastic foci. The incidence of islet cell hyperplasia is higher in male than in female rats as well as rats fed ad libitum.

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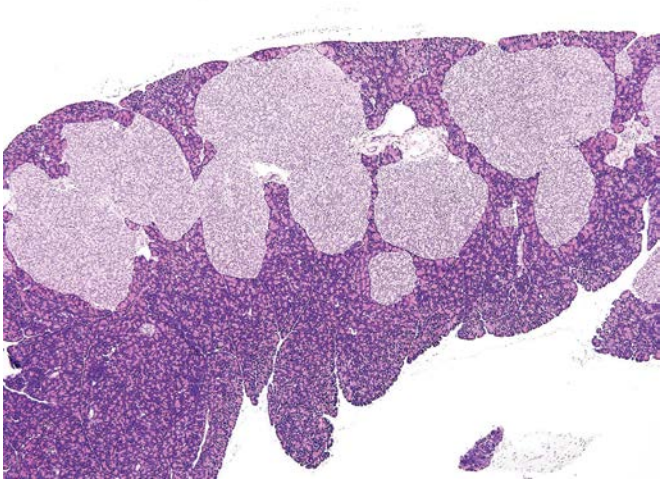


FIGURE 12 Endocrine pancreas cell hyperplasia, B6C3F1 mouse, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Reference

Frith, C.H. and Sheldon, W.D. 1996. Hyperplasia, adenoma and carcinoma of pancreatic islets, mouse. In: Jones, T.C., Mohr, U., Hunt, R.D. (eds.) *Monographs on Pathology of Laboratory Animals. Endocrine System*, 2nd ed. Berlin, Heidelberg, New York, Tokyo: Springer, pp. 361–367.

Infundibuloma, see the preferred term **Pituicytoma**.

Islet cell adenoma, benign is a neoplasm (adenoma) composed of cells from the islets of Langerhans. These tumors occur spontaneously in both mice and rats, but in general are rarer in mice than in rats. An islet cell adenoma is characterized as a well-circumscribed nodule that compresses the adjacent tissue and is composed of well- differentiated islet cells forming nests, cords, sheets, or ribbons supported by a fine fibrovascular stroma. Mitoses are rare and local invasion and metastasis are absent. Many islet cell tumors produce insulin as demonstrated by immunohistochemical reactivity, and are then referred to as **insulinomas**. Insulinomas do not typically cause hypoglycemia in rodents as in other species. Islet cell tumor cells may also contain glucagon, somatostatin, or pancreatic polypeptide as demonstrated by immunohistochemical (IHC) techniques. Islet size is often used as diagnostic criteria in discerning islet hyperplasia from adenomas. In **islet hyperplasia**, islets range in diameter from 350 to 700 microns, while islets with over a 700-micron diameter may considered adenomas. However, islet diameter alone should not be the sole diagnostic criteria for adenomas. β cell-specific *Men1* gene knockout mice typically will develop islet cell adenomas by 6 months of age and are commonly used to study multiple endocrine neoplasia (MEN).

Synonym(s): **Islet cell tumor, benign**; **endocrine pancreas adenoma**.

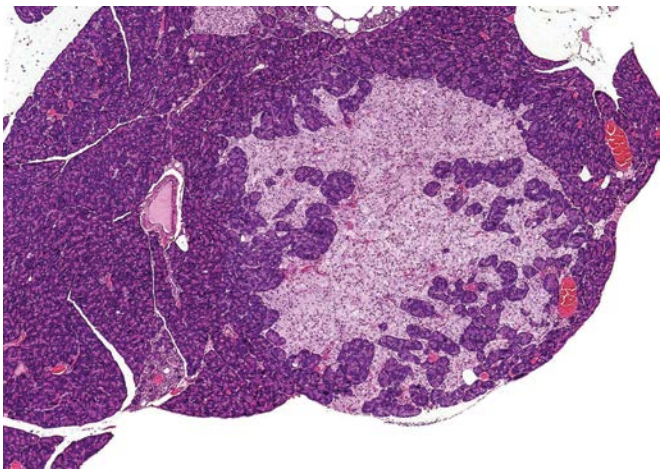


FIGURE 13 Islet cell adenoma, benign, Sprague Dawley rat, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

References

Riley, M.G.I., Boorman, G.A., and Hayashi, Y. 1990. Endocrine pancreas. In: Boorman, G.A., Eustis, S.L., Elwell, M.R., Montgomery, C.A., Jr., MacKenzie, W.F. (eds.) *Pathology of the Fischer Rat. Reference and Atlas*. San Diego, New York, London: Academic Press, pp. 545–552.

Riley, M.G.I., Boorman, G.A., McDonald, M.M., Longnecker, D., Solleveld, H.A., and Giles, H.D. 1990. Proliferative and metaplastic lesions of the endocrine pancreas, E-1. In: *Guides for Toxicologic Pathology*. Washington: STP/ARP/AFIP, pp. 1–7.

Islet cell carcinoma, malignant is a neoplasm composed of the cells of the islets of Langerhans, usually β cells, and is malignant. Similar to endocrine pancreas adenomas, these tumors occur spontaneously in both mice and rats, but are histologically locally invasive, and are composed of cells that are more atypical/pleomorphic, with frequent mitoses as compared to adenomas. These tumors may metastasize, typically to the liver.

Synonym(s): **Islet cell tumor, malignant**; **endocrine pancreas carcinoma**.

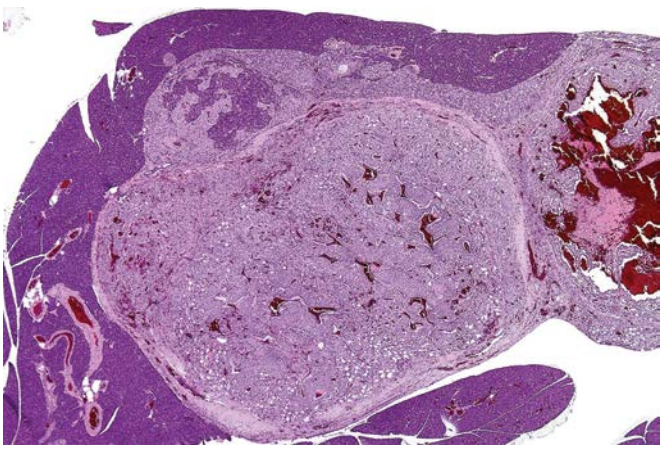


FIGURE 14 Islet cell carcinoma, malignant, Sprague Dawley rat, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Reference

Frith, C.H. and Sheldon, W.D. 1996. Hyperplasia, adenoma and carcinoma of pancreatic islets, mouse. In: Jones, T.C., Mohr, U., Hunt, R.D. (eds.) *Monographs on Pathology of Laboratory Animals. Endocrine System*, 2nd ed. Berlin, Heidelberg, New York, Tokyo: Springer, pp. 361–367.

Islet cell hyperplasia, see the preferred term **Endocrine pancreas cell hyperplasia**.

Islet cell tumor, benign, see the preferred term **Islet cell adenoma, benign**.

Islet cell tumor, malignant, see the preferred term **Islet cell carcinoma, malignant**.

Islet-acinar tumor, benign, see the preferred term **Acinar-islet cell tumor, benign**.

Islet-acinar tumor, malignant, see the preferred term **Acinar-islet cell tumor, malignant**.

Multiple endocrine neoplasia (MEN) encompasses several distinct clinical syndromes featuring tumors of the endocrine glands. Well-described MEN syndromes are autosomal dominant disorders. The subclassifications of MEN include MEN 1, MEN 2A, and MEN 2b; each of these subtypes is associated with specific endocrine tumors. MEN 1 is typically associated with pituitary adenomas, parathyroid hyperplasia, and pancreatic tumors. MEN 2A is associated with parathyroid hyperplasia, medullary thyroid carcinoma, and pheochromocytoma. MEN 2B is associated with mucosal neuromas, medullary thyroid carcinoma, and pheochromocytoma.

Reference

Multiple endocrine neoplasia. In: Genetics Home Reference, U.S. National Library of Medicine. https://ghr.nlm.nih.gov/condition/multiple-endocrine-neoplasia.

Neuroendocrine cell tumor, benign is a neoplasm that arises from cells with both endocrine and nervous system function. Neuroendocrine cell tumors occur in many organs including the intestine, lung, and pancreas. Tumors are generally composed of nests of polygonal-round cells separated by fine fibrovascular stroma. Neuroendocrine cell tumors are immunoreactive to pan-neuroendocrine tissue markers, such as chromogranin, synaptophysin, and neuron-specific enolase. In addition, they may be immunoreactive to a specific hormone or protein the tumor cells secrete, which is useful for diagnostic purposes. Although these tumors are expansile, they do not metastasize. Differential diagnoses include neuroendocrine cell hyperplasia and neuroendocrine cell dysplasia, which are differentiated by size. In general, hyperplastic foci are generally $\leq$150 microns and at least 5 cells thick, dysplastic foci form small nodules of >150 microns and are more than 5 cells thick, and tumors are >0.5 mm.

Synonym(s): **Neuroendocrine adenoma, carcinoid**

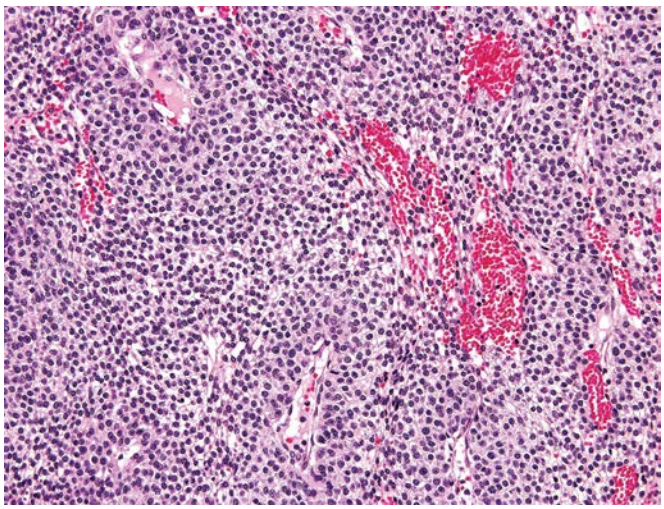


FIGURE 15 Neuroendocrine cell, tumor, benign, F344/N rat, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Link

http://surgpathcriteria.stanford.edu/

Neuroendocrine cell tumor, malignant is a neoplasm that arises from cells with both endocrine and nervous system function. The cytological features of malignant neuroendocrine tumors may be similar to that of the benign neuroendocrine tumor, and only the presence of metastasis or blatant tissue invasion may separate the benign from the malignant tumor.

Synonym(s): **Neuroendocrine carcinoma**.

Oncocytoma is a glandular tumor composed of large cells with granular, eosinophilic cytoplasm due to the presence of abundant mitochondria. These neoplasms occur uncommonly in the kidney, salivary glands, and endocrine glands, occur spontaneously in older rats, and are believed to arise

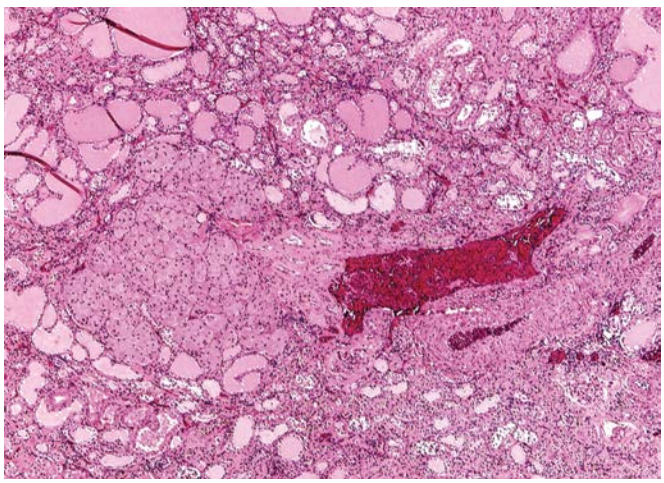


FIGURE 16 Oncocytoma (kidney), benign, F344/N rat, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

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from areas of hyperplasia. In male F344 rats, there appears to be an association of renal oncocytic proliferation and adenomas with chronic progressive nephropathy. Rats treated with *N*-nitrosomorpholine show a number of oncocytomas, the incidence of which increases with time. Both benign and malignant forms have been documented.

Synonym(s): **Oxyphilic adenoma**.

References

Hard, G.C., Betz, L.J., and Seely, J.C. 2012. Association of advanced chronic progressive nephropathy (CPN) with renal tubule tumors and precursor hyperplasia in control F344 rats from two-year carcinogenicity studies. *Toxicol Pathol* 40:473–481.

Nogueira, E. and Bannasch, P. 1998. Cellular origin of rat renal oncocytoma. *Lab Invest* 59(3):337–343.

Oxyphilic adenocarcinoma, see the preferred term **Oncocytoma**.

Oxyphilic adenoma, see the preferred term **Oncocytoma**.

Parafollicular cell hyperplasia, see the preferred term **Thyroid C cell hyperplasia**.

Pars distalis adenoma, benign is the most commonly observed neoplasm in rodents used in toxicological studies. Adenomas are commonly identified in aging rats, especially the Fisher 344 rat strain, and less commonly in aging dogs and cynomolgus monkeys. Adenomas are characterized by focal or multifocal, well demarcated, expansile nodules of neoplastic cells that compress adjacent parenchyma. Encapsulation is usually absent for benign tumors. Neoplastic cells form cords and nests within a fine fibrovascular stroma, and are polygonal with variably distinct cell borders, moderate eosinophilic or clear cytoplasm, central nucleus with one to several nucleoli, and a finely stippled chromatin pattern. Pars distalis carcinomas are composed of variably uniform to pleomorphic cells, and often have necrosis and hemorrhage within the mass. Neoplastic cells may form cords or sheets, have increased mitotic figures, and the stroma often has prominent vasculature. Carcinomas are invasive, effacing or replacing the normal architecture, and have metastatic potential. Carcinomas have been described in the rat and dog. When functional, pituitary tumors are unresponsive to feedback mechanisms; this leads to hypersecretion of hormones known as hyperpituitarism.

Synonym(s): **Pars distalis pituitary tumor, benign**.

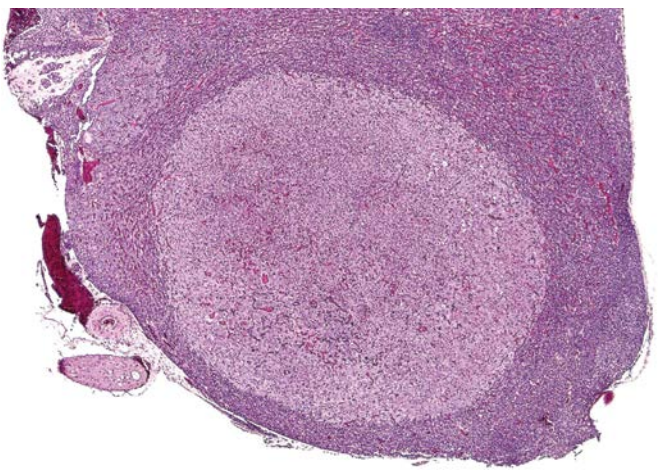


FIGURE 17 Pituitary, pars distalis adenoma, benign, Sprague Dawley rat, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

References

Attia, M.A. 1985. Neoplastic and nonneoplastic lesions in aging female rats with special reference to the functional morphology of the hyperplastic and neoplastic changes in the pituitary gland. *Arch Toxicol* 57:77–83.

Greaves, P. 2012. Pituitary Gland. In: *Histopathology of Preclinical Toxicity Studies. Interpretation and Relevance in Drug Safety Studies*. Amsterdam, Boston: Elsevier/AP, pp. 727–740.

Pars distalis carcinoma, malignant is a rare tumor described in rats and dogs. These tumors have features similar to that of the benign counterpart, but with malignant characteristics, including invasion and replacement of normal architecture and metastasis. When functional, pituitary tumors are unresponsive to feedback mechanisms, this leads to hypersecretion of hormones known as hyperpituitarism.

Synonym(s): **Pars distalis pituitary gland tumor, malignant**.

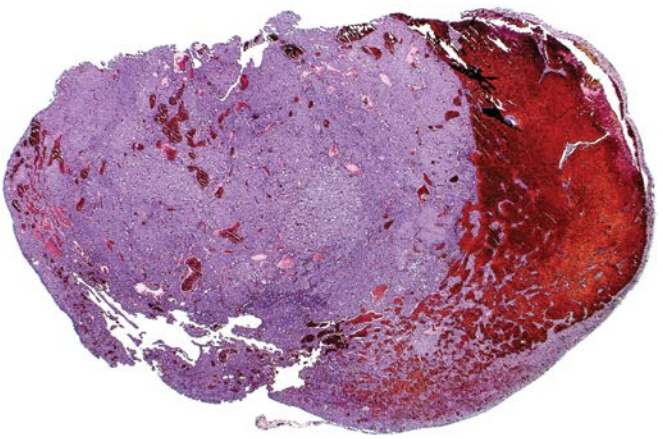


FIGURE 18 Pituitary, pars distalis carcinoma, malignant, Sprague Dawley rat, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

References

Greaves, P. 2012. Pituitary gland. In: *Histopathology of Preclinical Toxicity Studies. Interpretation and Relevance in Drug Safety Studies*. Amsterdam, Boston: Elsevier/AP, pp. 727–740.

Hosokawa, S., Fukuta, T., Imai, T., Sonoda, J., Aoki, T., Hayakawa, K., Motooka, S., and Nakanowatari, J. 1993. Pituitary carcinoma of pars distalis as a common neoplasm in Fischer-344 rats. *Toxicol Pathol* 21:283–287.

Pars distalis, pituitary hyperplasia is characterized by increased numbers of cells of normal morphology that form clusters delineated from the normal cellular population by alterations in cytoplasmic staining (usually pale), but do not generally compress the adjacent parenchyma. Hyperplastic cell may be multinucleated or have rare mitoses, differentiating it from hypertrophy; however, both hyperplasia and hypertrophy often occur together.

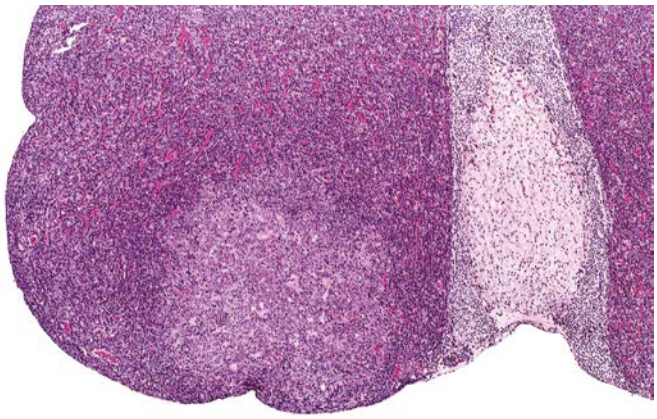


FIGURE 19 Pituitary, pars distalis, hyperplasia, Sprague Dawley rat, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

References

Attia, M.A. 1985. Neoplastic and nonneoplastic lesions in aging female rats with special reference to the functional morphology of the hyperplastic and neoplastic changes in the pituitary gland. *Arch Toxicol* 57:77–83.

Greaves, P. 2012. Pituitary gland. In: *Histopathology of Preclinical Toxicity Studies. Interpretation and Relevance in Drug Safety Studies*. Amsterdam, Boston: Elsevier/AP, pp. 727–740.

Pars distalis, pituitary hypertrophy is characterized by cellular enlargement of cells comprising the pituitary pars distalis having cytoplasmic pallor and may be noted in conjunction with hyperplasia.

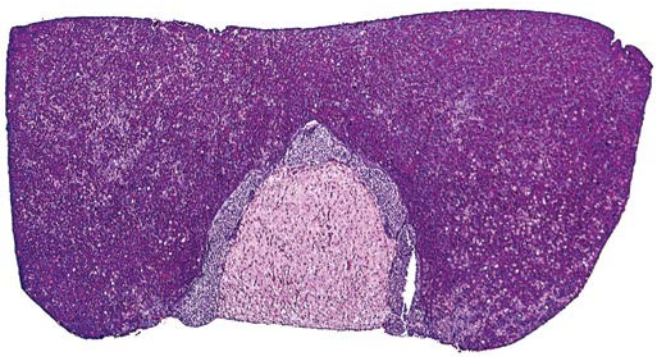


FIGURE 20 Pituitary gland, pars distalis hypertrophy, F344/N rat, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Reference

Attia, M.A. 1985. Neoplastic and nonneoplastic lesions in aging female rats with special reference to the functional morphology of the hyperplastic and neoplastic changes in the pituitary gland. *Arch Toxicol* 57:77–83.

Pars intermedia, pituitary hyperplasia is characterized by an increase in number of cells of the pars intermedia, often focal, resulting in expansion of this region of the pituitary gland. The hyperplastic response is usually diffuse in the rat.

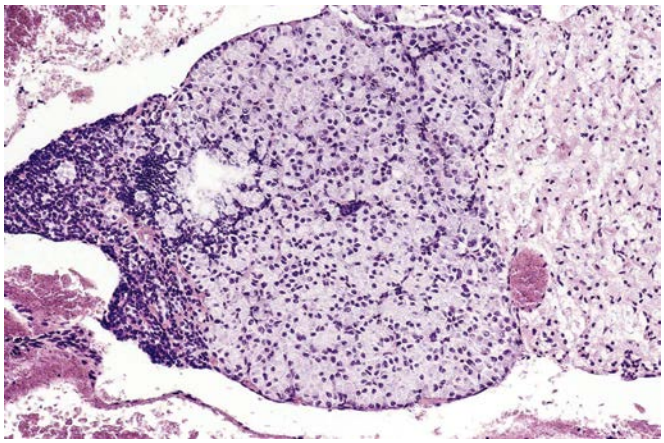


FIGURE 21 Pituitary gland, pars intermedia hyperplasia, B6C3F1 mouse, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

References

Greaves, P. 2012. Pituitary gland. In: *Histopathology of Preclinical Toxicity Studies. Interpretation and Relevance in Drug Safety Studies*. Amsterdam, Boston: Elsevier/AP, pp. 727–740.

Oishi, Y., Matsumoto, M., Yoshizawa, K., Fujihiro, S., Tsubura, A., and Morii, S. 1992. Spontaneous pituitary adenomas of the pars intermedia in mice and rats: Histopathological and immunohistochemical studies. *J Toxicol Pathol* 5: 223–231.

Pars nervosa, pituitary tumor, see the preferred term **Pituicytoma**.

Pheochromocytoma, benign is a neuroendocrine neoplasm of the chromaffin cells from the adrenal medulla. The tumor may be nonfunctional but result in adrenal insufficiency (Addison's disease) or functional with unregulated secretion of adrenaline. Histologically, benign tumors are composed of packets, cords, and nests of monomorphic polygonal cells with minimal to no pleomorphism or atypia, and a low mitotic rate. These tumors are expansile, but they are not invasive and do not metastasize. With time, benign pheochromocytomas may convert to the malignant form.

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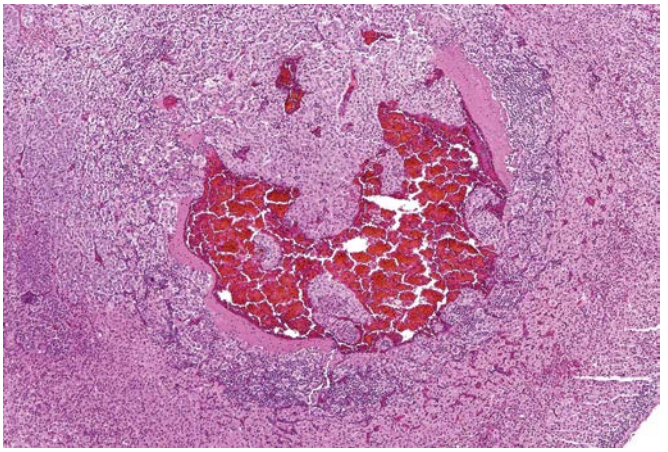


FIGURE 22 Adrenal gland, medulla, pheochromocytoma, benign, F344/N rat, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

References

Hill, G.D., Pace, V., Persohn, E., Bresser, C., Haseman, J.K., Tischler, A.S., and Nyska, A. 2003. A comparative immunohistochemical study of spontaneous and chemically induced pheochromocytomas in B6C3F1 mice. *Endocr Pathol* 14:81–91.

Tischler, A.S., Sheldon, W., and Gray, R. 1996. Immunohistochemical and morphological characterization of spontaneously occurring pheochromocytomas in the aging mouse. *Vet Path* 33(5):512–520.

Pheochromocytoma, malignant is a neuroendocrine neoplasm of the chromaffin cells from the adrenal medulla. The tumor may be nonfunctional, resulting in adrenal insufficiency (Addison's disease), or functional, with unregulated secretion of adrenaline. Histologically, malignant tumors are composed of packets, cords, and nests of polygonal cells with pleomorphism or atypia, and an increased mitotic rate as compared to the benign counterpart. Necrosis and infiltrative and/or metastatic behavior may be common. These tumors may occur spontaneously and are commonly reported as increased in incidence in rodent carcinogenicity studies, with strain-dependent variability.

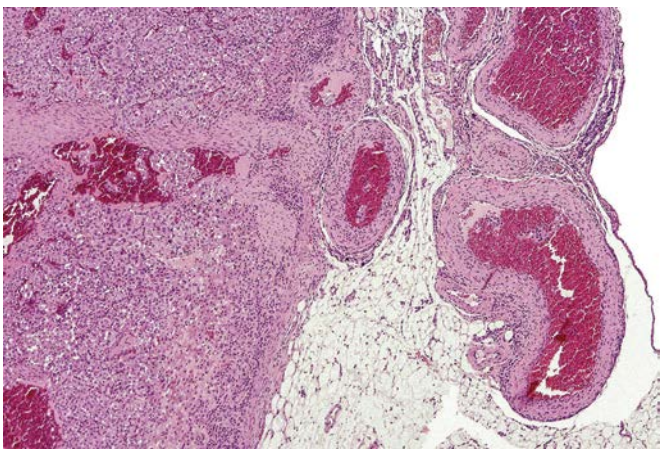


FIGURE 23 Adrenal gland, medulla, pheochromocytoma, malignant, F344/N rat, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

References

Hill, G.D., Pace, V., Persohn, E., Bresser, C., Haseman, J.K., Tischler, A.S., and Nyska, A. 2003. A comparative immunohistochemical study of spontaneous and chemically induced pheochromocytomas in B6C3F1 mice. *Endocr Pathol* 14:81–91.

Tischler, A.S., Sheldon, W., and Gray, R. 1996. Immunohistochemical and morphological characterization of spontaneously occurring pheochromocytomas in the aging mouse. *Vet Path* 33(5):512–520.

Pineal gland tumor, see the preferred terms **Pineocytoma**; **Pineoblastoma**.

Pineoblastoma, malignant is a rare neoplasm that originates from cells (pinealocytes) in the pineal gland and are comprised of clusters of cells with high nuclear-to-cytoplasmic ratio, irregular nucleoli, poorly delineated cell border, and high mitotic rate supported by a fibrovascular stroma. Cells may have a vascular orientation with palisading, and rosette formation may be observed; however, less-differentiated tumors may occur, and infiltration with the presence of necrosis and hemorrhage is most commonly associated with the malignant form of this tumor.

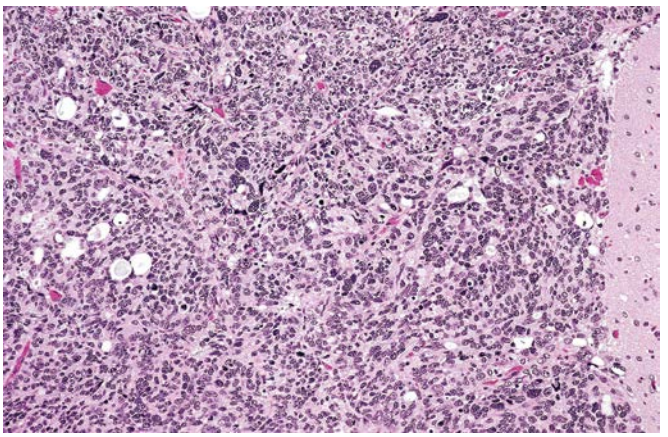


FIGURE 24 Pineoblastoma, malignant, Sprague Dawley rat, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Reference

Yamamoto, O., Mitsumori, K., Yoshida, T., Maita, K., and Shirasu, Y. 1991. Spontaneous malignant pineocytoma in a female Wistar rat. *J Vet Med Sci* 53:527–529.

Pineocytoma, benign is a rare neoplasm that originates from cells (pinealocytes) in the pineal gland. Pineocytomas are well-circumscribed, noninvasive, and are comprised of clusters of monomorphic cells supported by a fibrovascular stroma with a low to moderate mitotic rate. Cells may have a vasculocentric orientation with palisading, and rosette formation may be observed. Mixed tumors exhibiting variable differentiation and histologic features are occasionally noted.

Synonym(s): **Pinealoma**.

References

Al Zubaidy, A.J., and Malinowski, W. 1984. Spontaneous pineal body tumours (pinealomas) in Wistar rats; a histological and ultrastructural study. *Lab Anim* 18:224–229.

Burek, J.D., van Zwieten, M.J., and Solleveld, H.A. 1983. Pinealoma, Rat. The pineal gland. In: Jones, T.C., Mohr, U., Hunt, R.D. (eds.) *Monographs on Pathology of Laboratory Animals. Endocrine System*. Berlin, Heidelberg: Springer-Verlag, pp. 350–354.

Pituicytoma is a primary astrocytic tumor of the pars nervosa of the pituitary gland. These rare neoplasms have been described in the rat, nonhuman primate, dog, and cat. The tumors are generally expansile but are low-grade malignancies, and slow to invade locally or metastasize. Pituicytomas have morphologic features similar to the astrocytoma of the central nervous system. Neoplastic cells are spindle-shaped and arranged in poorly formed cords and bundles, or may be storiform in appearance (having a cartwheel pattern, such as spindle cells having elongated nuclei radiating from a center) with fibrillar eosinophilic cytoplasm and small hyperchromatic nuclei. Mineralization of the tumor may occur, and the mitotic index is highly variable.

Synonym(s): **Infundibuloma**; **pars nervosa tumor**.

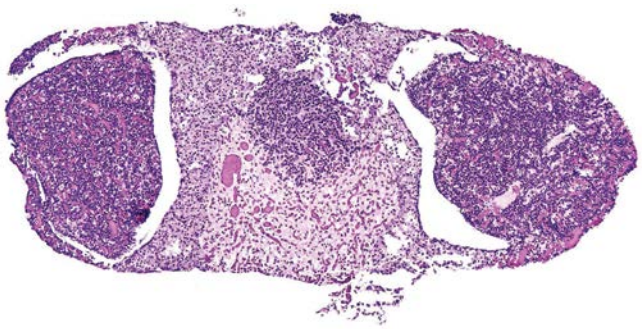


FIGURE 25 Pituitary, pituicytoma, B6C3F1 mouse, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Reference

Brandão, R.A., Braga, M.H., de Souza, A.A., Reis, B.L., Faraj de and Lima, F.B. 2010. Pituicytoma. *Surg Neurol Int* 1:79.

Pituitary gland tumor, see the preferred terms **Pars distalis adenoma, benign**; **Pars distalis carcinoma, malignant**.

Prolactin cell hyperplasia is a nonneoplastic increase in the number of prolactin cells (i.e., lactotroph, mammotroph) in the pars distalis of the pituitary gland that often occurs in conjunction with hypertrophy. There is nonencapsulated proliferation of cells that does not result in compression of the adjacent tissue. This change can be a spontaneous or induced lesion that is well reported in rodents, particularly rats, and can progress to pituitary neoplasia.

Reference

Attia, M.A. 1985. Neoplastic and nonneoplastic lesions in aging female rats with special reference to the functional morphology of the hyperplastic and neoplastic changes in the pituitary gland. *Arch Toxicol* 57:77–83.

Subcapsular cell adenoma, see the preferred term **Adrenal gland subcapsular cell tumor, benign**.

Subcapsular cell carcinoma, see the preferred term **Adrenal gland subcapsular cell tumor, malignant**.

Subcapsular cell hyperplasia, see preferred term **Adrenal gland subcapsular hyperplasia**.

Thyroid C cell adenoma, benign is a tumor in the thyroid gland comprised of normal-appearing C cells. These discrete masses are well demarcated and greater than five thyroid follicles in diameter. Although they frequently compress adjacent tissue, they are rarely surrounded by a fibrous capsule, and do not invade adjacent tissue, although cells may spill over into the adjacent follicles.

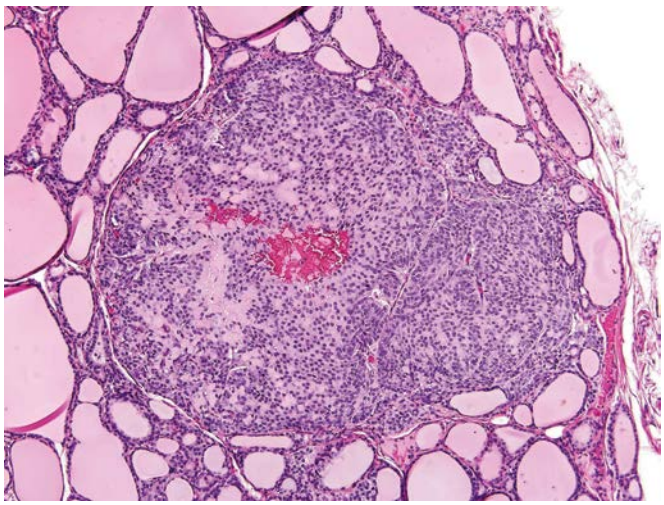


FIGURE 26 Thyroid gland, C cell adenoma, benign F344/N rat, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

References

Boorman, G.A., DeLellis, R.A., and Elwell, M.R. 1996. C-cell hyperplasia, C-cell adenoma, and C-cell carcinoma, thyroid, rat. In: Jones, T.C., Capen, C.C., Mohr, U. (eds.) *Monographs on Pathology of Laboratory Animals. Endocrine System*, 2nd ed. Berlin, Heidelberg, New York, Tokyo: Springer, pp. 262–274.

Martin-Lacave, I., Rojas, F., Bernabe, R., Utrilla, J.C., Fernandez-Santos, J.M., De Miguel, M., and Conde, E. 2002. Comparative immunohistochemical study of normal, hyperplastic and neoplastic C cells of the rat thyroid gland. *Cell Tissue Res* 309:361–368.

Thyroid C cell carcinoma, malignant is a malignant tumor of C cells in the thyroid gland. The cells in these masses can be very abnormal in appearance and have a high mitotic index. These tumors can invade the capsule of the thyroid gland, adjacent tissue, blood, and lymphatic vessels, and spread to distant sites.

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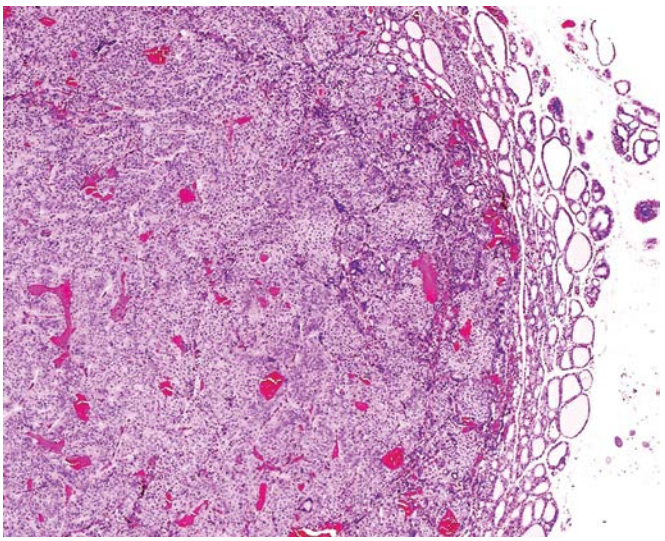


FIGURE 27 Thyroid gland, C cell carcinoma, malignant F344/N rat, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

References

Boorman, G.A., DeLellis, R.A., and Elwell, M.R. 1996. C-cell hyperplasia, C-cell adenoma, and C-cell carcinoma, thyroid, rat. In: Jones, T.C., Capen, C.C., Mohr, U. (eds.) *Monographs on Pathology of Laboratory Animals. Endocrine System*, 2nd ed. Berlin, Heidelberg, New York, Tokyo: Springer, pp. 262–274.

Martin-Lacave, I., Rojas, F., Bernabe, R., Utrilla, J.C., Fernandez-Santos, J.M., De Miguel, M., Conde, E. 2002. Comparative immunohistochemical study of normal, hyperplastic and neoplastic C cells of the rat thyroid gland. *Cell Tissue Res* 309:361–368.

Thyroid C cell hyperplasia is characterized by a focal or diffuse increase of C cells between thyroid follicles and/or within the follicular basement membrane. Hyperplastic C cells are usually identified by calcitonin immunohistochemistry.

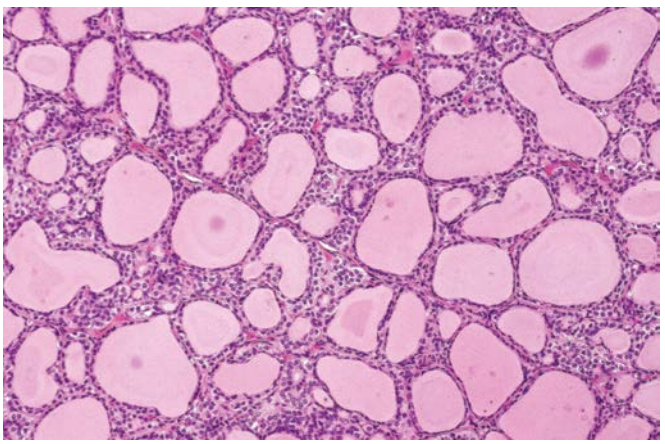


FIGURE 28 Thyroid gland, C cells, hyperplasia, Sprague Dawley rat, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Nodular and/or diffuse C cell hyperplasia can be seen with advanced age, as a response to long-term hypercalcemia in some animals and humans, or as part of multiple endocrine neoplasia (MEN).

Synonym(s): **C cell hyperplasia**; **clear cell hyperplasia**; **parafollicular cell hyperplasia**.

References

Boorman, G.A., DeLellis, R.A., and Elwell, M.R. 1996. C-cell hyperplasia, C-cell adenoma, and C-cell carcinoma, thyroid, rat. In: Jones, T.C., Capen, C.C., Mohr, U. (eds.) *Monographs on Pathology of Laboratory Animals. Endocrine System*, 2nd ed. Berlin, Heidelberg, New York, Tokyo: Springer, pp. 262–274.

Martin-Lacave, I., Rojas, F., Bernabe, R., Utrilla, J.C., Fernandez-Santos, J.M., De Miguel, M., and Conde, E. 2002. Comparative immunohistochemical study of normal, hyperplastic and neoplastic C cells of the rat thyroid gland. *Cell Tissue Res* 309:361–368.

Thyroid follicular adenoma, benign is a neoplasm arising from the thyroid gland follicular cells. Benign thyroid follicular tumors are typically well-demarcated nodules, may be encapsulated, compress the adjacent thyroid tissue, have single or multilayers of cuboidal-columnar epithelial cells with variable atypia, and may be subclassified as solid, follicular, papillary, or cystic. These tumors are relatively rare as a spontaneous background finding in rodents and primates and are believed to arise from preneoplastic lesions.

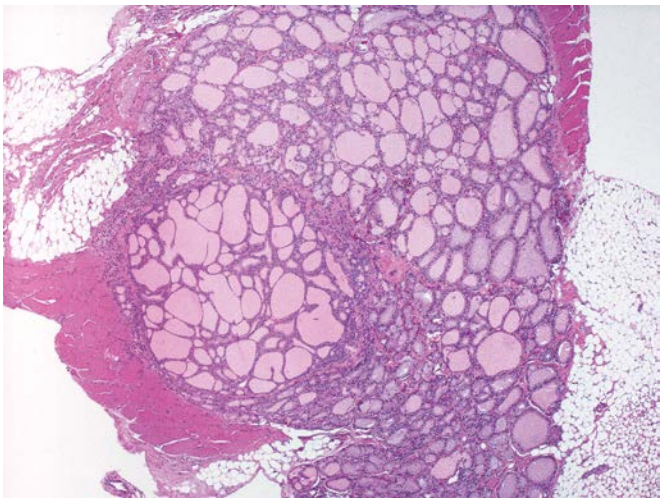


FIGURE 29 Thyroid gland, follicular adenoma, Sprague Dawley rat, H&E.

Reference

Boorman, G.A. and Elwell, M.R. 1996. Follicular cell hyperplasia, adenoma, and carcinoma, thyroid, rat. In: Jones, T.C., Capen, C.C., Mohr, U. (eds.) *Endocrine System. Monographs on Pathology of Laboratory Animals*. Berlin, Heidelberg: Springer.

Thyroid follicular carcinoma, malignant is a tumor of follicular epithelial cells that is generally thought to arise from

neoplastic progression to form a malignant mass. These tumors are subclassified as follicular, solid, papillary, or solid based on specific histologic features. Malignant thyroid follicular tumors are characterized by irregular, variably sized follicles formed by atypical/pleomorphic epithelial cells, solid tumors with malignant cells arranged in solid sheets or nodules, and papillary form, composed of irregular papillary structures with or without pleomorphic tubular structures. Pleomorphic malignant thyroid tumors are characterized by anaplastic or poorly differentiated cells arranged haphazardly with occasional giant or elongate cells present.

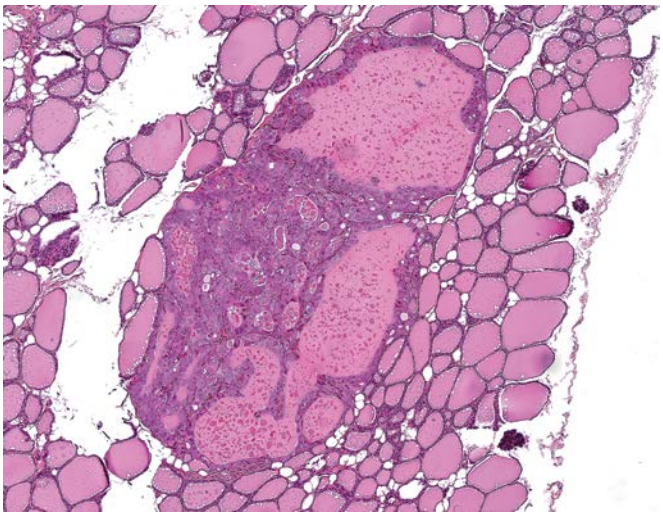


FIGURE 30 Thyroid gland, follicular carcinoma, malignant, cynomolgus monkey, H&E.

Reference

Boorman, G.A. and Elwell, M.R. 1996. Follicular cell hyperplasia, adenoma, and carcinoma, thyroid, rat. In: Jones, T.C., Capen, C.C., Mohr, U. (eds.) *Endocrine System. Monographs on Pathology of Laboratory Animals*. Berlin, Heidelberg: Springer.

Thyroid follicular hyperplasia is a proliferative lesion characterized by increased numbers of thyroid follicular cells that may be focal or diffuse. Diffuse hyperplasia is typically a response to chronic physiologic stimulation, often by thyroid-stimulating hormone (TSH), and is expected to be reversible once the stimulus is removed. Focal hyperplasia is considered a preneoplastic lesion in rodents. Hyperplastic nodules are composed of irregular cuboidal to columnar epithelial cells. Hyperplasia may be difficult to distinguish from a thyroid follicular adenoma; histologic features such as compression of the adjacent follicles, the presence of a capsule, and alterations of the cytoplasm-to-nuclear ratio are more consistent with adenoma than hyperplasia. The thyroid may also be grossly enlarged. There can be papillary structures that invaginate into the lumen. Hypertrophy and hyperplasia can occur together, which is usually a consequence of increased circulating TSH concentrations. Diffuse, TSH-mediated hyperplasia is observed with iodine deficiency and a wide variety of xenobiotic drugs and chemicals that disrupt normal thyroid hormone homeostasis.

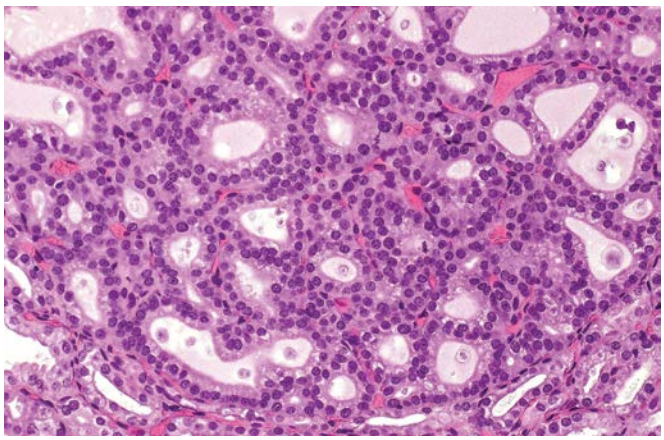


FIGURE 31 Thyroid gland, follicular hyperplasia, F344/N rat, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Reference

Boorman, G.A. and Elwell, M.R. 1996. Follicular cell hyperplasia, adenoma, and carcinoma, thyroid, rat. In: Jones, T.C., Capen, C.C., Mohr, U. (eds.) *Endocrine System. Monographs on Pathology of Laboratory Animals*. Berlin, Heidelberg: Springer.

Thyroid follicular hypertrophy is characterized by an increase in size and height of follicular cells, is normally diffuse in distribution, and can result in decreased amounts of intraluminal colloid. There are no papillary structures formed in this lesion. In general, increased follicular activity is observed more often in males than in females. Hypertrophy is commonly seen in toxicology studies induced by a variety of compounds and is expected to be a reversible lesion provided the stimulus is removed. Hypertrophy may progress to hyperplasia and neoplasia with prolonged stimulation.

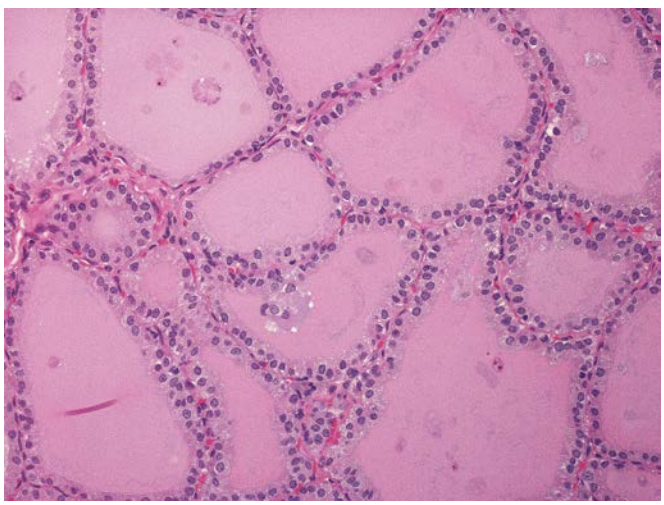


FIGURE 32 Thyroid gland, follicles, epithelial hypertrophy, cynomolgus monkey, H&E.

Reference

Greaves, P. 2012. Thyroid gland. In: *Histopathology of Preclinical Toxicity Studies. Interpretation and Relevance in Drug Safety Studies*. Amsterdam, Boston: Elsevier/AP, pp. 819–836.

A2

Thyroid parafollicular cell adenoma, see the preferred term **Thyroid C cell adenoma**.

Thyroid parafollicular cell carcinoma, see the preferred term **Thyroid C cell carcinoma**.

GASTROINTESTINAL TRACT

APUDoma (APUD = amine precursor uptake and decarboxylase), see the preferred term **Stomach neuroendocrine cell tumor, benign/malignant**.

Atypical gastric hyperplasia is an intraepithelial small focus with cytological characteristics seen in adenomas and should not be diagnosed as an adenoma but as atypical gastric hyperplasia.

Reference

Bertram, T.A., Markovits, J.E., and Juliana, M.M. 1996. Nonproliferative lesions of the alimentary canal in rats GI-1. In: *Guides for Toxicologic Pathology*. Washington, DC: STP/ARP/AFIP, pp. 1–16. Full-text: https://www.toxpath.org/docs/SSNDC/GINonproliferativeRat.pdf

Links

https://ntp.niehs.nih.gov/nnl/alimentary/glandular_stomach/hypat/glandular-stomach-hyperplasia-atypical-pdf_508.pdf
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4765498/

Brunner's gland carcinoma is a rare, spontaneously-occurring neoplasm of the duodenal submucosal glands in laboratory animals and humans. Brunner's gland carcinoma has been observed in transgenic mice (CB6/F1/Jic Tg rasH2 hemizygous) and Sprague Dawley rats after dosing with sunitinib malate, a multikinase inhibitor. Histologically, partial to complete loss of glandular structures accompanied by prominent desmoplasia and moderate pleomorphism are observed. Neoplastic cells have intensely stained eosinophilic, amphophilic, or basophilic cytoplasm. Attenuated glandular cells may line cystic areas that contain mucus. There can be extensive invasion through the muscularis mucosa and/or through the circular and longitudinal muscles, as well as the serosa of the duodenum. Knowledge of the site of the incipient lesion or the use of immunohistochemical methods are often required to diagnose the origin of this neoplasm, as invasion of a gastric glandular cell or duodenal enterocyte carcinoma can have similar morphologic features to those of a Brunner's gland carcinoma that has progressed.

Differential diagnoses: **Brunner's gland hyperplasia**; **Intestinal diverticulum**.

Link

http://www.phusewiki.org/wiki/images/c/c2/RasH2_historical_control_data.pdf

Brunner's gland hyperplasia is characterized by an increased number of glandular cells with an increase in overall gland size. There may be an increase in mitotic figures and no significant compression of adjacent tissue.

Reference

Whiteley, L.O. et al. 2001. Gastrointestinal Tract. In: Mohr, U. (ed.) *International Classification of Rodent Tumors, The Mouse*. WHO International Agency for Research and Cancer. Berlin, Heidelberg: Springer-Verlag, p. 50.

Carcinoid is a slow-growing type of neuroendocrine tumor (apudoma) that arises from enterochromaffin cells in the gastrointestinal tract. In some cases, metastasis may occur. Carcinoids of the midgut (jejunum, ileum, appendix, and cecum) are associated with the carcinoid syndrome.

Synonym(s): **Carcinoid tumor**.

Link

http://journals.sagepub.com/doi/pdf/10.1177/01926233890171P102

Carcinoid tumor, see the preferred term **Carcinoid**.

Enterochromaffin-like cell tumor, see the preferred term **Stomach neuroendocrine cell tumor, benign/malignant**.

Gastric intraepithelial neoplasia (GIN), see the preferred term **Atypical gastric hyperplasia**.

Gastrointestinal adenocarcinoma arises from the mucosal epithelium. Adenocarcinomas are infiltrative tumors which may be exo- and/or endophytic and grow in a variety of patterns which are used as descriptors (tubular, papillary, cystic, solid, scirrhous, mucinous, signet ring, undifferentiated). Neoplastic cells display varying degrees of atypia and the mitotic frequency is often prominent. Typically, these tumors incite significant fibrosis and inflammation in adjacent tissues. In humans, gastrointestinal adenocarcinomas occur most often in the large intestine (colon and rectum) and only occasionally in the small intestine (duodenum more frequently). This is also true in nonhuman primates; however, small intestinal adenocarcinoma has been noted as the leading neoplastic cause of death in aged common marmosets. In rodents, the small intestine (jejunum and ileum) are most commonly affected by spontaneous tumors, although induced tumors may predilect to the large intestine with morphologies that reflect their etiology; mice are considered more resistant than rats to chemical induction of intestinal tumors. A variety of concurrent factors have been associated with adenocarcinoma formation. They may occur de novo or more commonly, via progression from hyperplastic/dysplastic and adenomatous lesions, or in association with other comorbidities. Of these comorbidities, chronic inflammation and *Helicobacter* infection are of particular importance. In humans, chronic *H. pylori* infection is associated with an increased risk of developing gastric adenocarcinoma and rodent models of *Helicobacter* infection have demonstrated a similar association. Other examples abound, such as the lymphoplasmacytic colitis progressing to adenocarcinoma in cotton-top tamarins. Although the intestines are most frequently implicated, similar tumors may occur in the stomach: in rodents, the antrum of stomach is a predilection site for gastric adenocarcinoma.

Link

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4765498/

Gastrointestinal adenoma arises in rodents from the mucosal epithelium and most often in the antrum or pyloric region of the stomach: an exophytic growth of distorted mucosal epithelium that maintains some degree of normal architecture with glandular profiles and limited cellular atypia. Adenomas may invade beyond the lamina propria but remain bounded by a basement membrane, although this may be obscured by fibrosis and inflammation as a reactive change in the surrounding tissue. In rodents, papillary, polypoid, or sessile growth patterns (either gross or microscopic) are considered necessary to the diagnosis of adenoma (as opposed to atypical, intraepithelial hyperplasia, which is not considered adenomatous). Adenomas are most commonly identified in the duodenum and proximal jejunum but may occur anywhere along the tract.

Synonym(s): **Polyp**; **adenomatous polyp**; **polypoid adenoma**; **exocrine adenoma**.

Link

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4765498/

Gastrointestinal stromal tumors (GISTs) are benign or malignant tumors derived from the specialized smooth muscle cells (i.e., interstitial cells of Cajal) in the tunica muscularis or myenteric plexus. Benign forms are well-demarcated tumors with expansive growth and cells arranged in bundles with storiform architecture, and myxoid areas may be present. Spindle, epithelioid, or pleomorphic cell morphology are all recognized with indistinct cell borders and fibrillary cytoplasm. They can be spindle- or irregular-shaped nuclei and they are typically CD117 positive (cytokine receptor encoded by c-kit). Malignant forms exhibit a locally infiltrative growth pattern and cells may be arranged in similar manner with similar architecture to the benign forms. They are also typically CD117 positive and distant metastases may be present. It is generally difficult to differentiate GIST from leiomyomas/leiomyosarcomas or other soft tissue tumors based only on routine histologic sections. Immunohistochemical differentiation of the different tumor types, including GIST, needs to be performed in case of imbalances in the incidence of smooth muscle tumors in a given study.

Differential diagnoses: **Leiomyoma**; **Leiomyosarcoma**; **Schwannoma**.

Synonym(s): **Interstitial Cajal cell tumor, benign**; **gastrointestinal pacemaker cell tumor, benign/malignant**.

Link

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4765498/

Glandular stomach adenocarcinoma is a spontaneous neoplasm in rodents that is more common in several knockout and transgenic mouse strains (e.g., insulin-gastrin transgenic mice, gastrin knockout mice, K-ras transgenic mice, TGF alpha transgenic mice, and Wnt1 and COX-2 transgenic mice). Morphologic features may be tubular, papillary, cystic, solid, scirrhous, mucinous, and/or signet ring type with exophytic or endophytic growth patterns. The chemically induced adenocarcinoma occurs in rats; mice are less prone to develop this type of neoplasm. These are typically invasive growth, with nests and cords of neoplastic cells extending into the lamina propria or deeper layers resulting in loss of basement membrane integrity. They may also be associated with fibrous/scirrhous reaction and inflammation. Neoplastic cells may have basophilic or clear cytoplasm with cytologic and nuclear atypia, anaplasia, hyperchromatism, and increased numbers of mitotic figures. Induced adenocarcinomas occur predominantly in the antrum, and are observed with irradiation, diethylnitrosamine (DEN), nitroso compounds, and opioids. *Helicobacter* spp.–related carcinogenesis occurs in humans and the Mongolian gerbil but not in other laboratory animals. Morphological growth patterns include tubular, papillary, cystic, solid, scirrhous, mucinous, signet ring, undifferentiated, or mixed types.

Differential diagnoses: **Glandular stomach mucosal hyperplasia**; **Glandular stomach atypical mucosal hyperplasia**; **Glandular stomach diverticulum**; **Glandular stomach adenoma**; **Neuroendocrine cell tumor, malignant**.

Synonym(s): **Glandular stomach carcinoma**.

References

Miller, A.D. et al. Small intestinal adenocarcinoma in common marmosets (Callithrix jacchus). *Vet Pathol* 47(5):969–976.

Nambiar, P.R. et al. 2005. Gastritis-associated adenocarcinoma and intestinal metaplasia in a Syrian hamster naturally infected with *Helicobacter* species. *Vet Pathol* 42(3):386–390.

Panigrahi, D., Johnson, A.N., and Wosu, N.J. 1994. Adenocarcinoma arising from gastric heterotopia in the jejunal mucosa of a beagle dog. *Vet Pathol* 31(2):278–280.

Link

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4765498/

Glandular stomach adenoma is a spontaneously occurring neoplasm in rodents that is common in several knockout and transgenic mouse strains. Rodents administered synthetic progestin cyproterone acetate, diethylnitrosamine (DEN), and *N*-nitrosamine compounds develop adenoma and adenocarcinoma that typically arise in the antral or pyloric mucosa of the glandular stomach. Neoplastic cells are basophilic and less differentiated glandular epithelium, but with little atypia, and in some cases focal penetration by glandular diverticula into the lamina propria or deeper layers may be present but the basement membrane remains intact. The growth patterns may be polypoid, sessile, or papillary, with or without a fibrovascular stalk type.

Differential diagnoses: **Glandular stomach mucosa hyperplasia**; **Glandular stomach adenocarcinoma**; **Neuroendocrine cell tumor, benign**.

Synonym(s): **Glandular stomach polyp**; **glandular stomach adenomatous polyp, polypoid adenoma**; **exocrine adenoma**.

Reference

Jiang, Y. and Yu, Y. 2017. Transgenic and gene knockout mice in gastric cancer research. *Oncotarget* 10; 8(2):3696–3710.

Link

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Glandular stomach atypical mucosal hyperplasia is a focal proliferation of acinar or tubular epithelium with multiple layers and cellular atypia; most importantly, without invasion of surrounding tissue.

Link

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4765498/

Glandular stomach carcinoma, see the preferred term **Glandular stomach adenocarcinoma**.

Glandular stomach mucosal hyperplasia is characterized by proliferation of mucosal epithelium but no evidence of invasion. The glandular structure is preserved or only slightly altered (acinar hyperplasia); in cases of reactive hyperplasia, evidence of an underlying process such as inflammation, fibroplasia, ductal obstruction, or foreign material should be present.

Link

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4765498/

Glandular stomach polyp, see the preferred term **Glandular stomach adenoma**.

Granular cell tumor is a soft tissue, generally benign neoplasm considered to be of Schwann cell origin, but several cellular origins have been proposed. Granular cell tumors occur in many locations throughout the body. A review of granular cell tumors in dogs and cats showed that the majority arise in the oral cavity, although a survey of other sites and species included the digit, lung (horse), periocular tissue (cockatiel), and vulva. In rats, granular cell tumors are most typically associated with the tongue and female reproductive tract (cervix/vagina). In some strains of mice (B6C3F1), they have been described in the uterus. Regardless of species or location, the neoplastic cells are oval to polygonal, variably sized, with abundant, pale eosinophilic cytoplasm containing distinct intracytoplasmic granules which stain with periodic acid-Schiff stain (PAS) and were diastase resistant. Ultrastructural examination suggests that the granules are lysosomes. Depending on the site of origin, the immunohistochemical stains that have been applied include vimentin, S-100, neuron-specific enolase, L-antitrypsin, lysozyme, actin, and desmin. A summation of staining results suggests granular cell tumors can have similar morphologic features but may be of different cellular origins. In humans, granular tumors are most common in the skin, oral cavity (tongue), or digestive tract.

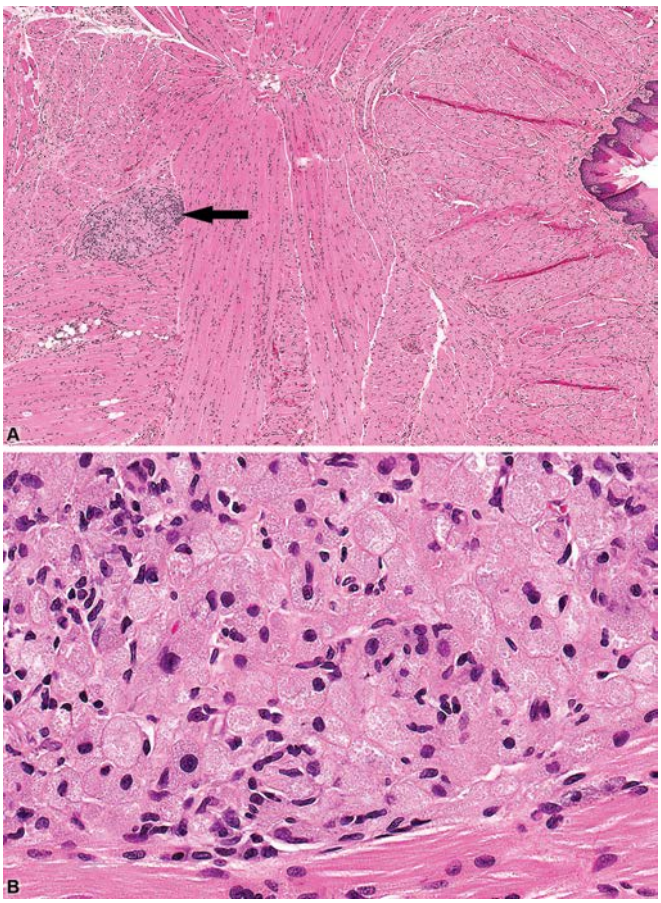


FIGURE 1 Tongue, rat. H&E. Granular cell tumor (A) 5×. Arrow = tumor. (B) 40× high magnification of tumor.

Link

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4765498/

Hyperplasia (gastrointestinal) may occur in many cell types/locations. For example, goblet cell hyperplasia and mucus hypersecretion occur with parasitic helminth infection, mediated by a T helper type 2 (Th2) response and IL-13 expression, which is considered the major effector cytokine in the hyperplastic response. Other examples abound, often in the context of genotoxic transformation such as in the rodent forestomach, where hyperplasia has a positive correlation to tumor formation.

Link

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4765498/

Intestinal adenocarcinoma is a malignant neoplasm arising from enterocytes of the intestinal mucosa and characterized by invasion through the muscularis mucosa or deeper layers of the intestinal wall, as well as into the mesentery and adjacent abdominal cavity organs. Spontaneous adenocarcinoma in rodents is more common in the small intestine, especially the jejunum and ileum, whereas induced adenocarcinomas are more frequent in the distal colon; both may show local invasion but have a low tendency to metastasize. *Helicobacter* spp. has been shown to be a colon cocarcinogen in some experimental mouse models involving genetically engineered mice or immunodeficient mice. Inflammatory mouse models of colon adenocarcinoma are often scirrhous- and mucinous-type neoplasms. The pattern of neoplastic growth may be solid, papillary, mucinous, signet ring, cystic, scirrhous, and/or undifferentiated types.

Differential diagnoses: **Intestinal diverticulum**; Intestinal atypical mucosal hyperplasia; **Intestinal adenoma**.

Synonym(s): **Intestinal carcinoma**.

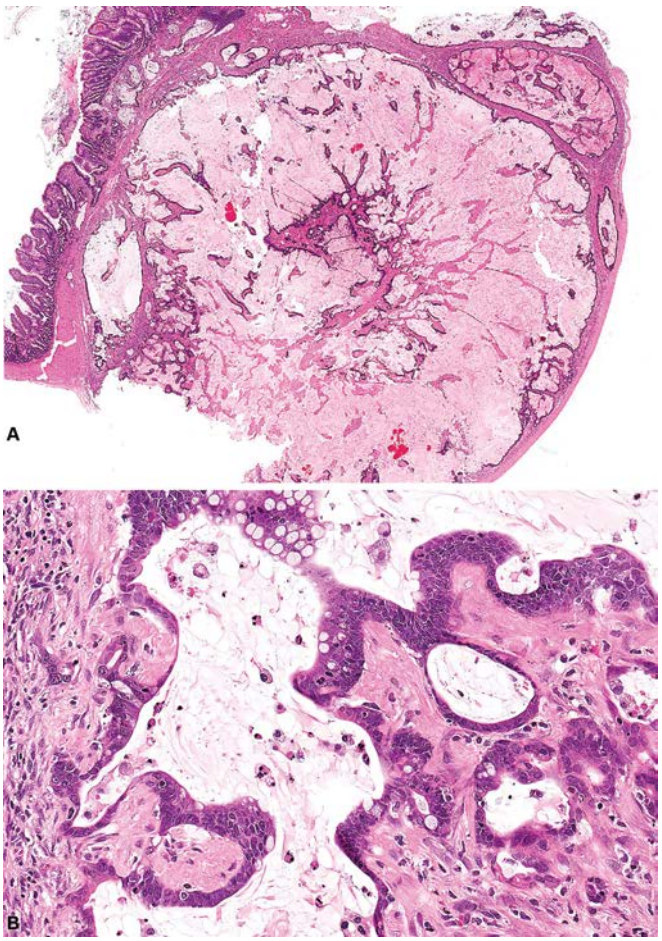


FIGURE 2 Jejunum, rat. H&E. Adenocarcinoma. Invasive glands/cysts, some mucous component. A = 1×, B = 20×.

Link

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4765498/

Intestinal adenoma is a polypoid, sessile, or papillary neoplasm arising from enterocytes. This benign neoplasm may have cellular atypia/dysplasia including cellular basophilia, loss of cellular polarity, hyperchromatic pleomorphic nuclei, and/or nuclear stratification. Intestinal adenoma may be associated with glandular or cystic diverticula and progress to malignancy in experimentally induced neoplasia. Squamous metaplasia and foci of mineralization may also be present. The stromal core in polypoid or papillary neoplasms is not present in sessile adenomas. The spontaneously occurring intestinal adenoma in mice is more commonly seen in the duodenum and anterior part of the jejunum while induced adenomas are more frequent in the distal colon. Morphological growth patterns include polypoid, papillary, and sessile types.

Differential diagnoses: **Intestinal diverticulum**; Intestinal atypical mucosal hyperplasia; **Intestinal adenocarcinoma**.

Synonym(s): **Intestinal polyp**; **intestinal adenomatous polyp**.

Link

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4765498/

Leiomyoma (gastrointestinal) is a benign intramural (muscular wall) neoplasm derived from the smooth muscle cells of the tunica muscularis. It is characterized by patterns of interlacing bundles and whorls of uniform spindle cells. The nuclei are typically "blunt-ended" or "cigar-shaped" in cells with eosinophilic cytoplasm containing longitudinal myofilaments a perinuclear clear space and immunoreactivity for desmin.

Differential diagnoses: **Leiomyosarcoma**; **Gastrointestinal stromal tumor (GIST)**; **Schwannoma**; **Fibroma**; **Sarcoma**; **Histiocytic sarcoma**.

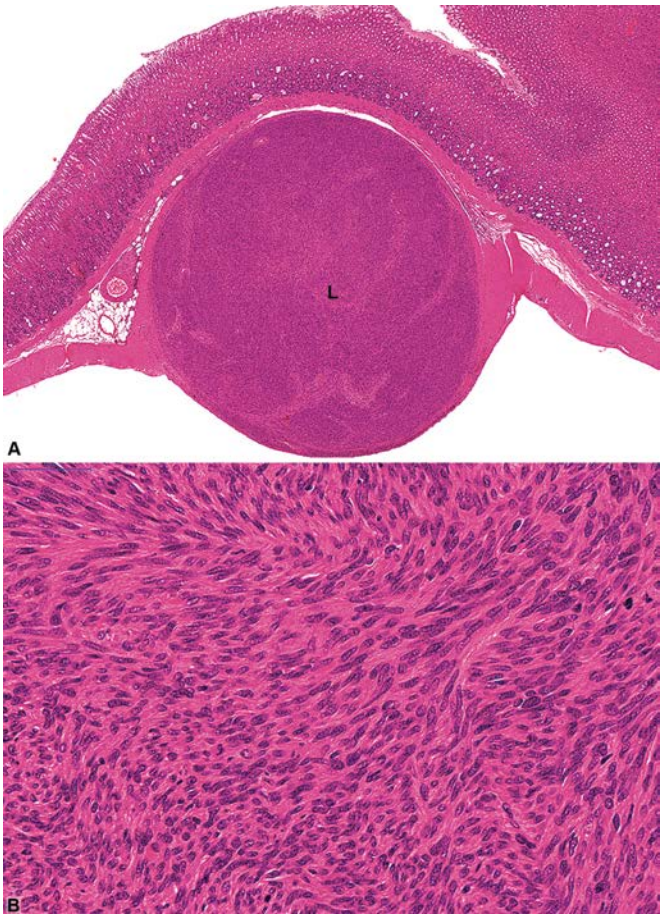


FIGURE 3 Glandular stomach, rat. H&E. (A) L = Leiomyoma. (B) = Higher magnification of section A demonstrates the monomorphic character of the spindle-shaped neoplastic cells. (Image reproduced with permission of the Japanese Society of Toxicologic Pathology from Nolte et al. 2016.)

Link

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4765498/

Leiomyosarcoma (gastrointestinal) is a malignant intramural neoplasm derived from the smooth muscle cells of the tunica muscularis. Morphologically it is similar to a leiomyoma, but more cellular pleomorphism and more prominent mitotic activity. Necrosis, cystic change, and mineralization may also be common features; both local invasion and distant metastases may occur.

Differential diagnoses: **Leiomyoma**; **Gastrointestinal stromal tumor (GIST)**; **Schwannoma**; **Fibroma**; **Sarcoma**; **Histiocytic sarcoma**.

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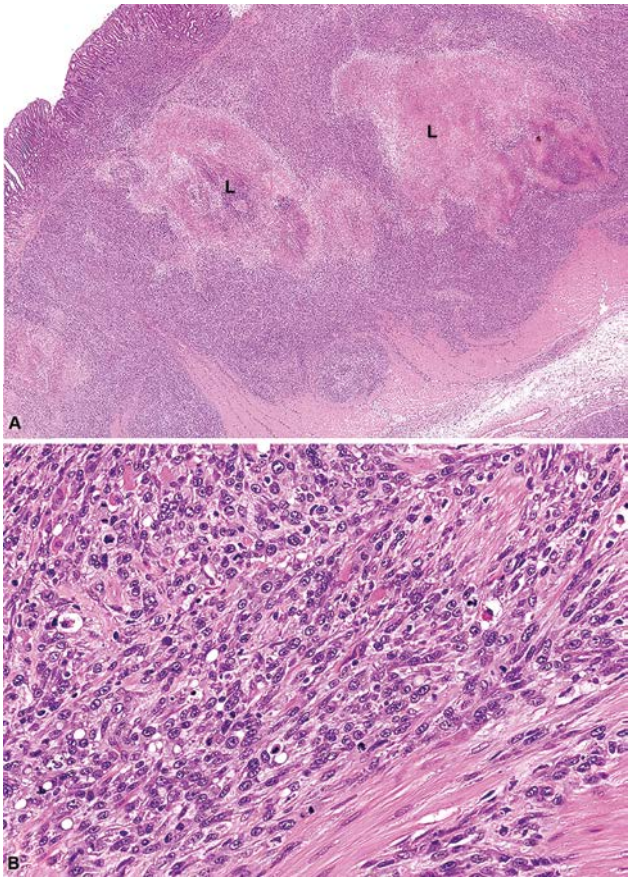


FIGURE 4 Nonglandular stomach, rat. H&E. (A) L = Leiomyosarcoma. (B) Higher magnification of section A, cellular pleomorphism is consistent with malignancy. (Image reproduced with permission of the Japanese Society of Toxicologic Pathology from Nolte et al. 2016.)

Link

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4765498/

Mucinous hyperplasia is characterized by increased numbers of epithelial cells that produce mucin, a glycoprotein constituent of mucus.

Myoepithelioma, malignant is a salivary gland tumor comprised of myoepithelial cells, which are found in glandular epithelium as a thin layer above the basement membrane and contain smooth muscle actin. Classically, they are found in the parotid gland or palate region of the oral cavity. A similar neoplasm may be found in the tongue, referred to as an ectomesenchymal chondromyxoid tumor.

Link

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4765498/

Nonglandular stomach benign basal cell tumor is a rare neoplasm characterized by the proliferation of the basal layer of the stratified squamous epithelium that lacks differentiation or keratinization. This neoplasm may exhibit an endophytic growth pattern of closely packed, small or oval cells from the stratum germinativum forming garlands or nests surrounded by palisade-like cells. There may be loss of rete pegs with intact basement membrane showing compression of the surrounding tissue or elevation of the overlying nonproliferative squamous epithelium.

Differential diagnoses: Nonglandular stomach basal cell hyperplasia; **Nonglandular stomach squamous cell carcinoma**.

Link

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4765498/

Nonglandular stomach malignant basal cell tumor is a very rare malignant neoplasm showing predominant proliferation of basal layer of the stratified squamous epithelium with absence of differentiation or keratinization. This neoplasm may exhibit endophytic growth pattern infiltrating into the lamina propria of the mucosa and submucosa. Neoplastic cells are round to oval closely packed nonspinous cells with dark nuclei and little cytoplasm with frequent mitotic figures, often forming palisade-like garlands or chains. Growth pattern suggests loss of the basement membrane integrity. Superficial layers appear almost normal, but are sometimes ulcerated.

Differential diagnoses: **Nonglandular stomach squamous cell carcinoma**; **Nonglandular stomach basal cell hyperplasia**; **Nonglandular stomach benign basal cell tumor**.

Synonym(s): **Nonglandular stomach basal cell carcinoma**.

Link

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4765498/

Nonglandular stomach squamous cell carcinoma is a forestomach neoplasm characterized microscopically by exophytic and/or endophytic growth of neoplastic stratified squamous epithelium with moderate to marked cellular atypia, pleomorphism, and mitotic activity. Macroscopically this neoplasm may be a firm, white irregular mucosal mass that is often ulcerated. Microscopically there is clear evidence of invasion into the submucosa, muscle layer, and serosa. Inflammation or fibroplasia in the lamina propria or submucosa are common features. Well-differentiated squamous cell carcinoma can be keratinized with the presence of epithelial nests (with or without keratinized cysts) and marked necrosis or hemorrhage. Neoplastic cells in poorly differentiated squamous cell carcinomas may appear as solid sheets or cords/strands with rare keratinization, but often show extensive invasion infiltrating the submucosa or adjacent tissue accompanied by a scirrhous response. These neoplasms may metastasize to the abdominal cavity, regional lymph nodes, or the lung. Spontaneous squamous cell carcinoma of the nonglandular stomach is rare in rats and mice but may occur at a higher background incidence in hamsters. They can be induced in rodents by administration of nitroso compounds as well as a number of genotoxic and nongenotoxic chemicals. Examples of genotoxins targeting the nonglandular stomach are polycyclic aromatic hydrocarbons (BP, MCA, DMBA), *N*-nitroso compounds (DEN, MNNG, MNU, 4-NQA), urethane, and dibenzocarbazole. Brca1-mutated mice show increased sensitivity to genotoxic carcinogenesis of the nonglandular stomach as a result of increased

oxidative stress and loss of p53. Nongenotoxins acting as nonglandular stomach carcinogens include butylated hydroxyanisole, caffeic acid, or ethyl acrylate, citrus oils, limonene, aristolochic acid, BHA antioxidant, ascorbic acid, and lipophilic statins. Chronic inflammation or local irritation of the nonglandular stomach mucosa due to physical trauma or chemical-induced irritation and/or ulceration associated with high-dose regimens may play a role in the continuous induction of cell proliferation and the ultimate development of carcinomas by nongenotoxic chemicals. Neoplasms induced by nongenotoxic chemicals in rodents, including rats, mice, and/or hamsters, are not generally considered to be a risk in humans as there is no direct counterpart of the nonglandular stomach. Well-differentiated squamous cell carcinoma may have a nearly normal appearing squamous epithelium but frequently have foci with central hyperkeratinization (keratin pearls); or in areas of invasion, there may be a predominance of polygonal and pleomorphic cells with varying degrees of keratinization. Poorly differentiated (anaplastic) type squamous cell carcinomas are characterized by solid sheets or strands of spindle cells leading to varying degrees desmoplasia. Keratinization may not be apparent. Cells show varying size (frequently larger than normal) and shape and nuclei are hyperchromatic, enlarged, and have prominent nucleoli.

Differential diagnoses: Nonglandular stomach squamous cell papilloma; **Nonglandular stomach benign basal cell tumor**; Nonglandular stomach malignant basal cell tumor; **Nonglandular stomach squamous cell hyperplasia**; Nonglandular stomach basal cell hyperplasia.

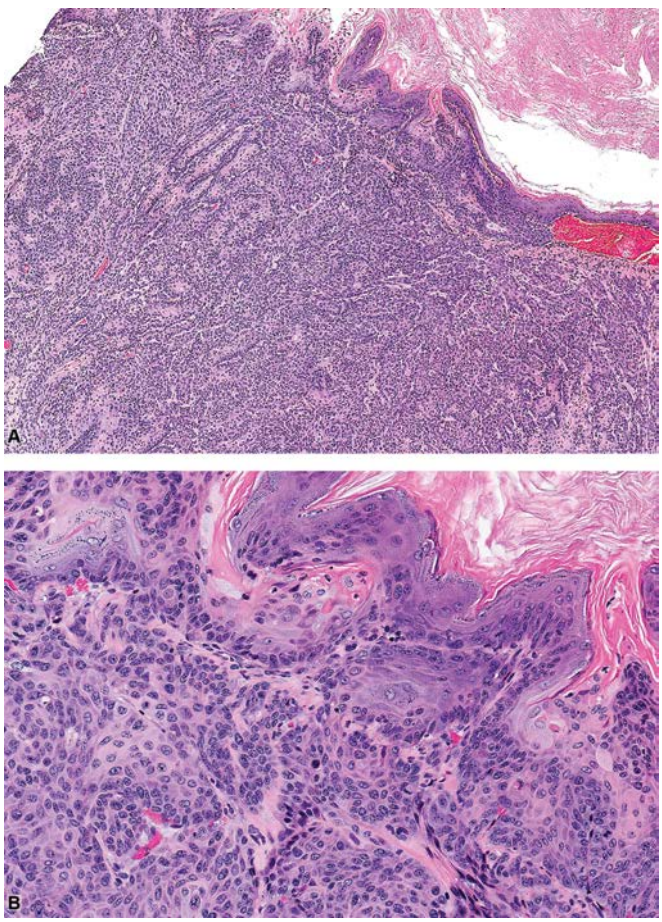


FIGURE 5 Stomach, rat, H&E. Nonglandular squamous cell carcinoma. A = 5×, B = 20×.

Link

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4765498/

Nonglandular stomach squamous cell hyperplasia is a proliferation and thickening of the stratum spinosum (layer of cells between the stratum granulosum and stratum basale) which is often associated with hyperkeratosis or parakeratosis. An exophytic growth pattern may show papillary projections with minimal or no branching and no fibrovascular stroma. Hyperplastic squamous cells with increased mitotic activity maintain polarity of differentiation to keratinocytes and are often associated with exaggerated rete peg formation due to increased number of basal cell layers. An endophytic growth pattern extends into the submucosa with cyst-like structures containing keratin, lined by well-differentiated squamous epithelium, with an intact basement membrane. Reactive squamous cell hyperplasia is a relatively common finding in oral gavage and dietary studies in rodents, and can be an adaptive change to irritation caused by a test article or the gavage procedure. The modifier "reactive" should be used if proliferation of stratified squamous epithelium is associated with or secondary to local erosion, ulcer, or inflammation. Nonglandular stomach carcinogens often induce dysplasia of the spinous and basal cells, especially if the hyperplasia is a precursor to a papilloma or squamous cell carcinoma. Squamous cell hyperplasia and basal cell hyperplasia may occur concurrently. Hyperkeratosis or parakeratosis alone should be distinguished from squamous cell hyperplasia. Acanthosis is a synonym for epidermal (squamous) hyperplasia of the skin, and should not be used for mucosal changes in the nonglandular stomach. The occurrence of nonglandular stomach hyperplasia in short-term rodent studies that may result from direct proliferative effects, or secondary to cytotoxicity of the test article, must be carefully evaluated for the mechanism and relevance to humans. Exposure to butylated hydroxyanisole and its structurally related phenols and acids, sodium metabisulphite and chronic vitamin A and zinc deficiency, are examples of test articles that may cause hyperplasia with hyperkeratosis. Mechanism-based hyperplasia is reported with HMG-CoA reductase inhibitors and Raf inhibitors.

Differential diagnoses: Nonglandular stomach squamous cell papilloma; Nonglandular stomach basal cell hyperplasia; **Nonglandular stomach squamous cell carcinoma**.

Synonym(s): **Nonglandular stomach squamous hyperplasia**; **nonglandular stomach squamous cell hyperplasia**.

Link

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4765498/

Oral cavity squamous cell carcinoma is a rare, spontaneous malignant neoplasm arising from epithelial squamous cells of the mucosal surface in the oral cavity of most laboratory animals that may be induced by exposure to N′-nitrosonornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone

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(NNK), benzene, tetrachloroazobenzene, and certain polychlorinated biphenyls (dioxin-like compounds) in rats. They are experimentally induced in mouse with administration of carcinogenic 4-nitroquinoline-1-oxide (4NQO) and Dimethyl-1,2,benzanthracene (DMBA). Genetically modified mouse models of oral cavity squamous cell carcinomas include LSL-KrasG12D mouse and Tgfbr1/Pten 2cKO mice. This neoplasm is comprised of atypical epithelial squamous cells with cellular/nuclear pleomorphism forming irregular cords, nests, or clusters with high mitotic figures. Invasion and destruction of basement membrane and adjacent tissue is common. Hyperkeratosis and keratin pearls may be present.

Differential diagnoses: Oral cavity squamous cell papilloma; Oral squamous cell hyperplasia.

Link

https://www.sciencedirect.com/science/article/pii/S1368837517302191

Polyp (gastrointestinal) is an abnormal growth of tissue projecting from a mucous membrane. It may be attached by a narrow stalk (pedunculated) or have a more flattened, nodular appearance (sessile). In the gastrointestinal tract, polyps are commonly found in the colon, stomach, and small intestine. Some polyps are neoplasms (benign or malignant) while others are nonneoplastic (e.g., inflammatory, hyperplasia, dysplasia). Neoplastic polyps are generally benign, although some can progress to malignancy.



FIGURE 6 Nonglandular stomach, rat. H&E. Squamous cell polyp.

Link

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4765498/

Salivary gland adenocarcinoma is a malignant neoplasm of ductal or acinar epithelium of the salivary glands. Neoplastic cells are large, pleomorphic, and polyhedral with amphophilic cytoplasm, large vesicular nuclei, and often multiple nucleoli with high a nucleus-to-cytoplasmic ratio. Neoplastic cells may form whorls or spindle patterns with high numbers of mitotic figures, areas of squamous differentiation, and necrosis. Invasion of the surrounding tissue and metastasis are often present. Spontaneous and treatment-related neoplasms of salivary glands are rare in rats and mice in carcinogenicity bioassays. Polyoma virus is also associated with salivary gland neoplasms in mice. Intraglandular injection of DMBA (7,12-dimethylbenz[a]anthracene) in female Wistar rats and female mice may result in submandibular gland adenocarcinoma. Salivary gland adenocarcinoma occurs in Smgb-TAG mice, transgenic mice with PLAG1 proto-oncogene overexpression, transgenic mice expressing a human Ha-ras oncogene, and in wap-ras transgenic mice. Growth patterns include acinar, tubular, papillary, solid, or mixed acinar/tubular types.

Differential diagnoses: **Salivary gland hyperplasia**; Salivary gland atypical hyperplasia; **Salivary gland adenoma**; **Mammary gland adenocarcinoma**.

Link

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4765498/

Salivary gland adenoma is a rare, spontaneous, benign neoplasm arising from ductal or acinar epithelium of the salivary glands. These are well-demarcated neoplasms composed of a glandular epithelium devoid of zymogen granules and surrounded partially or completely by a thin capsule with compression of the adjacent parenchyma or connective tissue. Macroscopically they may appear as reddish-yellow masses in the subcutis of the ventral neck. In mice, only acinar adenoma of the salivary glands has been described, while in rats, these neoplasms may develop different growth patterns including acinar, tubular, papillary, solid, or mixed acinar/tubular types. Mice that have the pleomorphic adenoma gene (PLAG1 or PLAG2) develop a high incidence of submandibular gland adenoma.

Differential diagnoses: **Salivary gland hyperplasia**; Salivary gland atypical hyperplasia; **Salivary gland adenocarcinoma**; **Mammary gland adenoma**.

Link

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4765498/

Salivary gland hyperplasia is focal, multifocal, or diffuse proliferation of ductal and/or acinar epithelium of the salivary glands often associated with inflammatory changes and fibrosis. Glandular architecture of salivary glands is preserved or minimally altered, with minimal compression of the surrounding tissue. Spontaneous hyperplastic changes of the salivary gland are rare in rodents, reported in transgenic mouse models expressing a human Ha-ras oncogene (*Cancer Res* 1991;51:3762–3767), PLAG1 (pleomorphic adenoma gene 1), transgenic mice (*Cancer Res* 2005 Jun 1;65(11):4544–4553), and MMTV-Fgf8 transgenic mice (*Oncogene* 1998;17:2711–2717).

Hyperplasia may be acinar type, ductal type (epidermal growth factor–induced ductal hyperplasia), or reactive type with ductal inflammation or ductal obstruction. Atypical hyperplasia is characterized by multiple layers of acinar/ductular epithelial cells with gradual loss of cellular polarity and differentiation, an amphophilic cytoplasm, and increased nucleus-to-cytoplasm ratio. Reactive salivary gland ductal hyperplasia is reported in

rodents, dogs, monkeys, and humans and can be associated with the presence of ductal calculi and stones, also reported in salivary glands of rats infected with the sialodacryoadenitis virus.

Differential diagnoses: **Salivary gland adenoma**; Ectopic parotid gland; Salivary gland acinar cell hypertrophy.

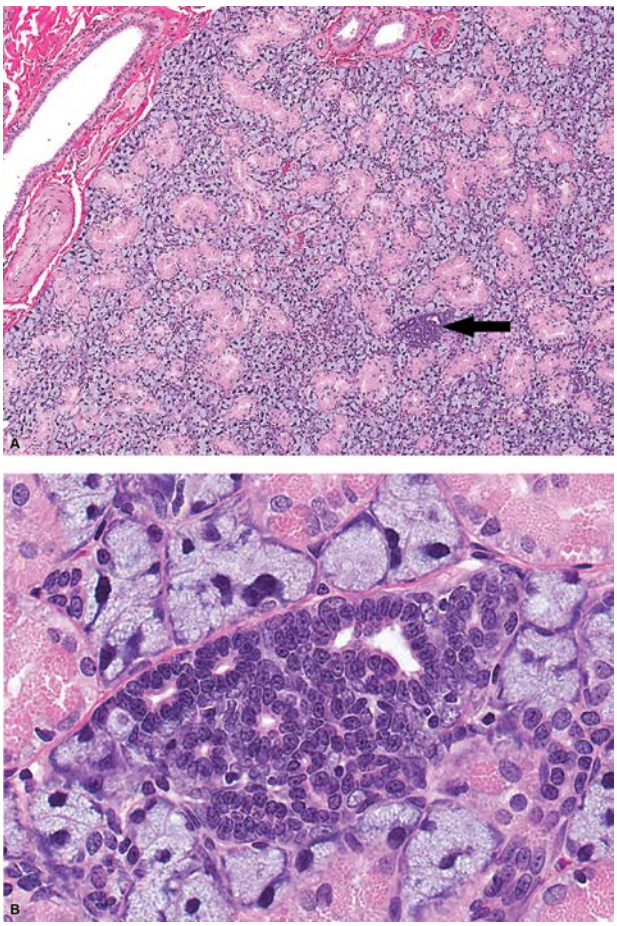


FIGURE 7 Submandibular salivary gland, rat, H&E. Focal hyperplasia (A) 4×. Arrow = hyperplasia. (B) 40× high magnification of hyperplasia.

Link

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4765498/

Salivary gland squamous cell carcinoma is characterized by well-differentiated islands and cords of neoplastic squamous cells with keratin formation that probably originates from ductular epithelial structures of the salivary glands. Spontaneous occurrence is rare in rodents, but xenobiotic-induced squamous cell carcinomas are reported following 7,12-dimethylbenz[a]anthracene (DMBA) treatment in rats and mice. These tumors may also occur spontaneously in mice with the ras oncogene. Some squamous cell carcinomas are markedly anaplastic and composed of fusiform cells with pleomorphic nuclei and numerous mitotic figures. Squamous cell carcinoma of the salivary glands should be distinguished from the more commonly occurring, locally invasive Zymbal's gland carcinoma that may develop in this anatomic location.

Differential diagnoses: **Salivary gland adenocarcinoma**; Zymbal's gland squamous cell carcinoma; Mammary gland adenosquamous carcinoma; Salivary gland squamous cell metaplasia; **Myoepithelioma, malignant**.

Link

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4765498/

Squamous cell hyperplasia of nonglandular stomach, focal/diffuse is a proliferation and thickening of the squamous layer of the nonglandular stomach in a local or extensive fashion. The focal form may take on an atypical morphology. Focal atypical hyperplasia represents an altered proliferation of mucosal epithelium. It may be associated with chronic inflammation. An example is the *Helicobacter pylori* mouse model. Although frequently considered as preneoplastic by nature, this needs to be proven in a given case in order to be classified as such.

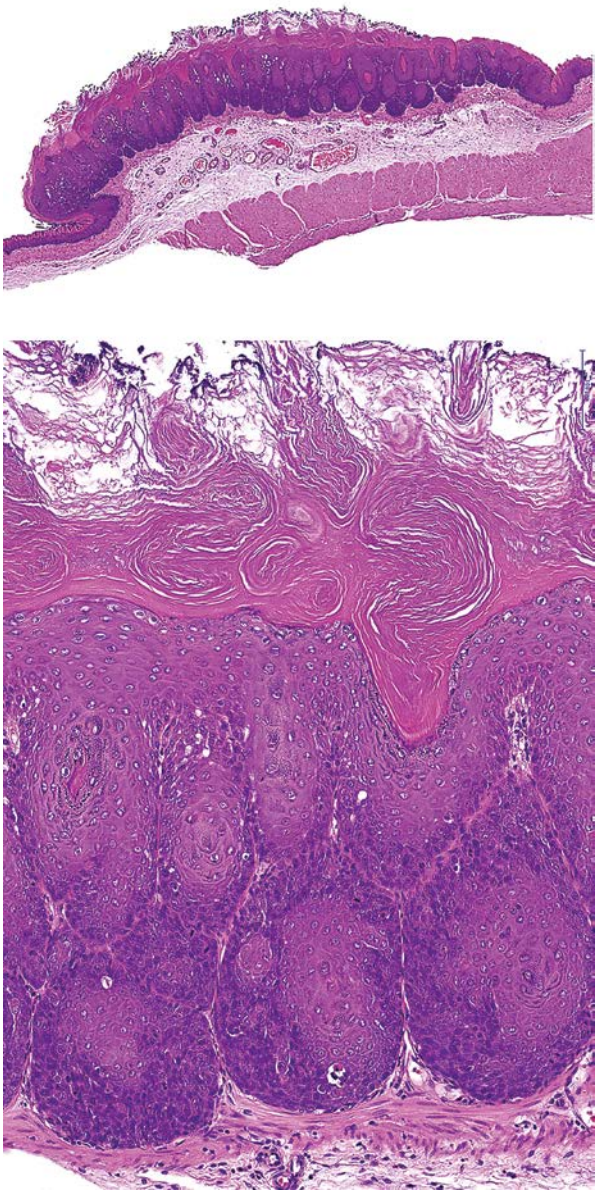


FIGURE 8 Nonglandular stomach, rat, H&E. Hyperplasia squamous cell focal. (Image reproduced with permission of the Japanese Society of Toxicologic Pathology from Nolte et al. 2016.)

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Differential diagnoses: **Adenoma**; **Adenocarcinoma**.

Synonym(s): **Regenerative hyperplasia, focal**; **hyperplasia, focal (mucosa), atypical**; **adenomatous hyperplasia**; **dysplasia**; **gastric intraepithelial neoplasia (GIN)**; **regenerative hyperplasia, diffuse**; **hypertrophic gastritis**; **mucosal hypertrophy**.

Link

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4765498/

Squamous cell papilloma (gastrointestinal) is a benign epithelial tumor growing exophytically (outwardly projecting) as a mass, often with finger-like fronds. In some cases, human or canine papillomavirus can result in formation of squamous cell papilloma (wart).

Link

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4765498/

Stomach neuroendocrine cell tumor, benign is a discrete, well-demarcated aggregate of neuroendocrine cells, which may arise from hyperplastic areas in the oxyntic mucosa (i.e., corpus region). Neuroendocrine cell hyperplasia and neoplasia may be seen in response to hypergastrinemia following antisecretory drug treatment.

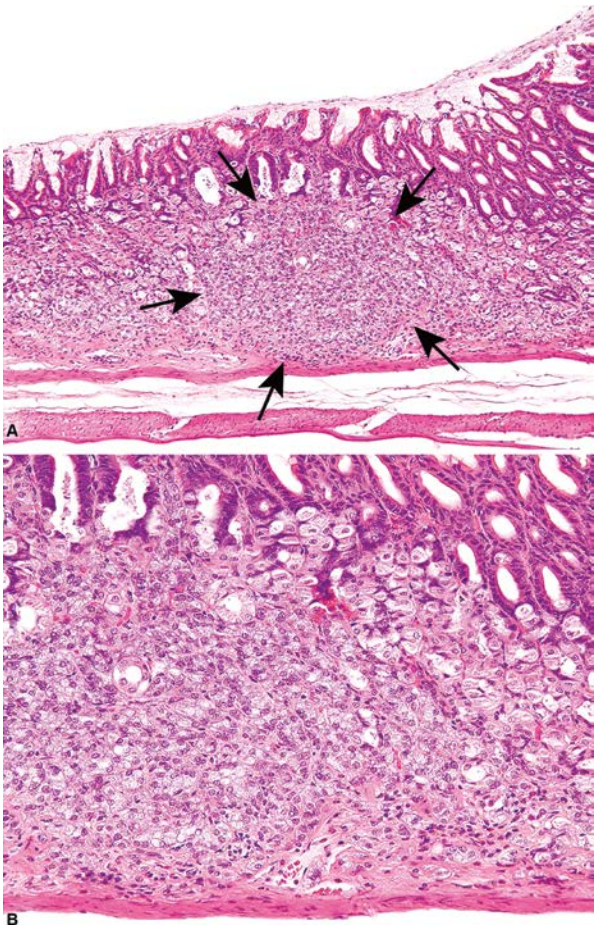


FIGURE 9 Glandular stomach, rat, H&E. Tumor, neuroendocrine cell, benign, on a background of disseminated neuroendocrine hyperplasia. Tumor outlined by arrows. Higher magnification. Note increased cytoplasmic eosinophilia and mild nuclear and cellular. (Image reproduced with permission of the Japanese Society of Toxicologic Pathology from Nolte et al. 2016.)

Differential diagnoses: Hyperplasia, neuroendocrine cell; **Tumor**; Neuroendocrine cell, malignant; Ectopic hepatocytes.

Synonym(s): **Enterochromaffin-like cell tumor**; **APUDoma (APUD = amine precursor uptake and decarboxylase)**; **intramucosal neuroendocrine cell tumor**.

Reference

Spencer, A.J., Barbolt, T.A., Henry, D.C., Eason, C.T., Sauerschell, R.J., Bonner, F.W. 1989. Gastric morphological changes including carcinoid tumors in animals treated with a potent hypolipidemic agent, ciprofibrate. *Toxicol Pathol* 17:7–15.

Link

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4765498/

Stomach neuroendocrine cell tumor, malignant is characterized by infiltration through muscularis mucosae by neoplastic, often less-differentiated cells arranged in cords or nodules or serosal deposits or distant metastases.

Differential diagnoses: **Hyperplasia**; Ectopic hepatocytes.

Synonym(s): **Neuroendocrine carcinoma**; **carcinoid**; **enterochromaffin-like cell tumor**; **APUDoma (APUD = amine precursor uptake, decarboxylase)**; **intramucosal neuroendocrine cell tumor (benign)**.

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https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4765498/

HEMATOPOIETIC SYSTEM

Bone marrow dysplasia is an abnormal maturation of one or more lineages of blood cell and is often considered a preneoplastic lesion. See **Hematopoietic dysplasia** for further information.

Bone marrow fibrosis occurs when fibrous connective tissue formed by fibroblasts as a result of a chronic inflammatory process involves the bone marrow cavity. This process may further be divided according to the predominant type of connective tissue (extracellular matrix proteins) present, either collagen or reticulin. Collagen versus reticulin cannot be easily distinguished in hematoxylin and eosin (H&E)-stained tissue sections. Special stains are needed for differentiation of the subtype.

Synonym(s): **Myelofibrosis**; **bone marrow stroma increased**.

Bone marrow hyperplasia, see the preferred term **Hematopoietic cells, hypercellularity**.

Bone marrow stroma, increased, see the preferred term **Bone marrow fibrosis**.

Chloroleukemia, see the preferred term **Myeloid leukemia**.

Eosinophilic leukemia is a tumor of eosinophilic granulocytic lineage. It has not been reported as a spontaneous finding in rodents. See **Myeloid leukemia** for further information.

Epitheliotropic cutaneous lymphoma is a skin-associated neoplasm of T cells. This tumor in later stages may metastasize to other organs and lymph nodes. It resembles mycosis fungoides, the most common T-cell lymphoma in humans, but is rare in rats.

Erythroblastic leukemia, see the preferred term **Erythroid leukemia**.

Erythrocytosis, see the preferred term **Polycythemia**.

Erythrodysplasia, see the preferred term **Erythroid hematopoietic dysplasia**.

Erythroid hematopoietic dysplasia is a condition in which immature erythroid cells in the bone marrow are abnormal. The abnormality can involve the size, shape, number, or organization of the cells. Chemotherapy and vitamin deficiency causing megaloblastic anemia are two primary causes of erythroid dysplasia. It can also occur in tandem with refractory anemia or myelodysplastic syndrome.

Synonym(s): **Erythrodysplasia**.

Erythroid hyperplasia is an increase of erythroid cells in the hematopoietic tissues. It is generally a reaction to increased demand (e.g., hemorrhage or hemolysis). Subsequently, the myeloid:erythroid (M:E) ratio in the bone marrow is decreased as the relative numbers of the erythroid lineage cells are increased. The number of immature red blood cells, (i.e., normoblasts) may be increased in the blood as well as the number of polychromatic erythrocytes and reticulocytes. In severe cases, other organs, in addition to spleen and bone marrow, are involved. As it is a form of (extramedullary) hematopoiesis, the cells are often admixed with low numbers of cells from other lineages, such as megakaryocytes and myeloblasts.

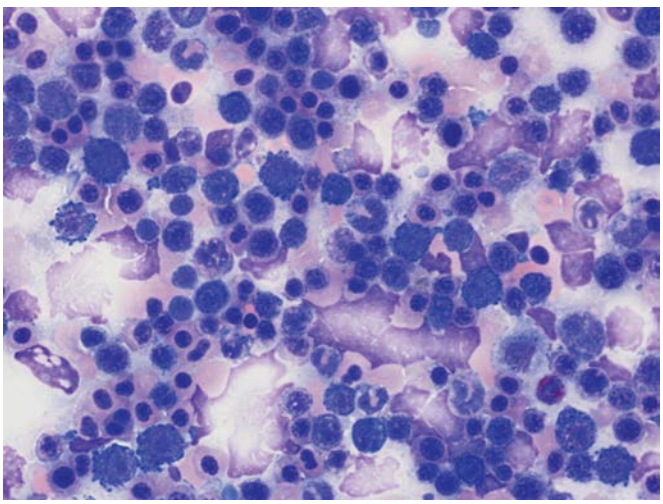


FIGURE 1 Erythroid hyperplasia, bone marrow, monkey (Giemsa).

Erythroid leukemia is a leukemic (bloodborne) neoplasm of the erythroid cell lineage in the bone marrow or spleen characterized by excessive proliferation of erythroblasts and normoblasts. Some tumors exhibit full differentiation with all stages, whereas others are less differentiated. Generally, they have an invasive growth pattern in spleen and liver, which may be markedly enlarged. Erythroid leukemia is a rare, spontaneous finding in rodents, but may be induced by radiation and trimethylbenz(a)anthrene.

Synonym(s): **Erythroleukemia**; **erythroblastic leukemia**.

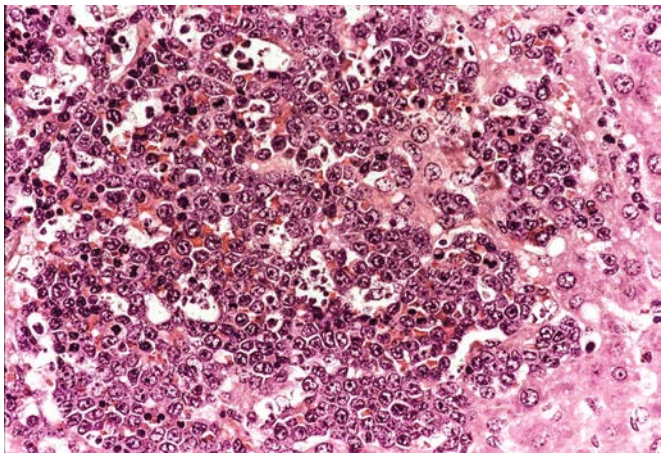


FIGURE 2 Erythroid leukemia, liver, mouse (H&E). (Image provided courtesy of Jerry Ward, Global Vet Pathology, Montgomery Village, MD.)

Erythroleukemia, see the preferred term **Erythroid leukemia**.

Follicular center cell lymphoma, see the preferred term **Pleomorphic lymphoma**.

Granulocytic hematopoietic dysplasia has asynchrony maturation or evidence of arrest at a stage of differentiation of the granulocytic lineages.

Granulocytic leukemia, see the preferred term **Myeloid leukemia**.

Granulocytic sarcoma, see the preferred term **Myeloid leukemia**.

Hematopoietic cells, hypercellularity is characterized by greater than normal numbers of hematopoietic cells. Normal cellularity of bone marrow is dependent on age and location (e.g., sternum vs femur), and may be assessed by estimating the ratio of cells to fat. The pathogenesis may involve increased production of blood cells in response to physiologic stimuli (e.g., increased white blood cells in response to inflammation or increased red cells associated with recent blood loss). Cells of one or more lineages may be affected, and should be identified, if possible. "Hypercellularity" is the preferred conventional term when a specific cell lineage is not identified. Optimally, evaluation of bone marrow should separately assess differentiation of each hematopoietic cell lineage, and specify which lineages are affected. "**Hematopoietic cells,**

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increased" with identification of affected cell type is the preferred term for enhanced histopathology as it is strictly descriptive, and does not imply a process.

Synonym(s): **Bone marrow hyperplasia**.

Hematopoietic cells, increased is characterized by greater than normal numbers of hematopoietic cells within the medullary cavity. This is the preferred term for enhanced histopathology terminology as it is strictly descriptive and does not imply process or pathogenesis. The affected cell lineage (i.e., erythroid, myeloid, granulocytic, monocytic, megakaryocytic, and lymphocytic, NOS [not otherwise specified]) should be identified, if possible.

Hematopoietic dysplasia is a hyperplasia of the bone marrow with an abnormal shift in maturation or abnormal cellular phenotype of one or more bone marrow cell lineages. The recognized subtypes are erythroid, myeloid (granulocytic, monocytic), megakaryocytic, lymphocytic, and NOS (not otherwise specified). Bone marrow dysplasia is an abnormal maturation of one or more lineages of resident marrow cells and is often considered a preneoplastic lesion.

Histiocytic sarcoma (HS) is a systemic tumor composed of a uniform population of round to oval and spindled cells with an abundant eosinophilic cytoplasm, showing a mixture of round, elongated, or folded nuclei. Multinucleated cells may often be present showing a Langerhans-type morphology. The mitotic rate is variable and minimal fibrosis and areas of necrosis surrounded by palisading cells may be present. HS is positive for lysosomal markers in both rats and mice. Distribution is not primarily lymphatic, in contrast to lymphomas. HS is often seen in subcutaneous tissues in the rat. In mice, HS may arise in the liver, omentum, mesentery, or uterus. Bone marrow may also be involved. Kidney has an increase of alpha 2u globulin-positive hyaline droplets in the proximal tubular epithelium.

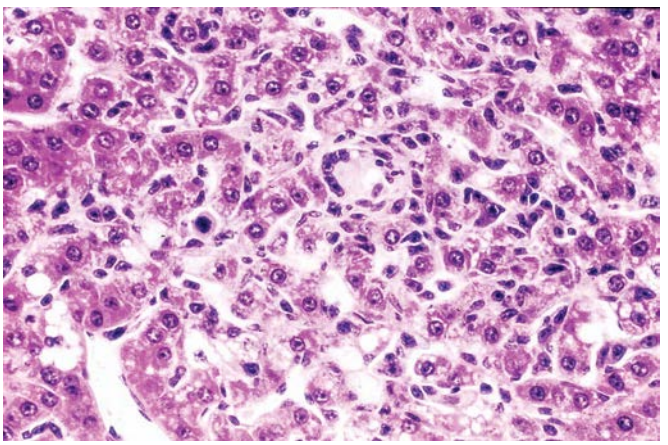


FIGURE 3 Histiocytic sarcoma, liver, mouse (H&E).

Immunoblastic lymphoma is a systemic tumor comprised of large blastic cells, where cells with plasmacytoid differentiation may also be present. These neoplastic cells have relatively abundant cytoplasm, large nuclei, and demonstrate a medium to high mitotic rate with an aggressive growth pattern. This type of lymphoma is rare in most rodent strains used in toxicologic pathology.

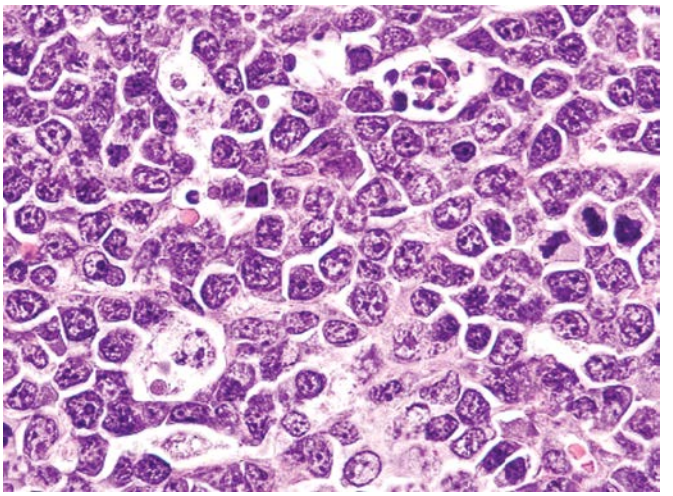


FIGURE 4 Lymphoma, immunoblastic, mouse (H&E). (Image provided courtesy of Jerry Ward, Global Vet Pathology, Montgomery Village, MD.)

Large granular lymphocyte (LGL) leukemia is one of the most common forms of lymphoma in the Fischer rat, with incidences reported to be >50%. It has also been occasionally observed in Sprague Dawley and Wister rat strains. LGL leukemia has been induced in genetically engineered mice but is not reported in the commonly used mouse strains such as the CD1, C57Bl, and NMRI. Its primary growth pattern, in contrast to other commonly observed lymphomas in rodents, and is leukemic (i.e., circulating in blood), the main organs involved being the spleen, liver, and bone marrow. White blood cell counts may be increased, but this is quite variable. Early, and possibly primary, lesions are found in the spleen. On Giemsa-stained blood smears, the cells resemble large granular lymphocytes with red cytoplasmic granules, and round to kidney-shaped nuclei. Cells react positively with the OX-8 antibody. Different stages are recognized, with stage 1 being the earliest lesion in which the spleen and liver are normal size, or are only slightly enlarged containing few OX-8-positive cells. In stage 2, the liver and spleen are moderately enlarged with numerous LGL cells in the red pulp and sinuses; however, the normal architecture is maintained. Stage 3 is the advanced stage, with generalized involvement, loss of architecture in the spleen and liver due to marked infiltrations, and the presence of aggregates of LGL cells. Infiltrates are also readily seen in other organs such as the lungs, kidneys, brain, and adrenal glands.

Synonym(s): **Mononuclear cell leukemia**; **LGL-NK lymphoma**.

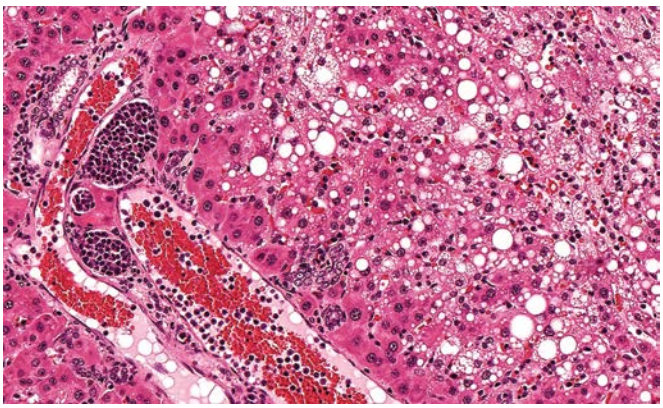


FIGURE 5 Large granular cell lymphoma (LGL), liver (H&E).

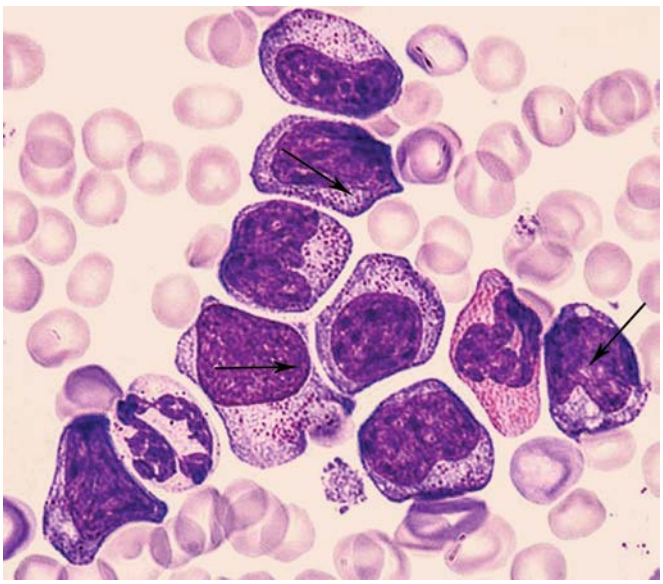


FIGURE 6 Large granular cell lymphoma (LGL), May-Grünwald-Giemsa (MGG)-stained blood film showing numerous large granular lymphocytes (arrow).

Leukemia, NOS (not otherwise specified) is the general term for a white blood cell neoplasm which leads to a high white blood cell count in the peripheral blood. In toxicological pathology, one generally is able to differentiate the cell lineage involved as lymphoid, myeloid, or erythroid in origin. Only in rare instances (e.g., due to advanced autolysis) is it impossible to further classify. In the latter instance, the diagnostic term leukemia, NOS may be warranted.

LGL-NK lymphoma, see the preferred term **Large granular lymphocyte (LGL) leukemia**.

Lymphoblastic lymphoma is a systemic neoplasm composed of lymphocytes characterized by medium to large-sized cells with a high nuclear-to-cytoplasmic ratio. The nuclei are blastic, and round, oval, irregular, or convoluted, often with prominent nucleoli and mitotic figures. Apoptosis and tingible body macrophages are frequently seen. The tumor has an aggressive growth pattern. There may be a leukemic phase with brain infiltration composed of lymphocytes of T- or B-cell origin. Lymphocytes of T-cell origin are more frequently observed in young animals, while lymphocytes of B-cell origin are more common in aged rodents.

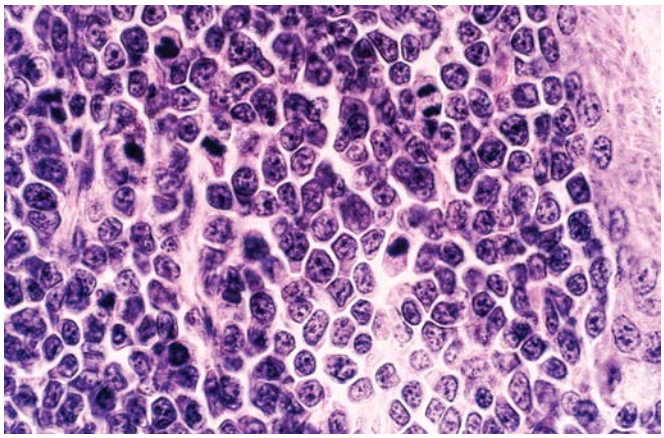


FIGURE 7 Lymphoma, lymphoblastic, small intestine, mouse (H&E).

Lymphocytic lymphoma is characterized by tumor cells that are well differentiated, small- to medium-sized lymphocytes of T- or B-cell origin, and morphologically similar to the normal circulating lymphocytes. The growth pattern is non-cohesive. Cells have scant cytoplasm, dense chromatin, and mitotic activity is generally low.

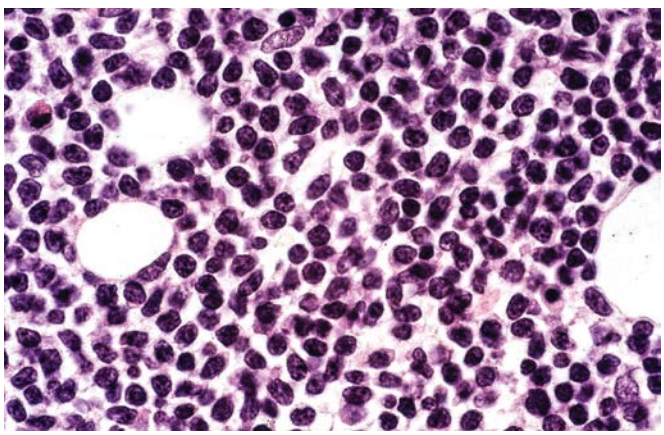


FIGURE 8 Lymphoma, lymphocytic, mouse (H&E).

Lymphoma is a malignant systemic lymphoid tumor, which is also found in bone marrow. When present in bone marrow, these neoplasms often become leukemic (i.e., circulating tumor cells in the blood). In toxicological pathology, systemic tumors are often categorized under "hematopoietic system" or as "organ," and the involved site listed as invaded or present. This designation prevents a single systemic tumor to be counted as present at multiple sites, thereby artificially increasing the tumor count in the study. Often, the lymphomas presented in rodent carcinogenicity studies are not further subtyped, which is commonly the case in human diagnostic pathology followed by therapy. This classification in humans relies heavily on the presence of

certain biomarkers for immunophenotyping, and degree of differentiation, as well as genetic and molecular characteristics. These are linked to treatment schedules and clinical outcome parameters that are not relevant in rodent carcinogenicity studies. A more practical, simplified World Health Organization (WHO) classification was developed based on morphology in hematoxylin and eosin (H&E)-stained tissues, and has fewer subtypes. In risk assessment, lymphomas are often combined in overall incidence in the assessment of treatment-related effects. Many pathologists also do not further subtype lymphomas in the histopathologic evaluation of their studies. The subtypes that are currently recognized and their morphological characteristics are listed below. In the bone marrow, tumor infiltration can be diffuse or nodular. As with all systemic tumors, multiple sites are often involved (e.g., lymph nodes, spleen, kidneys, and liver).

Synonym(s): **Lymphosarcoma**.

Lymphosarcoma, see the preferred term **Lymphoma**.

Marginal zone lymphoma is a systemic neoplasm of lymphocytes initially found in the spleen that may spread to lymph nodes and liver. The white pulp has widened marginal areas often coalescing follicles and diffuse infiltration of red pulp.

Mast cell leukemia is a malignant mast cell tumor in bone marrow characterized by atypical mast cells (a type of granulocyte derived from the myeloid stem cell lineage that is part of the immune system that contains many granules rich in histamine and heparin) in the peripheral blood. Mast cell accumulations/nodules may be present in hematopoietic and/or lymphoid tissues. Differentiation may vary, and histochemistry may be needed (e.g., CD117, tryptase, and mcp-1) to identify the neoplasm, which may be hampered in decalcified tissue.

Mast cell sarcoma is comprised of atypical, often pleomorphic mast cells that may be hypogranular. Mast cells are a type of granulocyte derived from the myeloid stem cell lineage that is part of the immune system and contains many granules rich in histamine and heparin. Due to hypogranularity, it is often difficult to distinguish from other sarcomas without the use of special stains.

Mast cell tumor is a neoplasm composed of mast cells, a type of granulocyte derived from the myeloid stem cell lineage that is part of the immune system and contains many granules rich in histamine and heparin. Nuclei are generally round but can be bilobed or multilobed. These tumors are further divided into mastocytomas for single-site lesions, and malignant mast cell tumor for multiple-site lesions.

Mastocytoma, benign is a single nodule comprised of well-differentiated mast cells, a type of granulocyte derived from the myeloid stem cell lineage that is part of the immune system that contains many granules rich in histamine and heparin. It is a benign neoplasm in the absence of pleomorphism, and without systemic involvement.

Mastocytoma, malignant is a term used for mast cell tumors in which multiple sites are involved, and a more infiltrative growth pattern exists. Mast cells are a type of granulocyte derived from the myeloid stem cell lineage that is part of the immune system and contains many granules rich in histamine and heparin. The tumor may show an infiltrative growth pattern in the absence of bone marrow involvement.

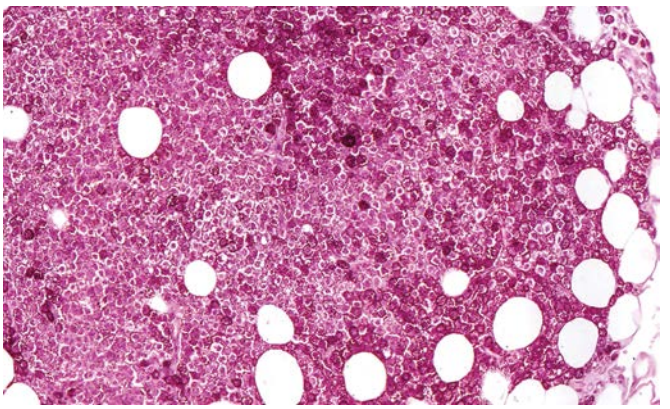


FIGURE 9 Mast cell tumor, mesentery, mouse.

Mastocytosis, see the preferred term **Mastocytoma, malignant**.

Megakaryocytic hematopoietic dysplasia has asynchronous maturation or evidence of arrest of the megakaryocytic lineages. It is observed in myelodysplastic syndrome, which affects mostly the megakaryocytic lineage, and is mainly characterized by thrombocytopenia. Giant platelets with abnormal granulations (hyper- or hypogranulation) are often observed in blood smears. Bone marrow appears normal to hypercellular, and megakaryocytes exhibit atypical features. Micromegakaryocytes, large mononuclear megakaryotic forms, or megakaryocytes with multiple small nuclei or abnormal granulations are observed. The other lineages, mostly erythroid, are also affected by dysplastic changes.

Synonym(s): **Thrombodysplasia**.

Megakaryocytic leukemia is a malignant tumor of the megakaryocytic lineage, often manifesting a preponderance of blast cells. These cells represent megakaryocytes with varying degrees of differentiation. Large aplastic platelets are present in the blood, and a pancytopenia may be present. Megakaryocytic leukemia has not been reported as a spontaneous lesion in rodents; however, this neoplasm may be induced by MuLV recombinant virus in mice.

Synonym(s): **Megakaryocytic myelosis**.

Megakaryocytic myelosis, see the preferred term **Megakaryocytic leukemia**.

Mononuclear cell leukemia, see the preferred term **Large granular lymphocyte (LGL) leukemia**.

Multiple myeloma, see the preferred term **Plasmacytic lymphoma**.

Myeloblastic leukemia, see the preferred term **Myeloid leukemia**.

Myelodysplastic syndrome (MDS) is a hematologic bone marrow disorder characterized by peripheral cytopenias, and dysplastic changes in the bone marrow that can be primary due to an acquired clonal mutation of a tumor suppressor gene or oncogene, or secondarily associated with drug, radiation treatment, or toxin exposure. The most distinguishing features of MDS include increased numbers of myeloblasts or rubriblasts, increased numbers of dysplastic cells ($\geq$10%), and megaloblastic changes in erythroid precursors within the bone marrow. MDS is present when the percentage of nonlymphoid blast cells is $\leq$20% of all nucleated cells based on the World Health Organization classification. MDS has been associated with drugs that interfere with DNA synthesis (e.g., alkylating agents, folate antagonists, and antimetabolites), and antibiotics (e.g., cephalosporins and chloramphenicol). MDS has been categorized into three categories based on the type of dysplastic features, and percentage of myeloblasts. MDS with refractory cytopenia (MDS-RC) is characterized by peripheral cytopenia(s) (often anemia), dysplastic changes most often observed in the erythroid lineage, and fewer than 5% myeloblasts. MDS with excess blasts (MDS-EB) is characterized by increased myeloblasts comprising 5–19% of the total nucleated cells. MDS with sideroblastic differentiation is characterized by anemia and sideroblasts with fewer than 5% myeloblasts in the bone marrow.

Myelofibrosis, see the preferred term **Bone marrow fibrosis**.

Myeloid is a term describing cells of bone marrow origin and/or used to describe hematopoietic tumors which are nonlymphoid in origin. The term myeloid leukemia is generally used for tumors arising from the granulocytic white blood cell series. See **Myeloid leukemia** for further information.

Myeloid hyperplasia represents an increase in the production of myeloid cells beyond that which is considered homeostatic, and is typically associated with infection or inflammation. The myeloid:erythroid (M:E) ratio is generally increased, with a predominance of late-stage myeloid cells (metamyelocytes, band, and segmented granulocytes). Myeloid hyperplasia can be so extensive that it resembles myeloid leukemia; however, the morphologic appearance of the cells is usually unaffected. Depending on the cause and the nature of the inflammatory reaction (e.g., acute or chronic), there may be a correlative inflammatory peripheral leukogram (e.g., neutrophilia).

Myeloid leukemia is a neoplasm of the myeloid cell lineage in the bone marrow or spleen. Differentiation can vary from immature and poorly differentiated blast cells to mature cells showing varying proportions of immature and segmented forms. Bone marrow and spleen are primarily involved, but other organs such as liver can also be affected. The spleen and liver are often enlarged and exhibit a dull red color with a greenish discoloration at necropsy; hence the older term for this tumor, "chloroleukemia." A very high white blood cell (WBC) count is occasionally present in tumor-bearing animals. In tissue sections, there are large numbers of myelocytes (i.e., ring form nucleated cells), and an invasive growth pattern. Myeloid leukemic cells are positive for lysosomal markers and granulocytic antigens. Generally, these cells are derived from neutrophilic lineage/differentiation. No leukemic cases/phases of eosinophilic or basophilic lineage tumors have been reported in rodents.

Synonym(s): **Myeloid leukemia**; **myeloblastic leukemia**; **chloroleukemia**; **granulocytic sarcoma**.

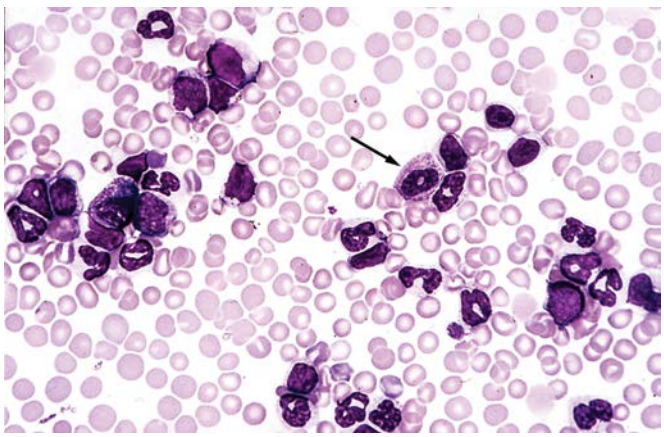


FIGURE 10 Myeloid leukemia, May-Grünwald-Giemsa (MGG)-stained blood smear, mouse.

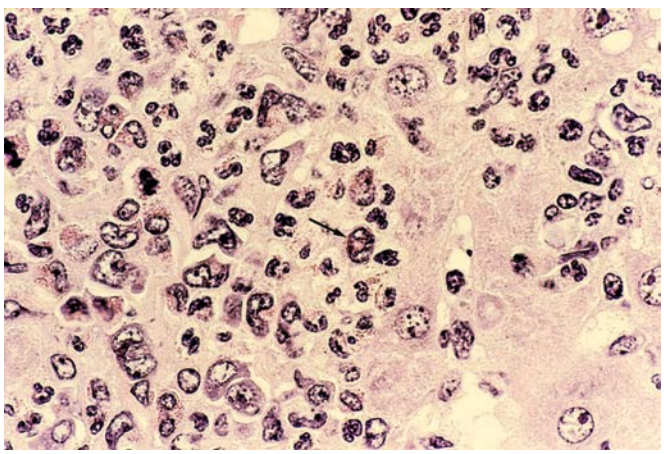


FIGURE 11 Myeloid leukemia, liver, mouse (H&E).

Myelostromal proliferation has the prefix *myelo*, meaning bone marrow or spinal cord. Myelostromal proliferation therefore means bone marrow stromal proliferation. See the preferred term **Bone marrow fibrosis**.

Plasmacytic lymphoma is a systemic tumor composed of mature or immature plasma cells with an obvious plasmacytoid differentiation. The cells have round nuclei, and abundant, often pyroniphillic cytoplasm. Mitotic figures are scant. In contrast to humans, the light chain determination is less useful in mice, since the majority of cells are kappa positive.

Synonym(s): **Multiple myeloma**; **plasmacytoma**.

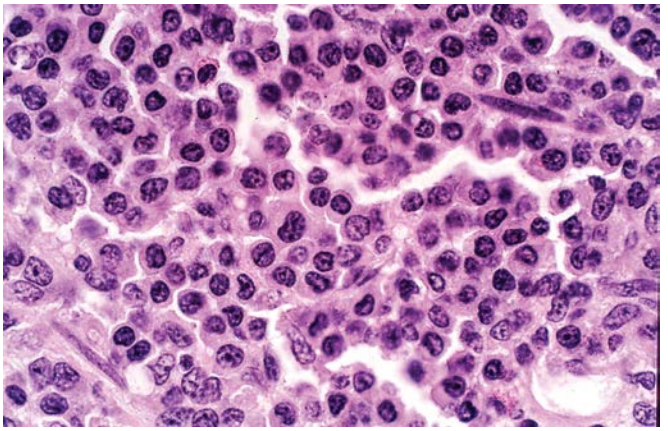


FIGURE 12 Lymphoma, plasmacytic, mouse (H&E).

Plasmacytoma, see the preferred term **Plasmacytic lymphoma**.

Pleomorphic lymphoma is a systemic tumor composed of lymphocytes showing a varying degree of pleomorphism, often composed of a mixture of small- or medium-sized to large cells, with proportions varying from site to site. Multinucleated cells are occasionally present. The cell morphology may mimic follicular cells with cleaved nuclei and a cohesive growth pattern, but in actuality, cells are of T- or B-cell origin, the latter being more frequent. If of B-cell origin, a diagnosis of follicular cell lymphoma is applicable.

Synonym(s): **Follicular center cell lymphoma**.

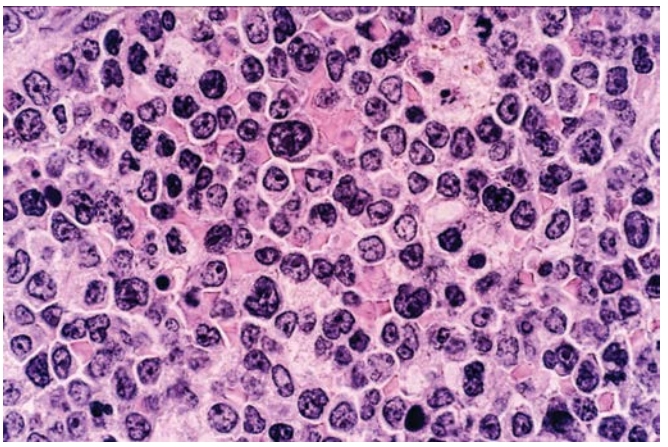


FIGURE 13 Lymphoma, pleomorphic, mouse (H&E).

Polycythemia, sometimes referred to as erythrocytosis, is characterized by an increase in red blood cell mass as evidenced by red blood cell counts, hemoglobin, and/or hematocrit above the reference range for the species. Polycythemia can be relative due to hemoconcentration. In hemoconcentration, the red blood cell mass increase is due to a loss of plasma volume rather than a true increase in red blood cell production. Polycythemia can be seen in instances of splenic contraction secondary to either exercise or an epinephrine response. In this case, the increase in red blood cell mass is due to the release of red blood cells stored in the spleen and is not associated with increased red blood cell production. Other instances of polycythemia result from increased red blood cell production in the bone marrow and are considered either primary, if due to a neoplastic process (i.e., erythroid neoplasia or polycythemia vera), or secondary if due to an increase in erythropoietin concentration leading to increased red blood cell production. Decreased blood oxygen concentration is a trigger for increased erythropoietin production and increased red blood cell production. Humans and animals living at high altitude, and athletes tend to have a higher red blood cell mass owing to an increased need for oxygen due to lower ambient atmospheric oxygen concentrations, or exercise, respectively. Pathological conditions affecting the lung or heart will also lead to increased erythropoietin production due to decreased oxygen concentrations. Increased erythropoietin concentrations without the physiological trigger of decreased blood concentration is observed mostly in tandem with renal or liver neoplasia; the neoplasms themselves constitutively produce erythropoietin which leads to increased red blood cell production. Endocrine disorders that stimulate erythropoiesis may also result in polycythemia.

Synonym(s): **Erythrocytosis**.

Polycythemia vera is a myeloproliferative disorder associated with increased red blood cell mass, thrombocytosis, and increased white blood cell counts. In contrast to polycythemia, polycythemia vera is not associated with evidence of dehydration, and levels of erythropoietin are low normal to low. It has been described in most animal species.

Thrombodysplasia, see the preferred term **Megakaryocytic dysplasia**.

LIVER, GALLBLADDER, AND EXOCRINE PANCREAS

Area of basophilic cellular alteration, see the preferred term **Basophilic focus of cellular alteration**.

Area of clear cellular alteration, see the preferred term **Clear cell focus of cellular alteration**.

Area of eosinophilic cellular alteration, see the preferred term **Eosinophilic focus of cellular alteration**.

Basophilic focus, see the preferred term **Basophilic focus of cellular alteration**.

Basophilic focus of altered hepatocytes, see the preferred term **Basophilic focus of cellular alteration**.

Basophilic focus of cellular alteration is a focal accumulation of hepatocytes with increased cytoplasmic basophilia compared to the surrounding hepatocytes in the liver. Hepatocytes in a basophilic focus merge with the adjacent hepatocyte cords, with little or no compression of the adjacent

parenchyma. The basophilic focus is generally considered a proliferative lesion. It is observed as a spontaneous finding most often in rats and less frequently in mice in animals older than 1 year of age, and its incidence and numerical frequency may be increased following treatment with xenobiotics, especially those that are liver carcinogens. In rats, the pattern of cytoplasmic basophilic staining in a focus may be diffuse or segmented into bands, the latter described as having a "tigroid" pattern.

Differential diagnoses: **Hepatocellular hyperplasia, regenerative**; **Hepatocellular hyperplasia, non-regenerative**; **Hepatocellular adenoma**; **Hepatocellular carcinoma**.

Synonym(s): **Area of basophilic cellular alteration**; **basophilic focus of altered hepatocytes**; **basophilic preneoplastic focus**.

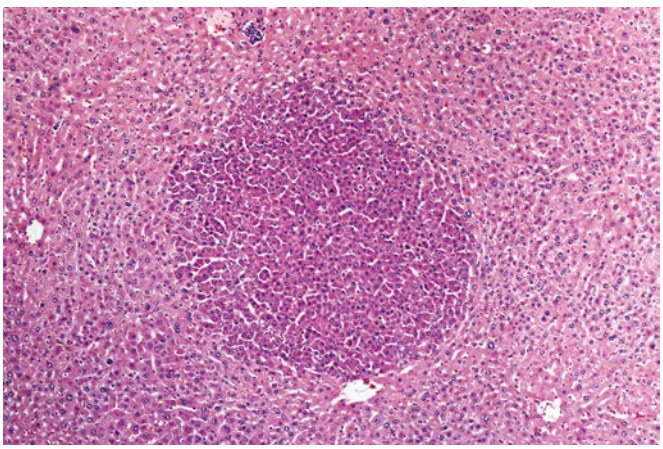


FIGURE 1 Basophilic focus of cellular alteration, rat liver, H&E. (Reproduced with permission of Elsevier from Cattley, R. and Cullen, J. 2013. In: Haschek, W.M., Rousseux, C.G., Wallig, M.A., Bolon, B., Ochoa, R. (eds.) *Handbook of Toxicologic Pathology*, 3rd ed. San Diego, CA: Academic Press, Elsevier, pp. 1509–1566.)

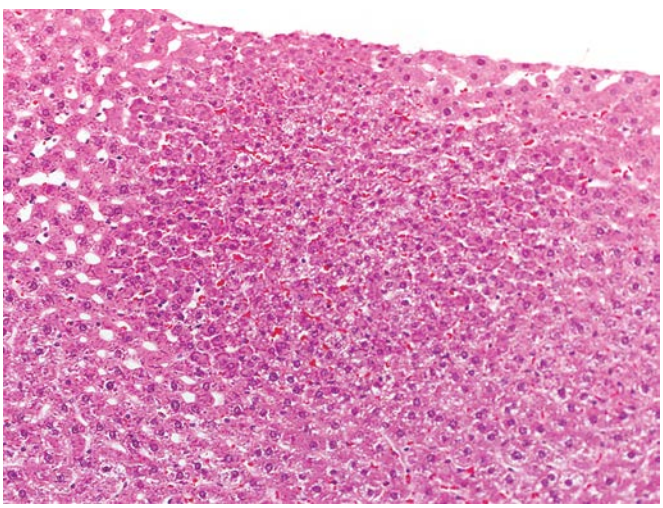


FIGURE 2 Basophilic focus of cellular alteration with "tigroid pattern," rat liver, H&E. (Figure courtesy of R. Cattley, Auburn University.)

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Basophilic preneoplastic focus, see the preferred term **Basophilic focus of cellular alteration**.

Benign cholangioma, see the preferred term **Cholangioma**.

Benign cystic cholangioma, see the preferred term **Cholangioma, cystic**.

Benign hemangioendothelioma, see the preferred term **Hepatic hemangioma**.

Benign hepatocellular tumor, see the preferred term **Hepatocellular adenoma**.

Benign hepatoma, see the preferred term **Hepatocellular adenoma**.

Bile duct adenocarcinoma, see the preferred term **Cholangiocarcinoma**.

Bile duct adenoma, see the preferred term **Cholangioma**.

Bile duct adenomatosis, see the preferred term **Cholangiofibrosis**.

Bile duct carcinoma, see the preferred term **Cholangiocarcinoma**.

Bile duct hyperplasia is a lesion characterized by increased numbers of bile ducts within variable numbers of portal areas in the liver. The bile duct epithelium is well differentiated but may appear atrophic and sometimes even manifest necrosis. Cells may also contain hyalinized (clear or translucent-like) cytoplasm. Cystic dilation of hyperplastic ducts may occur, as well as periductal fibrosis. Bile duct hyperplasia may occur spontaneously as an aging lesion but may also occur following xenobiotic administration. An association with xenobiotic-induced oval cell hyperplasia has been observed.

Differential diagnoses: **Bile duct adenoma**; **Biliary adenoma**; Bile duct cyst; **Bile duct hyperplasia**; **Cholangiofibrosis**; **Cholangiocellular adenoma**; **Cholangioma**; **Cholangiocarcinoma**.

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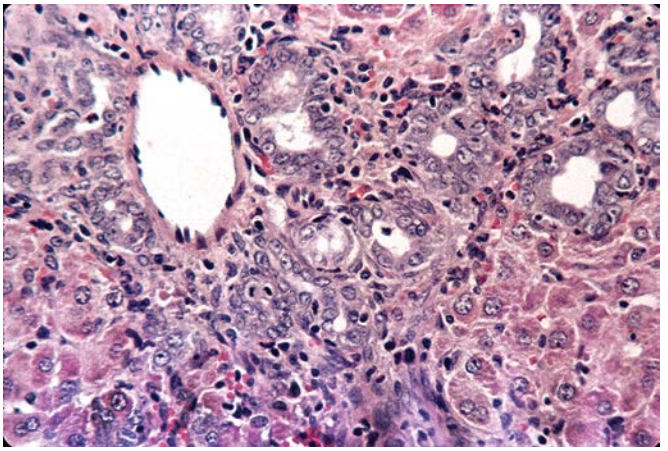


FIGURE 3 Bile duct hyperplasia, rat liver, H&E. (Reproduced with permission of CRC Press from Cattley, R. et al. 2013. In: Sahota, P., Popp, J., Hardisty, J., Gopinath, C. (eds.) *Toxicologic Pathology: Nonclinical Safety Assessment*. Boca Raton, FL: CRC Press, Taylor & Francis Group, pp. 313–366.)

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Bile ductule cell hyperplasia, see the preferred term **Oval cell hyperplasia**.

Biliary adenoma, see the preferred term **Cholangioma**.

Cholangiocarcinoma is a malignant neoplasm that originates from bile duct epithelial cells. These neoplasms are characterized by the appearance of a liver mass that histologically resembles proliferation of glands lined by atypical biliary epithelium that may form solid and papillary structures. Nuclear pleomorphism may be prominent. The presence of fibrosis in these neoplasms is variable. A particular subtype of cholangiocarcinoma is the intestinal type, in which the neoplastic cells may differentiate to resemble intestinal epithelium, with mucus production. For cholangiocarcinomas, there is usually evidence of local invasion, and metastasis may occur either within the liver or to other organs. In laboratory animals, cholangiocarcinoma rarely occurs spontaneously, but has been reported following administration with chemical agents (e.g., thioacetamide, furan).

Differential diagnoses: **Cholangiofibrosis**; **Cholangioma**; **Hepatocellular carcinoma**.

Synonym(s): **Bile duct adenocarcinoma**; **cholangiocellular adenocarcinoma**; **bile duct carcinoma**; **cholangiocellular carcinoma**; **malignant cholangioma**.

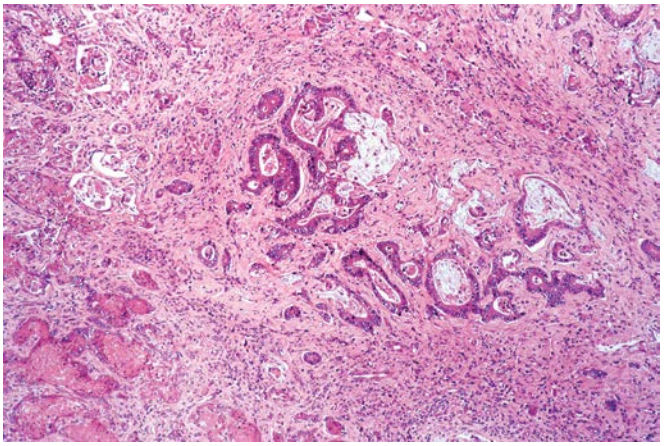


FIGURE 4 Cholangiocarcinoma, rat liver, H&E. (Reproduced with permission of Elsevier from Cattley, R. and Cullen, J. 2013. In: Haschek, W.M., Rousseux, C.G., Wallig, M.A., Bolon, B., Ochoa, R. (eds.) *Handbook of Toxicologic Pathology*, 3rd ed. San Diego, CA: Academic Press, Elsevier, pp. 1509–1566.)

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http://cancerres.aacrjournals.org/content/53/2/254.full-text.pdf

Cholangiocellular adenocarcinoma, see the preferred term **Cholangiocarcinoma**.

Cholangiocellular adenoma, see the preferred term **Cholangioma**.

Cholangiocellular carcinoma, see the preferred term **Cholangiocarcinoma**.

Cholangiofibrosis is a lesion characterized by the accumulation of variably dilated glands that contain mucus and that are irregularly separated by the accumulation of connective tissue and inflammatory cells. The glands typically mimic intestinal epithelium, and will replace liver tissue without forming a mass. In extreme instances, the entire liver lobe may be affected, though it is often not increased in size and may even manifest a size decrease. The lesion is observed in rats exclusively and occurs following treatment with hepatotoxic chemicals and not spontaneously. Some reports suggest that cholangiofibrosis may originate in livers following oval cell hyperplasia. Some have suggested that cholangiofibrosis may progress to cholangiocarcinoma, but the evidence for this has not been generally accepted.

Differential diagnoses: **Cholangiocarcinoma**; **Bile duct hyperplasia**.

Synonym(s): **Hepatic bile duct adenomatosis**; **hepatic intestinal cell metaplasia**; **hepatic adenofibrosis**.

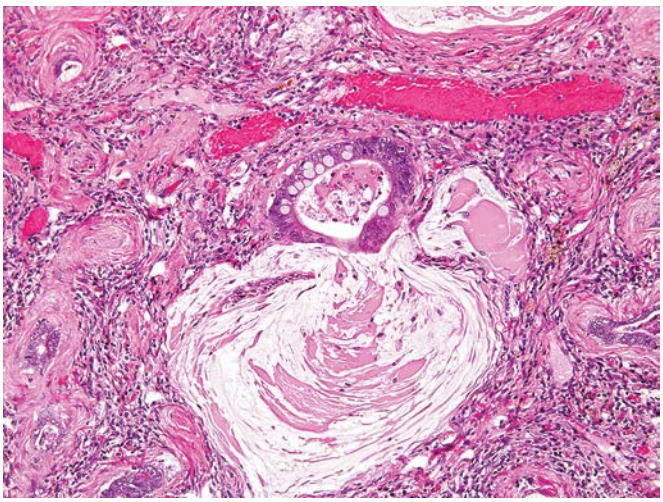


FIGURE 5 Cholangiofibrosis, rat liver, H&E. (Reproduced with permission of the Society of Toxicologic Pathology from Thoolen, B. et al. 2010. *Toxicol Pathol* 38(7 Suppl):5S–81S.)

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Cholangioma is a benign neoplasm that originates from bile duct epithelial cells. These neoplasms are characterized by the appearance of a liver mass that histologically resembles a proliferation of glands lined by biliary epithelium. In some lesions the glands remain small, but in others they may become cystic. The neoplasm will compress but not invade the adjacent liver tissue. This neoplasm is rare in laboratory animals, whether as a spontaneous finding or following administration of chemical agents.

Differential diagnoses: Bile duct cyst; **Bile duct hyperplasia**; **Cholangiofibrosis**; **Cholangiocarcinoma**.

Synonym(s): **Bile duct adenoma**; **biliary adenoma**; **cholangiocellular adenoma**; **benign cholangioma**.

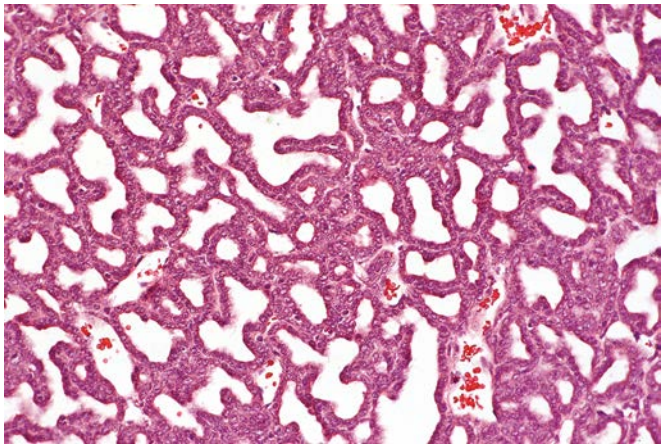


FIGURE 6 Cholangioma, rat liver, H&E. (Reproduced with permission of CRC Press from Cattley, R. et al. 2013. In: Sahota, P., Popp, J., Hardisty, J., Gopinath, C. (eds.) *Toxicologic Pathology: Nonclinical Safety Assessment*. Boca Raton, FL: CRC Press, Taylor & Francis Group, pp. 313–366.)

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Cholangioma, cystic is a benign neoplasm that originates from bile duct epithelial cells. These neoplasms are characterized by the appearance of a liver mass that histologically resembles cystic glands lined by biliary epithelium. The neoplasm will compress but not invade the adjacent liver tissue but may sometimes contain entrapped hepatocytes between the neoplastic glands. Cystic cholangioma rarely occurs in laboratory animals either spontaneously or following administration of chemical agents.

Differential diagnoses: Bile duct cyst; **Bile duct hyperplasia**; **Cholangiofibrosis**; **Cholangiocarcinoma**.

Synonym(s): **Cystic bile duct adenoma**; **cystic biliary adenoma**; **cystic cholangiocellular adenoma**; **benign cystic cholangioma**.

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Clear cell focus of altered hepatocytes, see the preferred term **Clear cell focus of cellular alteration**.

Clear cell focus of cellular alteration is a focal accumulation of hepatocytes with cytoplasm composed of clear spaces.

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These hepatocytes merge with the adjacent hepatocyte cords with little or no compression of the adjacent parenchyma. In some foci with basophilic or eosinophilic staining, clear cells may be observed, but the designation of such lesions is conventionally termed as basophilic or eosinophilic foci. The clear cell focus is generally considered a proliferative lesion. It is observed as a spontaneous finding most often in rats and less frequently in mice in animals older than 1 year of age, and its incidence and numerical frequency may be increased following treatment with xenobiotics, especially those that are liver carcinogens. In rats treated with alkylating agents such as nitrosamines, clear cell foci may be the predominant type of foci numerically.

Differential diagnoses: **Hepatocellular hyperplasia, regenerative**; **Hepatocellular hyperplasia, non-regenerative**; **Hepatocellular adenoma**; **Hepatocellular carcinoma**.

Synonym(s): **Area of clear cellular alteration**; **clear cell focus of altered hepatocytes**; **clear cell preneoplastic focus**.

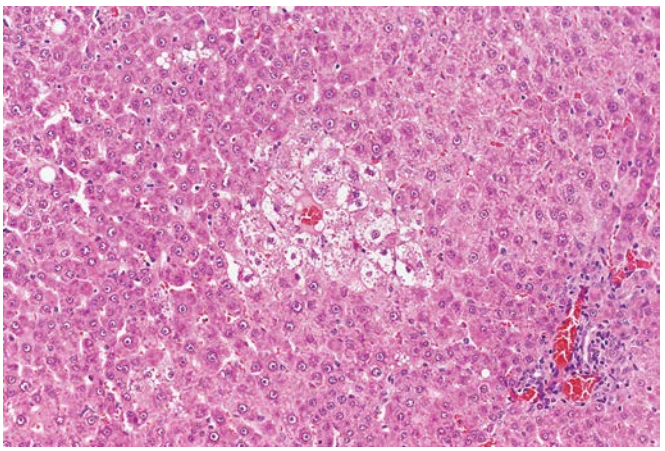


FIGURE 7 Clear cell focus of cellular alteration, rat liver, H&E. (Reproduced with permission of Elsevier from Cattley, R. and Cullen, J. 2013. In: Haschek, W.M., Rousseux, C.G., Wallig, M.A., Bolon, B., Ochoa, R. (eds.) *Handbook of Toxicologic Pathology*, 3rd ed. San Diego, CA: Academic Press, Elsevier, pp. 1509–1566.)

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http://www.journal-of-hepatology.eu/article/S0168-8278(13)00057-3/fulltext

Clear cell preneoplastic focus, see the preferred term **Clear cell focus of cellular alteration**.

Cystic bile duct adenoma, see the preferred term **Cholangioma, cystic**.

Cystic biliary adenoma, see the preferred term **Cholangioma, cystic**.

Cystic cholangiocellular adenoma, see the preferred term **Cholangioma, cystic**.

Cystic hyperplasia, bile duct, see the preferred term **Bile duct hyperplasia**.

Ductal cell tumor (benign or malignant) is considered synonymous with **cholangioma** (benign) or **cholangiocarcinoma** (malignant). See **Cholangioma** and **Cholangiocarcinoma** for further information.

Embryonal hepatoma, see the preferred term **Hepatoblastoma**.

Embryonal tumor of liver, see the preferred term **Hepatoblastoma**.

Eosinophilic focus, see the preferred term **Eosinophilic focus of cellular alteration**.

Eosinophilic focus of altered hepatocytes, see the preferred term **Eosinophilic focus of cellular alteration**.

Eosinophilic focus of cellular alteration is a focal accumulation of hepatocytes with increased cytoplasmic eosinophilia compared to the surrounding hepatocytes in the liver. Hepatocytes in an eosinophilic focus merge with the adjacent hepatocyte cords, with little or no compression of the adjacent parenchyma. The eosinophilic focus is generally considered a proliferative lesion. It is observed as a spontaneous finding most often in rats and less frequently in mice in animals older than 1 year of age, and its incidence and numerical frequency may be increased following treatment with xenobiotics. In rats and mice treated with inducers of cytochrome P450 enzyme inducers that are activators of nuclear receptors CAR and PXR, eosinophilic foci may be the predominant type of focus numerically.

Differential diagnoses: **Hepatocellular hyperplasia, regenerative**; **Hepatocellular hyperplasia, non-regenerative**; **Hepatocellular adenoma**; **Hepatocellular carcinoma**.

Synonym(s): **Area of eosinophilic cellular alteration**; **eosinophilic focus of altered hepatocytes**; **eosinophilic preneoplastic focus**.

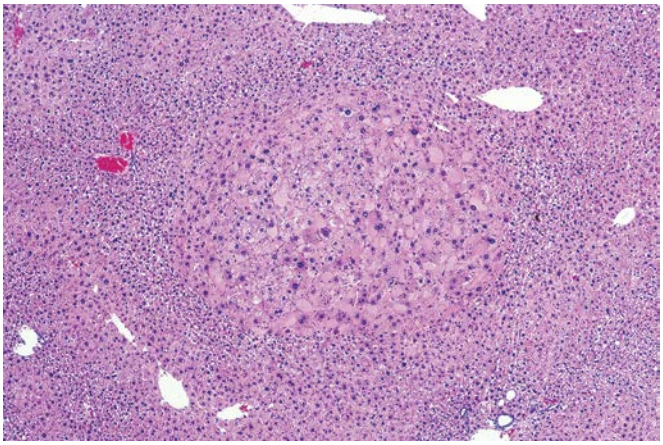


FIGURE 8 Eosinophilic focus of cellular alteration, rat liver, H&E. (Reproduced with permission of CRC Press from Cattley, R. et al. 2013. In: Sahota, P., Popp, J., Hardisty, J., Gopinath, C. (eds.) *Toxicologic Pathology: Nonclinical Safety Assessment*. Boca Raton, FL: CRC Press, Taylor & Francis Group, pp. 313–366.)

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Cattley, R., Popp, J., and Vonderfect, S. 2013. Liver, gallbladder, and pancreas. In: Sahota, P., Popp, J., Hardisty, J., Gopinath, C. (eds.) *Toxicologic Pathology: Nonclinical Safety Assessment*. Boca Raton, FL: CRC Press, Taylor & Francis Group, pp. 313–366.

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Eosinophilic preneoplastic focus, see the preferred term **Eosinophilic focus of cellular alteration**.

Focal eosinophilic cellular change, see the preferred term **Eosinophilic focus of cellular alteration**.

Focal hepatocellular hyperplasia, see the preferred term **Hepatocellular hyperplasia, non-regenerative**.

Gallbladder adenocarcinoma is a rare spontaneous malignant neoplasm arising from epithelium of the gallbladder in aging laboratory animals. Neoplastic cells show disordered growth with cellular atypia and mitotic figures, often invading the wall of the gallbladder or of the adjacent tissue. Gallbladder adenocarcinomas are reported in 2- to 3-month-old homozygous BK5.erbB2 mice overexpressing the wild-type rat erbB2 gene in basal epithelial cells of the gallbladder. A low incidence of treatment-related gallbladder adenocarcinoma has been reported in mice following long term administration of *N-N*-propyl-*N*-formylhydrazine or 2-acetamidofluorene.

Differential diagnoses: **Gallbladder hyperplasia**; **Gallbladder adenoma**; **Gallbladder glandular metaplasia**.

Reference

Thoolen, B. et al. 2010. Proliferative and nonproliferative lesions of the rat and mouse hepatobiliary system. *Toxicol Pathol* 38(7 Suppl):5S–81S.

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http://journals.sagepub.com/doi/abs/10.1177/0192623310386499 ?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_ dat=cr_pub%3dpubmed

Gallbladder adenoma is a rare spontaneous, often solitary mass of well-differentiated gallbladder epithelial cells lining a papillary, fibrovascular stroma. The pattern of growth is disordered and papillary- or cauliflower-like with cellular atypia and mitotic figures. Gall bladder adenomas have been reported in LXRβ−/− female mice, 12-month-old Pten+/− mice, as well as following long-term administration of *N*-methyl-*N*-formylhydrazine, *N-N*-propyl-*N*-formylhydrazine, 2-acetamidofluorene or PPAR gamma agonist, and PPAR alpha/gamma agonists, all in mice.

Differential diagnoses: Gallbladder focal hyperplasia; **Gallbladder adenocarcinoma**; **Gallbladder glandular metaplasia**.

Synonym(s): **Gallbladder papillary adenoma**.

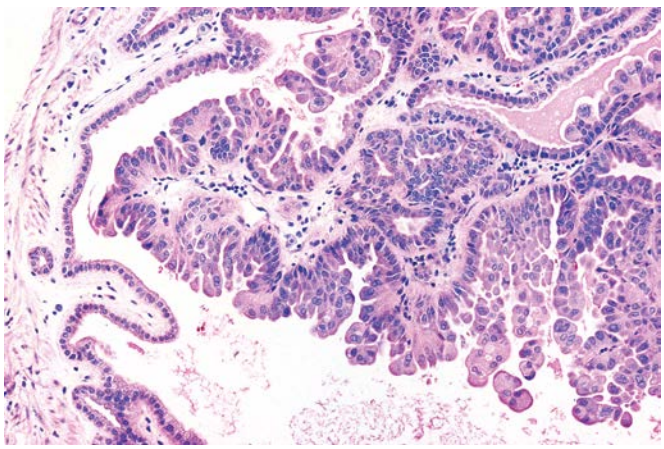


FIGURE 9 Gallbladder adenoma, mouse liver, H&E. (Reproduced with permission of CRC Press from Cattley, R. et al. 2013. In: Sahota, P., Popp, J., Hardisty, J., Gopinath, C. (eds.) *Toxicologic Pathology: Nonclinical Safety Assessment*. Boca Raton, FL: CRC Press, Taylor & Francis Group, pp. 313–366.)

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Gallbladder hyperplasia is often a small lesion with a few single-layered, well-differentiated hyperplastic cells lining papillary folds, and small papillary projections that occur due to irritation of the mucosa. Cystic mucinous gallbladder hyperplasia may be caused by long-term administration of oral contraceptive steroids and synthetic progestogens in dogs.

Differential diagnoses: **Gallbladder adenoma**; **Gallbladder adenocarcinoma**; **Gallbladder glandular metaplasia**.

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Gallbladder papillary adenoma, see the preferred term **Gallbladder adenoma**.

Hepatic adenocarcinoma, see the preferred term **Hepatocellular carcinoma**.

Hepatic adenofibrosis, see the preferred term **Cholangiofibrosis**.

Hepatic adenoma, see the preferred term **Hepatocellular adenoma**.

Hepatic bile duct adenomatosis, see the preferred term **Cholangiofibrosis**.

Hepatic cell carcinoma, see the preferred term **Hepatocellular carcinoma**.

Hepatic hemangioma is a benign neoplasm of endothelial cells originating from blood vessels and sinusoids in the liver. Hemangiomas consist of vascular spaces (often containing blood cells) lined by endothelial cells that show minimal atypia and rare mitoses. Hemangiomas are well demarcated, although not commonly encapsulated, and they compress the surrounding parenchyma, a feature useful to distinguish a hemangioma from angiectasis.

Differential diagnoses: **Hepatic angiectasis**; **Hepatic angiomatous hyperplasia**; **Lymphangioma**; **Hepatic hemangiosarcoma**; Hemangiopericytoma, benign.

Synonym(s): **Benign hemangioendothelioma**.

Reference

Thoolen, B. et al. 2010. Proliferative and nonproliferative lesions of the rat and mouse hepatobiliary system. *Toxicol Pathol* 38(7 Suppl):5S–81S.

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http://journals.sagepub.com/doi/abs/10.1177/0192623310386499?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed

Hepatic hemangiosarcoma is a malignant neoplasm of the endothelial cells lining blood vessels and sinusoids in the liver. It can be differentiated from a hemangioma by indistinct boundaries, local invasion, cellular pleomorphism, and a notable mitotic index. Metastasis to distant sites and organs is expected.

Differential diagnoses: Granulation tissue; **Hepatic hemangioma**; Hemangiopericytoma, malignant; Fibrosarcoma.

Synonym(s): **Malignant hemangioendothelioma**.

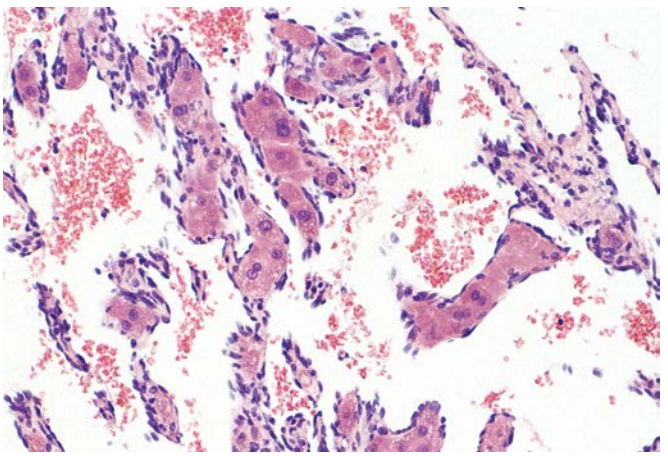


FIGURE 10 Hepatic hemangiosarcoma, mouse liver, H&E. (Reproduced with permission of CRC Press from Cattley, R. et al. 2013. In: Sahota, P., Popp, J., Hardisty, J., Gopinath, C. (eds.) *Toxicologic Pathology: Nonclinical Safety Assessment*. Boca Raton, FL: CRC Press, Taylor & Francis Group, pp. 313–366.)

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https://academic.oup.com/carcin/article/25/3/309/2390620

Hepatic histiocytic sarcoma is a neoplasm of the monocyte/macrophage lineage (histiocytes). In the liver, it can arise from resident Kupffer cells as well as circulating histiocytes. Metastasis to the liver from other sites is not uncommon. Neoplastic cells vary in size and often contain abundant, pale-staining cytoplasm. Nuclei are pleomorphic and often kidney-shaped, and mitotic figures are often present. The neoplastic cells arrange themselves along sinusoids and form small aggregates. Multiple tissues and organs are affected, as this tumor is considered a systemic neoplasm.

Differential diagnoses: **Malignant fibrous histiocytoma**; Lymphoma, malignant.

Synonym(s): **Kupffer cell sarcoma**.

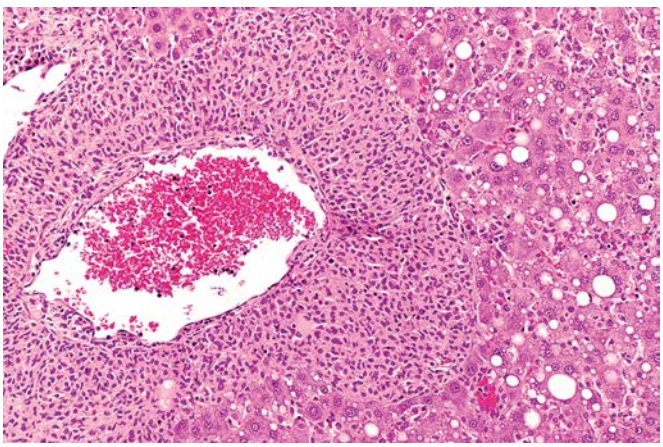


FIGURE 11 Hepatic histiocytic sarcoma, mouse liver, H&E. (Reproduced with permission of the Society of Toxicologic Pathology from Thoolen, B. et al. 2010. *Toxicol Pathol* 38(7 Suppl):5S–81S.)

Reference

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Hepatic intestinal cell metaplasia, see the preferred term **Cholangiofibrosis**.

Hepatic lipoma, see the preferred term **Ito cell tumor**.

Hepatic perisinusoidal fat-storing cell tumor, see the preferred term **Ito cell tumor**.

Hepatic stellate cell hyperplasia, see the preferred term **Ito cell hyperplasia**.

Hepatic stellate cell tumor, see the preferred term **Ito cell tumor**.

Hepatoblastoma is a malignant neoplasm occasionally observed in mice but rarely seen in other animals. This neoplasm is characterized as a nodule composed of small cells with hyperchromatic nuclei and scant cytoplasm, often arranged in trabeculae, rosettes, or gland-like structures. Mitotic activity is usually high, and metastasis has been reported. Formation of organoid structures, vascular cavities, fibrous connective tissue, and bone may be observed, and even squamous differentiation. Hepatoblastomas may be observed in mice treated with carcinogens, and individual hepatoblastomas are often observed within or adjacent to other hepatocellular neoplasms (i.e., hepatocellular carcinomas, and especially hepatocellular adenomas). As with hepatocellular neoplasms, susceptibility of mice to carcinogen-induced hepatoblastomas may be influenced by the mouse strain.

Differential diagnoses: **Hepatocellular carcinoma**; **Cholangiocarcinoma**; **Hepatic histiocytic sarcoma**.

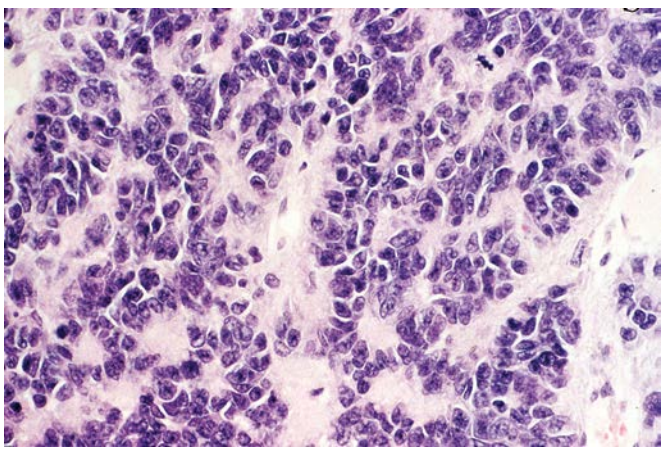


FIGURE 12 Hepatoblastoma, mouse liver, H&E. (Reproduced with permission of CRC Press from Cattley, R. et al. 2013. In: Sahota, P., Popp, J., Hardisty, J., Gopinath, C. (eds.) *Toxicologic Pathology: Nonclinical Safety Assessment*. Boca Raton, FL: CRC Press, Taylor & Francis Group, pp. 313–366.)

A2

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Hepatocarcinoma, see the preferred term **Hepatocellular carcinoma**.

Hepatocellular adenoma is a benign neoplastic proliferation of hepatocytes that frequently occurs in rodents, either as spontaneous lesions, and following treatment with genotoxic and non-genotoxic carcinogenic xenobiotics (see **Hepatocarcinogen** for further information), or in certain strains of genetically engineered mice. Several factors such as species, strain, housing, and diet affect the background incidence in rodents. Histologically, adenomas are nodular, often compressing the adjacent normal parenchyma. Neoplastic hepatocytes may show irregular growth patterns with distortion of the normal lobular architecture but with minimal cellular atypia. Hepatotoxin-induced adenomas may manifest features of hepatocellular degeneration (see **Hepatocellular degeneration** for further information) such as intracytoplasmic inclusions (see **Hepatocellular inclusions** for further information), hyaline bodies, or vacuolation. Adenomas may be diagnosed along with foci of cellular alteration (see **Focus of cellular alteration** for further information) and hepatocellular carcinomas (see **Hepatocellular carcinoma** for further information) in rodent carcinogenicity studies. Induced genetic alterations of autophagy regulators (ATG5 and ATG7), cell cycle regulators (Plk4, p21, p53), protein ubiquitination (Gp78, Parkin, Trim24), genome stability maintenance (Annexin 7, Nibrin, Shugoshin 1), metabolic function (Acyl-CoA oxidase 1, farnesoid X receptor, glycine *N*-methyltransferase, Mdr2), Hippo signaling pathway (Mst1/2, neurofibromin 2), Jak/Stat signaling pathway (Shp2), NF-κB signaling pathway (cylindromatosis, Galectin-3, Nemo, Tak1) PI3K/Akt/mTOR signaling pathway (Lkb1, Pten), and TGF-β signaling pathway (β-spectrin) are reported to cause a higher incidence of both adenomas and carcinomas in mice.

Differential diagnoses: **Hepatocellular hyperplasia, regenerative**; **Hepatocellular hyperplasia, Non-regenerative**; **Hepatocellular carcinoma**.

Synonym(s): **Hepatic adenoma**; **benign hepatoma**; **benign hepatocellular tumor**.

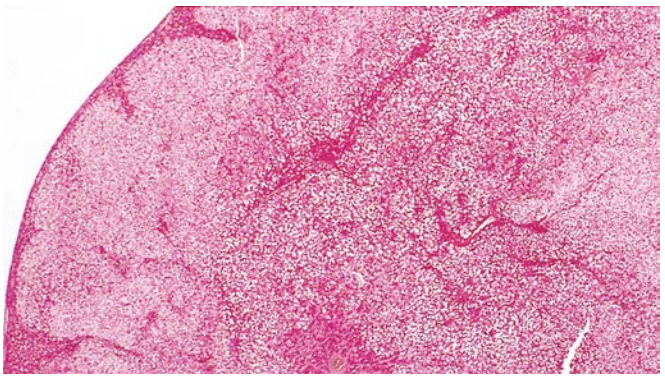


FIGURE 13 Hepatocellular adenoma, mouse liver, H&E. (Figure courtesy of R. Cattley, Auburn University.)

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Kawai, M. et al. 2008. Hepatocarcinogenic susceptibility of fenofibrate and its possible mechanism of carcinogenicity in a two-stage hepatocarcinogenesis model of rasH2 mice. *Toxicol Pathol* 36(7):950–957.

Kline, C. et al. 2008. Src kinase induces tumor formation in the c-SRC C57BL/6 mouse. *Int J Cancer* 122(12):2665–2673.

Kress, T.R. et al. 2016. Identification of MYC-dependent transcriptional programs in oncogene-addicted liver tumors. *Cancer Res* 76(12):3463–3472.

Renard, C. et al. 2000. Hepatocellular carcinoma in WHV/N-Myc2 transgenic mice: oncogenic mutations of beta-catenin and synergistic effect of p53 null alleles. *Oncogene* 18;19(22):2678–2686.

Thieringer, F. et al. 2012. Liver-specific overexpression of matrix metalloproteinase 9 (MMP-9) in transgenic mice accelerates development of hepatocellular carcinoma. *Mol Carcinog* 51(6):439–448.

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Hepatocellular carcinoma are locally infiltrating, malignant neoplasms of hepatocytes that lack distinct demarcation. Increased mitotic index and marked cellular pleomorphism may occur with loss of normal lobular

architecture. Vascular invasion, local invasion, and metastases to the lungs may be observed. Variable histological patterns of neoplastic growth have resulted in subclassifications including (1) acinar or glandular, characterized by acinar structures with generally a single layer of cells surrounding a central clear space; (2) solid, consisting of poorly differentiated, small, hyperchromatic, and pleomorphic cells with inconspicuous stroma; (3) trabecular, being the most common pattern in rats, with well-differentiated neoplastic hepatocytes forming multilayered trabeculae alternating with sinusoids; and (4) adenoid, with highly basophilic cuboidal cells surrounding luminal structures, and only described in mice. Hepatocellular carcinomas occur in rodents, either as spontaneous lesions following treatment with genotoxic and nongenotoxic carcinogenic xenobiotics (see **Hepatocarcinogen** for further information) or in certain strains of genetically engineered mice. Several factors such as species, strain, housing, and diet affect the background incidence in rodents. Induced genetic alterations of autophagy regulators (ATG5 and ATG7), cell cycle regulators (Plk4, p21, p53), protein ubiquitination (Gp78, parkin, TRIM24), genome stability maintenance (Annexin 7, nibrin, Shugoshin 1), metabolic function (Acyl-CoA oxidase 1, farnesoid X receptor, glycine *N*-methyltransferase, Mdr2), Hippo signaling pathway (Mst1/2, neurofibromin 2), Jak/Stat signaling pathway (Shp2), NF-κB signaling pathway (cylindromatosis, galectin-3, NEMO, Tak1) PI3K/Akt/mTOR signaling pathway (Lkb1, Pten), TGF-β signaling pathway (β-spectrin) are reported to cause a higher incidence of both adenomas and carcinomas in mice.

Differential diagnoses: **Hepatocellular hyperplasia, regenerative**; **Hepatocellular hyperplasia, non-regenerative**; **Hepatocellular adenoma**.

Synonym(s): **Hepatic adenocarcinoma**; **hepatic cell carcinoma**; **liver cell carcinoma**; **malignant hepatoma**; **hepatocarcinoma**.

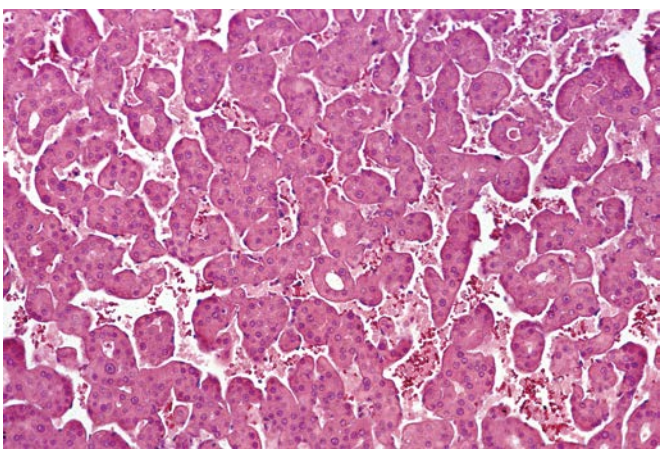


FIGURE 14 Hepatocellular carcinoma, rat liver, H&E. (Reproduced with permission of CRC Press from Cattley, R. et al. 2013. In: Sahota, P., Popp, J., Hardisty, J., Gopinath, C. (eds.) *Toxicologic Pathology: Nonclinical Safety Assessment*. Boca Raton, FL: CRC Press, Taylor & Francis Group, pp. 313–366.)

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Kline, C. et al. 2008. Src kinase induces tumor formation in the c-SRC C57BL/6 mouse. *Int J Cancer* 122(12):2665–2673.

Kress, T.R. et al. 2016. Identification of MYC-dependent transcriptional programs in oncogene-addicted liver tumors. *Cancer Res* 76(12):3463–3472.

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Hepatocellular hyperplasia, see the preferred term **Hepatocellular hyperplasia, regenerative**.

Hepatocellular hyperplasia, non-regenerative is characterized by a proliferation of hepatocytes, often focal, that may span several lobules and be associated with blood-filled spaces. The hepatocytes do not show significant tinctorial changes, and lobular architecture of the liver is discernible; however, mitotic activity is increased, and there may be some compression on the surrounding tissue. These foci of proliferation are not generally associated with parenchymal damage versus the regenerative variety of hepatocellular hyperplasia.

Differential diagnoses: **Hepatocellular hyperplasia, regenerative**; **Hepatocellular carcinoma**; **Hepatocellular adenoma**; **Basophilic focus of cellular alteration**; **Eosinophilic focus of cellular alteration**.

Synonym(s): **Focal hepatocellular hyperplasia**.

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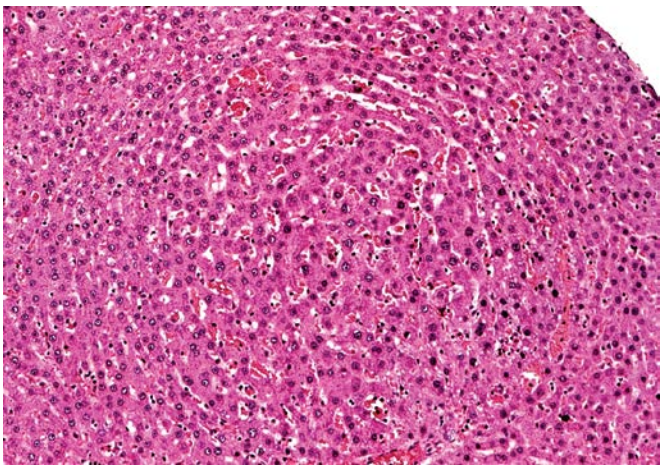


FIGURE 15 Hepatocellular hyperplasia, non-regenerative, rat liver, H&E. (Reproduced with permission of the Society of Toxicologic Pathology from Thoolen, B. et al. 2010. *Toxicol Pathol* 38(7 Suppl):5S–81S.)

Reference

Thoolen, B. et al. 2010. Proliferative and nonproliferative lesions of the rat and mouse hepatobiliary system. *Toxicol Pathol* 38(7 Suppl):5S–81S.

Link

http://journals.sagepub.com/doi/abs/10.1177/0192623310386499?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed

Hepatocellular hyperplasia, regenerative is characterized by a proliferation of hepatocytes, focal to multifocal, that occurs as a result of hepatocellular loss and is generally accompanied by concomitant chronic inflammation and fibrosis. This form of hyperplasia results in the form of nodules surrounded by connective tissue and contains the normal components of the hepatic lobule, though the architecture is often disturbed.

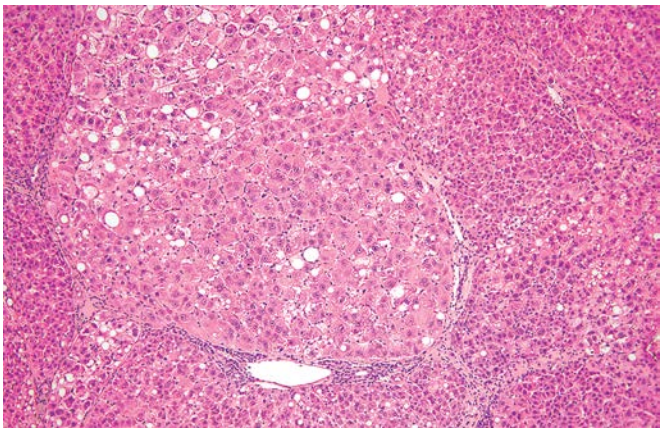


FIGURE 16 Hepatocellular hyperplasia, regenerative, rat liver, H&E. (Reproduced with permission of the Society of Toxicologic Pathology from Thoolen, B. et al. 2010. *Toxicol Pathol* 38(7 Suppl): 5S–81S.)

Differential diagnoses: **Hepatocellular hyperplasia, non-regenerative**; **Hepatocellular carcinoma**; **Hepatocellular adenoma**; **Basophilic focus of cellular alteration**; **Eosinophilic focus of cellular alteration**.

Synonym(s): **Hepatocellular hyperplasia**; **regenerative hyperplasia**; **nodular regeneration**.

Reference

Thoolen, B. et al. 2010. Proliferative and nonproliferative lesions of the rat and mouse hepatobiliary system. *Toxicol Pathol* 38(7 Suppl):5S–81S.

Link

http://journals.sagepub.com/doi/abs/10.1177/0192623310386499?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed

Hepatocholangiocellular adenoma is a benign neoplasm with proliferative mixture of both hepatocytes and intrahepatic bile duct epithelium. It is a rare spontaneous or induced neoplasm reported in the B6C3F1 mouse and F344 rat, and in liver-specific TR1 knockout mice. Histologically these adenomas are characterized by cords of neoplastic hepatocytes admixed with slightly dilated acini lined by cuboidal or flattened neoplastic bile duct cells, and hepatocytes may form ducts or ductules. The hepatocholangiocellular adenoma must be distinguished from hepatocellular adenomas that have impinged upon areas of bile duct hyperplasia.

Differential diagnoses: **Hepatocellular adenoma**; **Cholangioma**; **Hepatocholangiocellular carcinoma**.

Reference

Thoolen, B. et al. 2010. Proliferative and nonproliferative lesions of the rat and mouse hepatobiliary system. *Toxicol Pathol* 38(7 Suppl):5S–81S.

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http://journals.sagepub.com/doi/abs/10.1177/0192623310386499?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed

Hepatocholangiocellular carcinoma is a malignant neoplasm with a proliferative mixture of both hepatocytes and intrahepatic bile duct epithelium. It is a rare spontaneous neoplasm, and induced neoplasm reported in B6C3Fl mouse and F344 rat having cords of neoplastic hepatocytes forming trabecular solid or glandular patterns while biliary neoplastic cells may form acini or small nests without lumen, and sometimes glandular structures lined by both components. Hepatocholangiocellular carcinoma are reported following diethylnitrosamine or azo dye treatment in rats, 2-acetylaminoflurene or benzidine hydrochloride treatment in mice, in farnesoid X receptor-null mice, and in liver-specific Hat1 knockout mice.

Differential diagnoses: **Hepatocellular carcinoma**; **Cholangiocarcinoma**; **Hepatocholangiocellular adenoma**.

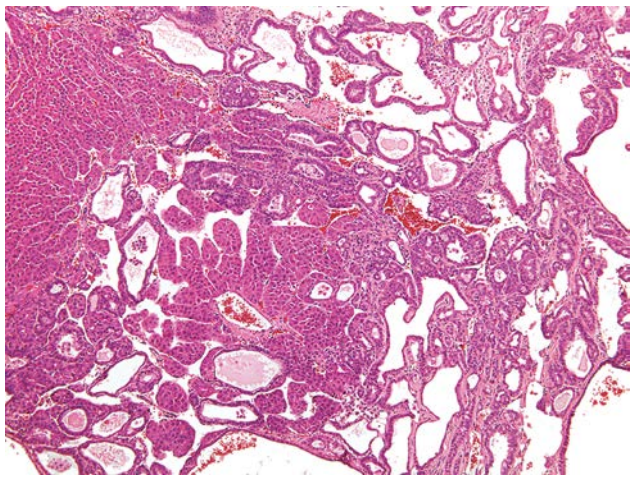


FIGURE 17 Hepatocholangiocellular carcinoma, rat liver, H&E. (Reproduced with permission of the Society of Toxicologic Pathology from Thoolen, B. et al. 2010. *Toxicol Pathol* 38(7 Suppl):5S–81S.)

Reference

Thoolen, B. et al. 2010. Proliferative and nonproliferative lesions of the rat and mouse hepatobiliary system. *Toxicol Pathol* 38(7 Suppl):5S–81S.

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Hepatocholangiocellular tumor (benign or malignant) see the preferred terms **Hepatocholangiocellular adenoma** and **carcinoma**.

Ito cell hyperplasia is a focal or diffuse increase in numbers of Ito cells (also known as stellate cells or perisinusoidal fat-storing cells). These cells may form clusters, or extend along rows of hepatocytes, and contain multiple cytoplasmic clear vacuoles of varying size. They may be associated with a collagenous matrix. Ito cells may be labeled via immunohistochemical procedures using vimentin, actin, and desmin as markers. This lesion is rare and observed mainly in mice. A relationship between Ito cell hyperplasia and Ito cell neoplasia has been hypothesized. (See **Ito cells** for further information.)

Differential diagnoses: **Hepatocellular lipidosis**; **Ito cell tumor**.

Synonym(s): **Hepatic stellate cell hyperplasia**; **perisinusoidal fat-storing cell hyperplasia**.

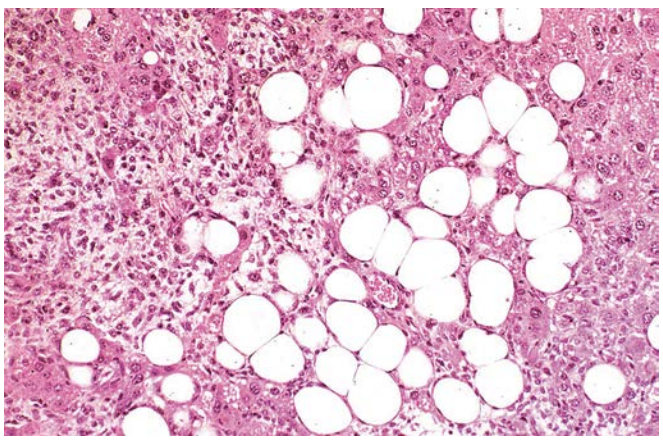


FIGURE 18 Ito cell hyperplasia, mouse liver, H&E. (Reproduced with permission of the Society of Toxicologic Pathology from Thoolen, B. et al. 2010. *Toxicol Pathol* 38(7 Suppl):5S–81S.)

References

Thoolen, B. et al. 2010. Proliferative and nonproliferative lesions of the rat and mouse hepatobiliary system. *Toxicol Pathol* 38(7 Suppl):5S–81S.

Tillmann, T. et al. 1999. Ito cell tumor: Immunohistochemical investigations of a rare lesion in the liver of mice. *Toxicol Pathol* 27(3):364–369.

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http://journals.sagepub.com/doi/abs/10.1177/0192623310386499?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed

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Ito cell tumor is a benign neoplasm composed of hepatic Ito cells (also known as stellate cells or perisinusoidal fat-storing cells). These cells vary in appearance from lipid-containing cells containing clear cytoplasmic vacuoles to spindle shape with minimal cytoplasm. The cells form a mass that compresses adjacent hepatic parenchyma and are generally considered benign. Spindle cells may be more frequently present in the periphery of the mass and may be associated with a collagenous matrix. Ito cell tumors in mice may be identified by immunohistochemistry for the following markers: vimentin, actin, desmin, and proliferating cell nuclear antigen. Increased amounts of laminin and tenascin, two extracellular matrix proteins of the liver, have also been reported in these tumors. This lesion is rare and observed mainly in mice. Ito cell hyperplasia may represent part of a continuum of progression to neoplasia.

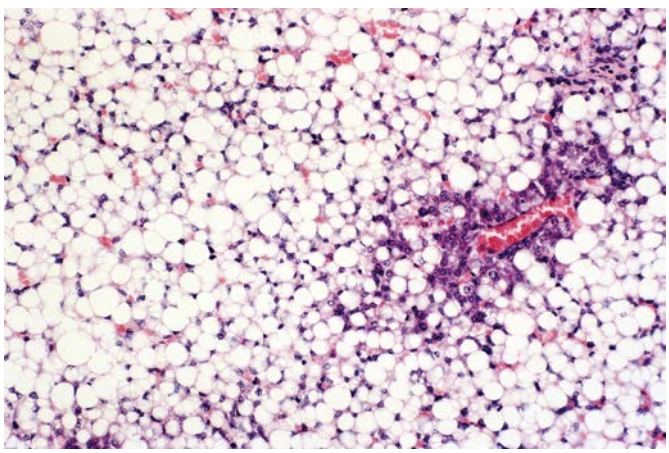


FIGURE 19 Ito cell tumor, mouse liver, H&E. (Reproduced with permission of Elsevier from Cattley, R. and Cullen, J. 2013. In: Haschek, W.M., Rousseux, C.G., Wallig, M.A., Bolon, B., Ochoa, R. (eds.) *Handbook of Toxicologic Pathology*, 3rd ed. San Diego, CA: Academic Press, Elsevier, pp. 1509–1566.)

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Differential diagnoses: **Hepatocellular lipidosis**; **Ito cell hyperplasia**; **Hepatic liposarcoma**.

Synonym(s): **Hepatic stellate cell tumor**; **hepatic perisinusoidal fat-storing cell tumor**; **hepatic lipoma**.

References

Thoolen, B. et al. 2010. Proliferative and nonproliferative lesions of the rat and mouse hepatobiliary system. *Toxicol Pathol* 38(7 Suppl):5S–81S.

Tillmann, T. et al. 1999. Ito cell tumor: Immunohistochemical investigations of a rare lesion in the liver of mice. *Toxicol Pathol* 27(3):364–369.

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Kupffer cell hypertrophy/hyperplasia is characterized by an increase in number and/or size of Kupffer cells in small aggregates or nodules within the sinusoids of the liver. In advanced instances, the lesion may consist of nodules or sheets of oval- to spindle-shaped cells. The pathogenesis of this lesion is activation of Kupffer cells by cytokines, and it may be associated with increased phagocytic activity as evidenced by the accumulation of foreign material within their cytoplasm. Kupffer cell hypertrophy/hyperplasia is a rare lesion that may occur spontaneously. It should be differentiated from oval cell proliferation, inflammatory cell infiltration, and histiocytic sarcoma.

Differential diagnoses: **Kupffer cell proliferation**; **Histiocytic sarcoma**; **Hepatic mononuclear cell infiltration**; **Oval cell hyperplasia**.

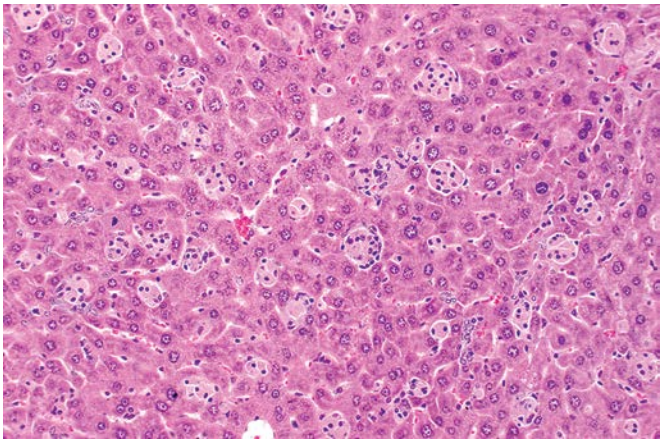


FIGURE 20 Kupffer cell hypertrophy/hyperplasia, mouse liver, H&E. (Reproduced with permission of the Society of Toxicologic Pathology from Thoolen, B. et al. 2010. *Toxicol Pathol* 38(7 Suppl):5S–81S.)

Reference

Thoolen, B. et al. 2010. Proliferative and nonproliferative lesions of the rat and mouse hepatobiliary system. *Toxicol Pathol* 38(7 Suppl): 5S–81S.

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http://journals.sagepub.com/doi/abs/10.1177/0192623310386499?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed

Kupffer cell sarcoma, see the preferred term **Hepatic histiocytic sarcoma**.

Liver cell carcinoma, see the preferred term **Hepatocellular carcinoma**.

Malignant cholangioma, see the preferred term **Cholangiocarcinoma**.

Malignant hemangioendothelioma, see the preferred term **Hepatic hemangiosarcoma**.

Malignant hepatoma, see the preferred term **Hepatocellular carcinoma**.

Nodular regeneration, see the preferred term **Hepatocellular hyperplasia, regenerative**.

Oval cell hyperplasia is a lesion characterized by increased numbers of oval cells (small cells with oval nuclei that arise in the periphery of the portal tracts that line the short and narrow passages that conduct bile between the bile canaliculi and bile ducts and can differentiate into either hepatocytes or bile duct epithelium). In oval cell hyperplasia, these cells are present as multifocal accumulations within the periportal hepatocellular

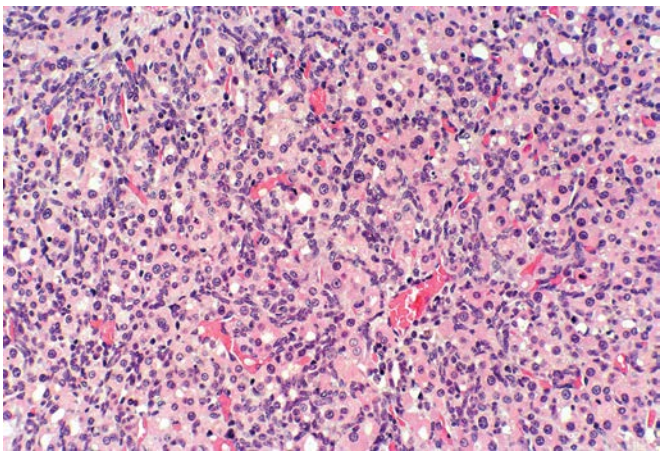


FIGURE 21 Oval cell hyperplasia, mouse liver, H&E. (Reproduced with permission of CRC Press from Cattley, R. et al. 2013. In: Sahota, P., Popp, J., Hardisty, J., Gopinath, C. (eds.) *Toxicologic Pathology: Nonclinical Safety Assessment*. Boca Raton, FL: CRC Press, Taylor & Francis Group, pp. 313–366.)

parenchyma. The cells occasionally form incomplete duct-like structures, and label for keratin. Oval cell proliferation results from xenobiotic treatment that leads to hepatocellular injury loss, often when the xenobiotic prevents regenerative proliferation by the surviving hepatocytes. In mice, oval cell hyperplasia has also been associated with hepatic *Helicobacter* sp. infections. In some instances, oval cell hyperplasia may precede the development of hepatocellular and/or cholangiocellular neoplasia.

Differential diagnoses: **Bile duct hyperplasia**; **Fibrosis**; **Hepatic periportal inflammatory cell infiltrate**.

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Cattley, R. and Cullen, J. 2013. Liver and gall bladder. In: Haschek, W.M., Rousseux, C.G., Wallig, M.A., Bolon, B., Ochoa, R. (eds.) *Handbook of Toxicologic Pathology*, 3rd ed. San Diego, CA: Academic Press, Elsevier, pp. 1509–1566.

Cattley, R., Popp, J., and Vonderfect, S. 2013. Liver, gallbladder, and pancreas. In: Sahota, P., Popp, J., Hardisty, J., Gopinath, C. (eds.) *Toxicologic Pathology: Nonclinical Safety Assessment*. Boca Raton, FL: CRC Press, Taylor & Francis Group, pp. 313–366.

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https://onlinelibrary.wiley.com/doi/abs/10.1002/bies.20311

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4278240/

Pancreatic acinar cell adenocarcinoma is a malignant neoplasm of pancreatic acinar cells that may vary in histological appearance from well-differentiated with glandular, trabecular, or solid growth patterns to a pleomorphic or anaplastic tumor with cellular pleomorphism composed of small rounded cells or spindle cells. Loss of acinar architecture is evident in pleomorphic or anaplastic tumors with evidence of local invasion or distant metastases. These malignant tumors may show scirrhous reactions and encapsulation. There are sex and strain differences in sensitivity to spontaneous and chemically-induced neoplasms in laboratory animals, with rare spontaneous incidences in rats and mice. Treatment-related acinar cell adenocarcinomas are more common in rats and mice than the ductal cell variety that are more common in humans and hamsters. A number of genotoxic and nongenotoxic substances such as *N*-nitroso compounds, 7,12-dimethylbenz(a)anthracene (DMBA), azaserine, gabapentin, clofibrate, peroxisome proliferators, nafenopin, 4-hydroxyaminoquinoline, choline-deficient diet, and soya flour can induce these tumors in laboratory animals. Mice are resistant to those induced by corn oil and soya. Pancreatic acinar cell adenocarcinoma is reported in several transgenic mouse models including those bearing the elastase promoter-SV40-early antigen construct (Ela-1-SV40 T) and Ela-1-Myc transgene.

Differential diagnoses: **Pancreatic acinar cell adenoma**; **Pancreatic ductal cell adenocarcinoma**.

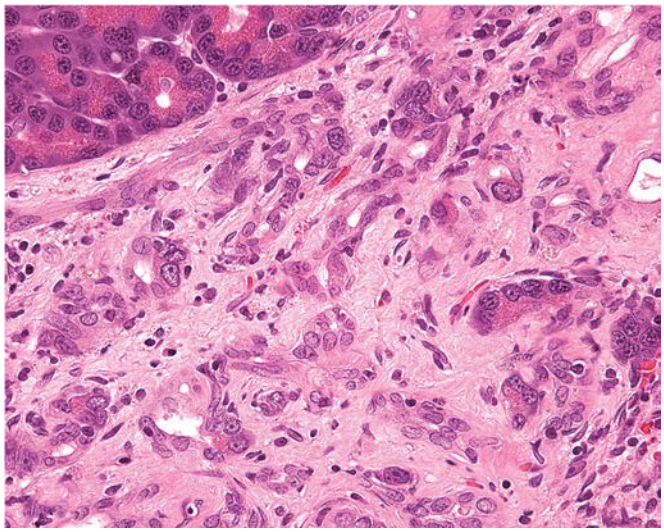


FIGURE 22 Pancreatic acinar cell adenocarcinoma, rat pancreas, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Nolte, T. et al. 2016. *J Toxicol Pathol* 29(1 Suppl):1S–125S.)

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Cattley, R., Popp, J., and Vonderfect, S. 2013. Liver, gallbladder, and pancreas. In: Sahota, P., Popp, J., Hardisty, J., Gopinath, C. (eds.) *Toxicologic Pathology: Nonclinical Safety Assessment*. Boca Raton, FL: CRC Press, Taylor & Francis Group, pp. 313–366.

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Nolte, T. et al. 2016. Nonproliferative and proliferative lesions of the gastrointestinal tract, pancreas and salivary glands of the rat and mouse. *J Toxicol Pathol* 29(1 Suppl):1S–125S.

Obourn, J. et al. 1997. Mechanisms for the pancreatic oncogenic effects of the peroxisome proliferator Wyeth-14,643. *Toxicol Appl Pharmacol* 145(2):425–436.

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Pancreatic acinar cell adenoma is a benign neoplasm of the exocrine pancreas that is normally grossly apparent as a nodular or multinodular, sharply circumscribed mass. Histologically, these tumors are composed of well-differentiated pancreatic acinar cells with a variable mitotic index and

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nuclear polymorphism. Compression of the adjacent tissue is often present, with or without encapsulation.

Differential diagnoses: **Pancreatic acinar cell hyperplasia**; **Pancreatic acinar cell adenocarcinoma**.

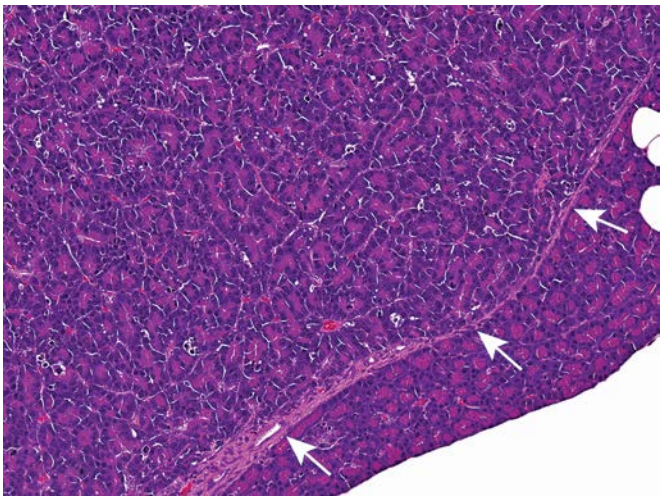


FIGURE 23 Pancreatic acinar cell adenoma, rat pancreas, H&E; arrows depict fibrous capsule. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Nolte, T. et al. 2016. *J Toxicol Pathol* 29(1 Suppl):1S–125S.)

References

Cattley, R., Popp, J., and Vonderfect, S. 2013. Liver, gallbladder, and pancreas. In: Sahota, P., Popp, J., Hardisty, J., Gopinath, C. (eds.) *Toxicologic Pathology: Nonclinical Safety Assessment*. Boca Raton, FL: CRC Press, Taylor & Francis Group, pp. 313–366.

Myers, B., Hathcock, J., Shiekh, N., and Roebuck, B. 1991. Effects of dietary soya bean trypsin inhibitor concentrate on initiation and growth of putative preneoplastic lesions in the pancreas of the rat. *Food Chem Toxicol* 29(7):437–443.

Nolte, T. et al. 2016. Nonproliferative and proliferative lesions of the gastrointestinal tract, pancreas and salivary glands of the rat and mouse. *J Toxicol Pathol* 29(1 Suppl):1S–125S.

Obourn, J. et al. 1997. Mechanisms for the pancreatic oncogenic effects of the peroxisome proliferator Wyeth-14,643. *Toxicol Appl Pharmacol* 145(2):425–436.

Links

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Pancreatic acinar cell hyperplasia are focal proliferations of acinar cells that are often larger than average, accompanied by increased number of cells per acinus. Acinar cell hyperplasia has a low spontaneous incidence in rats, mice, and hamsters, but increases with age, and can be induced by dietary or hormonal manipulation as well as by the administration of various chemicals. Treatment of rats with raw soya flour, which contains a trypsin inhibitor, leading to overproduction of cholecystokinin (CCK) that is trophic to pancreatic acini, can induce focal hypertrophy and hyperplasia. Direct administration of CCK or similar synthetic peptides (e.g., pentagastrin) also results in acinar growth due to direct stimulation. Focal hyperplasia can be induced by corn oil or carcinogens such as azaserine and 4-HAQO. The PPAR-alpha activators cause acinar hyperplasia and adenomas by decreasing the flow or altering the composition of bile that results in cholestasis and increased cholecystokinin (CCK) secretion by duodenal endocrine cells. Acinar cell hyperplasia progressing to adenoma/adenocarcinoma is observed in several transgenic mouse models, including those bearing the elastase promoter-SV40-early antigen construct (Ela-1-SV40 T) and Ela-1-Myc transgene, transgenic mice with pancreatic Myc expression and transforming growth factor alpha transgenic mice.

Differential diagnoses: **Pancreatic acinar cell adenoma**; **Pancreatic basophilic focus**; **Pancreatic cell hypertrophy**.

Synonym(s): **Pancreatic eosinophilic focus**.

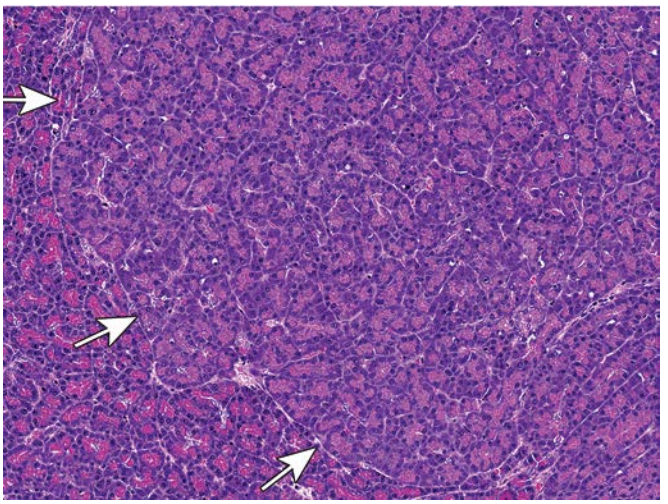


FIGURE 24 Pancreatic acinar cell hyperplasia, rat pancreas, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Nolte, T. et al. 2016. *J Toxicol Pathol* 29(1 Suppl):1S–125S.)

References

Cattley, R., Popp, J., and Vonderfect, S. 2013. Liver, gallbladder, and pancreas. In: Sahota, P., Popp, J., Hardisty, J., Gopinath, C. (eds.) *Toxicologic Pathology: Nonclinical Safety Assessment*. Boca Raton, FL: CRC Press, Taylor & Francis Group, pp. 313–366.

Nolte, T. et al. 2016. Nonproliferative and proliferative lesions of the gastrointestinal tract, pancreas and salivary glands of the rat and mouse. *J Toxicol Pathol* 29(1 Suppl):1S–125S.

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Pancreatic ductal cell adenocarcinoma is a malignant tumor arising from neoplastic intrapancreatic duct epithelium

characterized by cell atypia and invasion of duct-like structures, often accompanied by a dense fibrous stroma. There are no spontaneous ductal cell hyperplasias or neoplasias described in rats and mice, but they do occur in humans and hamsters. Pancreatic ductal adenocarcinomas are induced by DMBA implantation in mice, and in genetically engineered models with KRAS mutations, including PDX-1-Cre/Lox-Stop-Lox (LSL)-KRAS or p48/LSL-KRAS mice which have been modified with deletions or mutations of Ink4, p53, Mist, Smad4, or TGFβ.

Differential diagnosis: **Pancreatic acinar cell adenocarcinoma**.

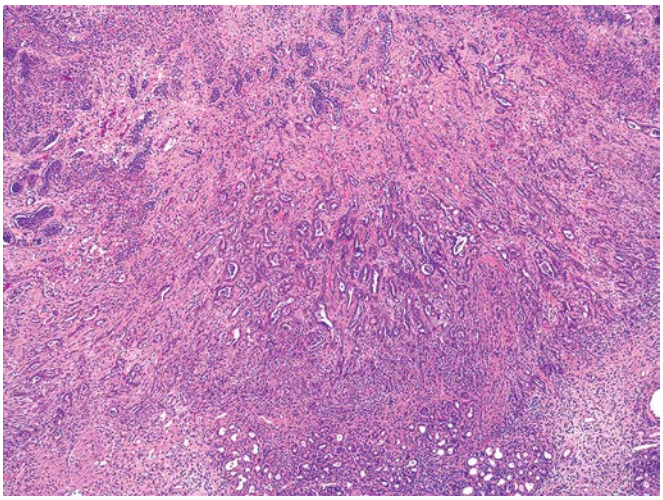


FIGURE 25 Pancreatic ductal cell adenocarcinoma, rat pancreas, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Nolte, T. et al. 2016. *J Toxicol Pathol* 29(1 Suppl):1S–125S.)

References

Cattley, R., Popp, J., and Vonderfect, S. 2013. Liver, gallbladder, and pancreas. In: Sahota, P., Popp, J., Hardisty, J., Gopinath, C. (eds.) *Toxicologic Pathology: Nonclinical Safety Assessment*. Boca Raton, FL: CRC Press, Taylor & Francis Group, pp. 313–366.

Nolte, T. et al. 2016. Nonproliferative and proliferative lesions of the gastrointestinal tract, pancreas and salivary glands of the rat and mouse. *J Toxicol Pathol* 29(1 Suppl):1S–125S.

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Pancreatic ductal cell adenoma is a benign neoplasm arising from intrapancreatic ducts. Histologically, this tumor is characterized as a complex of ductular structures lined by a high cuboidal epithelium resembling that of normal ductules. Pancreatic ductal adenomas may occur after administration with 7,12-dimethylbenz[a]anthracene (DMBA), infection with reovirus 3, feeding a Western-style diet, and in transgenic mice with KRAS oncogene.

Differential diagnosis: **Pancreatic ductal cell hyperplasia**.

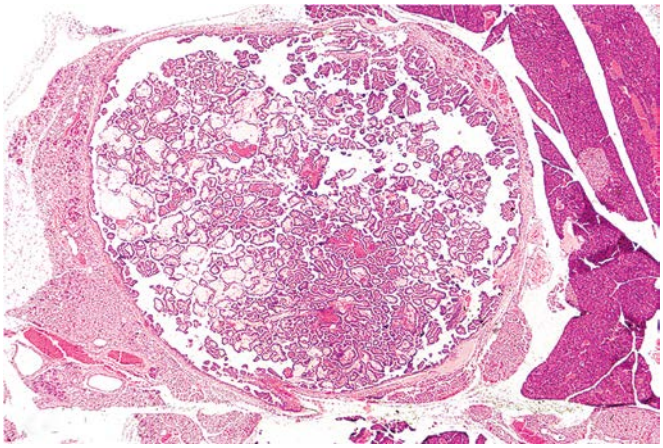


FIGURE 26 Pancreatic ductal cell adenoma, mouse pancreas, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Nolte, T. et al. 2016. *J Toxicol Pathol* 29(1 Suppl):1S–125S.)

Reference

Nolte, T. et al. 2016. Nonproliferative and proliferative lesions of the gastrointestinal tract, pancreas and salivary glands of the rat and mouse. *J Toxicol Pathol* 29(1 Suppl):1S–125S.

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https://www.ncbi.nlm.nih.gov/pubmed/26973378

Pancreatic ductal cell hyperplasia is characterized by increased numbers of intralobular and interlobular pancreatic ducts with hyperchromatic duct cells. Papillae formation and cellular pleomorphism may be present. Pancreatic duct epithelial hyperplasia can be associated with circumscribed areas of pancreatic necrosis, inflammation, and fibrosis. The incidence of this lesion is common in rats, where it may arise spontaneously, and even greater in hamsters and humans. It is not observed spontaneously in mice. Mutations in the KRAS2, p16/CDKN2A, TP53, and MAD4/DPC4 genes have been linked to ductal hyperplasia and neoplasms in both transgenic mice and humans. Intra- and interlobular pancreatic ducts are more often affected than the extrapancreatic ducts. Pancreatic intraepithelial neoplasia (PanIN), having hyperplastic and dysplastic epithelial lesions of the pancreatic ducts, has been identified as the precursor of pancreatic ductal adenocarcinoma. Transgenic mouse models for human pancreatic cancer may develop atypical ductal hyperplasia with mucin accumulation within tall columnar cells lining the ducts. Morphologically they range from ducts lined with an increased number of monomorphic tall columnar mucinous cells to multilayered lesions with cribriform growth and loss of cell polarity. Varying levels of cellular pleomorphism and atypia may be present. Ductal hyperplasia which progresses to adenocarcinoma (see **Pancreatic ductal adenocarcinoma** for further information.) may occur under experimental conditions after administration of dimethylbenzanthracene, infection with reovirus 3, feeding a Western-style diet, and in transgenic mice with KRAS oncogene. K-ras-mutant

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mice with Ela- or cytokeratin-19 gene promoter develop only hyperplasia (early mouse PanIN lesions) without the formation of frank adenocarcinoma. Mucus metaplasia in hyperplastic duct epithelium may occur in transgenic mouse models of pancreatic neoplasia.

Differential diagnosis: **Pancreatic ductal cell adenoma**.

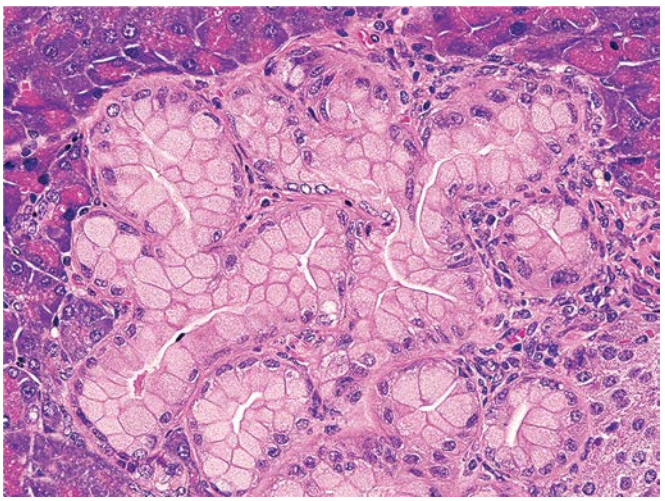


FIGURE 27 Pancreatic ductal cell hyperplasia, mouse pancreas, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Nolte, T. et al. 2016. *J Toxicol Pathol* 29(1 Suppl):1S–125S.)

Reference

Nolte, T. et al. 2016. Nonproliferative and proliferative lesions of the gastrointestinal tract, pancreas and salivary glands of the rat and mouse. *J Toxicol Pathol* 29(1 Suppl):1S–125S.

Link

https://www.ncbi.nlm.nih.gov/pubmed/26973378

Pancreatic eosinophilic focus, see the preferred term **Pancreatic acinar cell hyperplasia**.

Perisinusoidal fat-storing cell hyperplasia, see the preferred term **Ito cell hyperplasia**.

Regenerative hyperplasia, see the preferred term **Hepatocellular hyperplasia, regenerative**.

LYMPHOID SYSTEM

Alveolar (lung) histiocytosis, see the preferred term **Macrophage hyperplasia**.

Histiocytic aggregates, see the preferred term **Macrophage hyperplasia**.

Histiocytic hyperplasia, see the preferred term **Macrophage hyperplasia**.

Histiocytic infiltrates, see the preferred term **Macrophage hyperplasia**.

Hodgkin's lymphoma is a very specific form of lymphoma that is predominantly found in humans but has also been described as rarely occurring in other species, where it is often referred to as "Hodgkin's-like" lymphoma. It is distinguished histologically by the presence of Reed-Sternberg cells, neoplastic giant cells that contain two nuclei with very prominent nucleoli that have been described as "owl-eye" nuclei. Hodgkin's lymphoma in humans is often associated with the Epstein-Barr virus (approximately 50% of cases), and is usually of B lymphocyte origin, although typical B lymphocyte surface antigens such as CD20 and B220 are generally not expressed by the tumor cells. Instead, neoplastic cells often express CD30 and CD15. The tumor is most typically found in lymph nodes, with cervical lymph nodes being most commonly involved, although splenic involvement is seen in approximately 30% of cases. Histologically, the tumor consists of sheets of neoplastic lymphocytes containing the characteristic Reed-Sternberg cells. Histologic variants of Reed-Sternberg cells include lacunar Reed-Sternberg cells, which have single but multilobulated nuclei; popcorn Reed-Sternberg cells, which are smaller but also have highly lobulated nuclei; and pleomorphic Reed-Sternberg cells, which have multiple pleomorphic nuclei. Classification of these histologic variants is not as important for the treatment and prognosis of this tumor as it is for other forms of lymphoma.

References

Kuppers, R., Engert, A., and Hansmann, M-L. 2012. Hodgkin lymphoma. *J Clin Invest* 122:3439–3447.

Link

https://www.jci.org/articles/view/61245.

Lymph node dendritic cell hyperplasia is characterized by an increased number or prominence of interdigitating cells within T-cell zones of the paracortex that is often accompanied by an expanded paracortex. Interdigitating cells are antigen-presenting dendritic cells within the lymphoid tissue. Dendritic cells are bone marrow–derived monocyte-macrophage lineage cells. They reside within the epithelial compartments of skin and mucosa where they encounter and process antigen. Subsequently, dendritic cells migrate to lymphoid tissues via lymphatics where they home to T-cell zones and present antigen, primarily to T cells and B cells. Antigen-presenting cells also reside within B-cell follicles and are distinguished as follicular dendritic cells. Dendritic cells secrete cytokines and orchestrate the repertoire of potential lymphocyte responses. Interdigitating cells are morphologically characterized as being larger than lymphocytes, with pale cytoplasm and a nucleus with irregular contours. Transmission electron microscopy shows branching (dendritic) cytoplasmic processes interfacing with surrounding lymphocytes.

Reference

Elmore, S.A. 2006. Histopathology of the lymph nodes. *Toxicol Pathol* 34:425–454.

Link

http://journals.sagepub.com/doi/full/10.1080/01926230600964722.

Lymph node plasma cell hyperplasia is characterized by increased numbers of plasma cells, usually located within the medullary cords but potentially extending into the deeper paracortex. Plasma cells are fully differentiated B cells that produce immunoglobulin of a single isotype and specificity. They are morphologically identified as lymphocytes with a lower nuclear-to-cytoplasm ratio, slightly basophilic cytoplasm, a perinuclear clear space (Golgi apparatus), and a nucleus with prominent heterochromatin, often described as a "clockface" pattern.

References

Elmore, S.A. 2006. Histopathology of the lymph nodes. *Toxicol Pathol* 34:425–454.

Ward, J.M., Rehg, J.E., and Morse, III, H.C. 2012. Differentiation of rodent immune and hematopoietic system reactive lesions from neoplasias. *Toxicol Pathol* 40:425–434.

Links

http://journals.sagepub.com/doi/full/10.1080/01926230600964722
http://journals.sagepub.com/doi/10.1177/0192623311431467

Lymph node reticular cell hyperplasia is characterized by increased numbers or prominence of stromal cells within lymphoid tissue. Fibroblastic reticular cells (FRC) and their secreted reticulin fibers form the stroma of the lymph node. They have pale cytoplasm and irregular-shaped nuclei. They are difficult to see in standard hematoxylin and eosin (H&E)-stained sections and require immunohistochemistry (IHC) or silver stains for definitive identification. FRC are positive for cytokeratins 8 and 18 and are positive by Gomori's silver reticulin stain. Flattened FRC and macrophages line sinuses. FRC are diffusely distributed throughout the lymph node, being most prominent in the paracortex. Increased FRC and reticulin fibers should be differentiated from collagen fibrosis and scarring of the lymph node.

Reference

Thomazy, V.A., Vega, F., Medeiros, L.J., Davies, P.J., and Jones, D. 2003. Phenotypic modulation of the stromal reticular network in normal and neoplastic lymph nodes: Tissue transglutaminase reveals coordinate regulation of multiple cell types. *Am J Pathol* 163:165–174.

Link

https://doi.org/10.1016/S0002-9440(10)63640-1

Lymph node, macrophage hyperplasia, intrasinusoidal is characterized by increased size, number, and prominence of macrophages lining sinuses within the lymph node. Lymphatic sinuses allow drainage of lymph through the lymph node. The sinuses are lined by flattened fibroblastic reticular cells and macrophages. Macrophages are bone marrow–derived cells of the monocyte-macrophage lineage. Intrasinusoidal macrophages can be increased by recruitment of cells via the lymphatics or can proliferate in situ in response to proinflammatory stimuli. Macrophages are phagocytic, remove particulate debris from draining lymph, and secrete cytokines that contribute to regulation of the local environment of the lymph node. Sinusoidal macrophages may contain pigment depending upon the phagocytized material (e.g., carbon from tattoo ink, hemosiderin pigments from erythrocytes).

Differential diagnoses: **Inflammation**; **Granuloma**; **Mast cell hyperplasia**; **Histiocytic sarcoma**.

Synonym(s): **Sinus histiocytosis**; **histiocytic hyperplasia**; **histiocytic infiltrate**; **histiocytic aggregates**; **increased macrophage cellularity**; **macrophage accumulation**; **macrophage infiltrate**; **macrophage infiltration**; **prominent macrophages**.

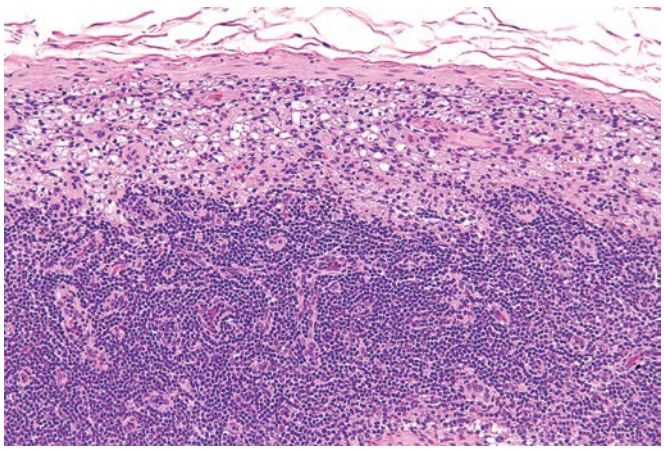


FIGURE 1 Subcapsular intrasinusoidal macrophage hyperplasia in a dog lymph node.

Lymphoid hyperplasia is characterized by an increase in numbers of lymphocytes or an increase in size or prominence of lymphoid compartments within lymphoid tissues. Modifiers may be added to specify the location or compartment involved (e.g., follicular hyperplasia, paracortical hyperplasia, medullary hyperplasia). An increase in lymphocytes occurs as a result of immune stimulation via increased recruitment, decreased loss, or proliferation in situ. Lymphoid tissues may be macroscopically enlarged, and accompanying histologic features of a proinflammatory state are often present. Differentiation from lymphoid neoplasia is required.

Differential diagnosis: **Lymphoma**.

Synonym(s): **Lymphoid tissue, increased cellularity**.

References

Elmore, S.A. 2006. Histopathology of the lymph nodes. *Toxicol Pathol* 34:425–454.

Suttie, A.W. 2006. Histopathology of the spleen. *Toxicol Pathol* 34:466–503.

Ward, J.M., Rehg, J.E., and Morse, III, H.C. 2012. Differentiation of rodent immune and hematopoietic system reactive lesions from neoplasias. *Toxicol Pathol* 40:425–434.

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Links

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http://journals.sagepub.com/doi/10.1177/0192623311431467

Lymphoid tissue, increased cellularity, see the preferred term **Lymphoid hyperplasia**.

Lymphoma, extranodal marginal zone B cell, see the preferred term **Mucosa-associated lymphoid tissue lymphoma**.

Lymphoma, follicular center cell is a form of lymphoma that is so named because it is composed of multiple nodules or follicle-like structures that are evident at low microscopic magnifications. This multinodular appearance is most common in humans and dogs but is not as common a feature in murine rodents, where it often presents as diffuse sheets of cells with little or no nodular/follicular formation. It can occur in both lymph nodes and spleen but is most commonly seen as a spontaneously occurring finding in the spleen of aged rodents, particularly in mice. In mice and rats it is most commonly characterized by a proliferation of diffuse sheets of pleomorphic-sized and -shaped cells (including cleaved cells) that invade and efface normal lymphoid architecture. Neolastic cells have a high mitotic index. Despite the pleomorphic cytologic appearance of this tumor, it is of B lymphocyte origin, and expresses B lymphocyte cell surface markers such as B220. It is believed to be of germinal center cell origin due to the presence of large pleomorphic cells that are often cleaved; hence the name "follicular center cell" lymphoma. In rodents, this tumor was formerly referred to as a reticulum cell sarcoma as well as pleomorphic or mixed cell lymphoma. The pleomorphic nature of the neoplastic cells distinguishes the follicular center cell lymphoma from nodular lymphoid hyperplasia as well as the other forms of lymphoma. The immunohistochemistry for B lymphocyte markers is diagnostic.

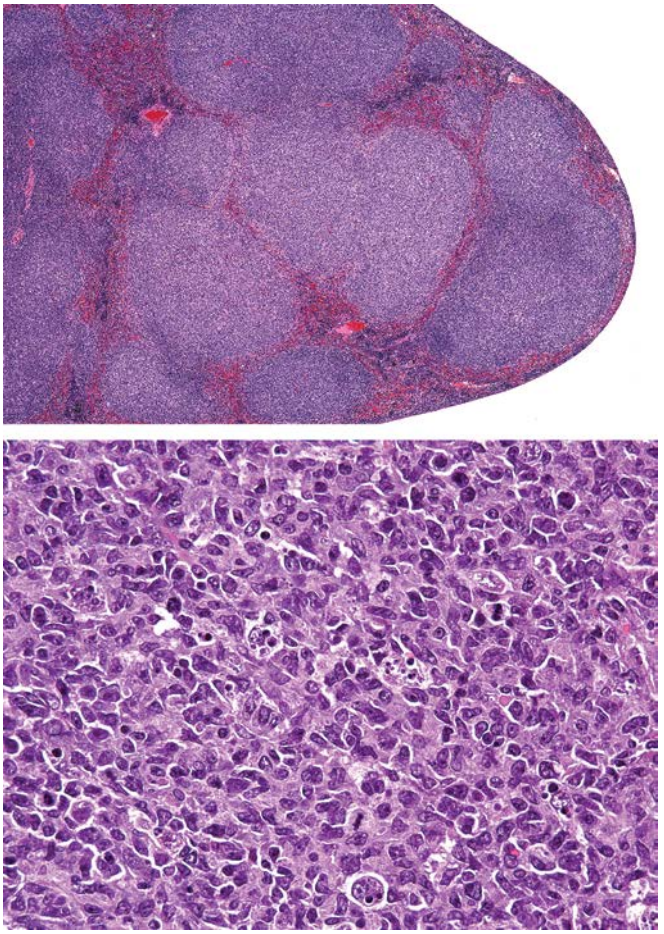


FIGURE 2 Follicular center cell lymphoma with a multinodular presentation in the spleen of an aged mouse. At higher magnification, the pleomorphic cellular nature of the tumor is evident, with variably sized and shaped cells and nuclei, variable numbers of nucleoli, a high mitotic index, and individually necrotic tumor cells. (Figures courtesy of Jerold Rehg, St. Jude Children's Research Hospital.)

Differential diagnoses: Other forms of **lymphoma**; Splenic nodular lymphoid hyperplasia.

Synonym(s): **Reticulum cell sarcoma**; **pleomorphic lymphoma**; **pleomorphic mixed cell lymphoma**.

References

Suttie, A.W. 2006. Histopathology of the spleen. *Toxicol Pathol* 34:466–503.

Ward, J.M., Rehg, J.E., and Morse, III, H.C. 2012. Differentiation of rodent immune and hematopoietic system reactive lesions from neoplasias. *Toxicol Pathol* 40:425–434.

Link

http://journals.sagepub.com/doi/10.1177/0192623311431467

Lymphoma, thymic is a malignant neoplasm composed of sheets of neoplastic homogeneous lymphocytes. This neoplasm originates in the thymus, is of T-cell origin, and may spread to the surrounding tissues and organs such as the liver, spleen, and lymph nodes. They may be spontaneous or toxicologically induced. There may be an intermediate stage called atypical hyperplasia which has been induced by phenolphthalein in an NTP study using both B6C3F1 and p53–deficient mice. Atypical hyperplasia may be unilateral or bilateral with features such as loss of cortical demarcation and replacement of normal thymocytes by sheets of large, atypical lymphocytes with a variable mitotic index. There may be fewer small lymphocytes scattered throughout. Once the cells have extended beyond the capsule, then a diagnosis of thymic lymphoma would be appropriate. The neoplastic lymphocytes in a thymic lymphoma are morphologically different from the normally present heterogeneous thymocytes. The neoplasm may be a lymphoblastic type, composed of large, transformed lymphocytes (lymphoblasts) with prominent amphiphilic cytoplasm, or smaller more hyperchromatic lymphocytes with scant cytoplasm. There may be a "starry

sky" appearance due to the presence of tingible body macrophages that have engulfed apoptotic cell debris. Mitotic figures are common.



FIGURE 3 Thymus atypical hyperplasia in a C56BL/6 P53+/– mouse. The paler staining thymic lobe affected by atypical hyperplasia is on the left and the normal lobe is on the right. The atypical cells have not extended beyond the thymic capsule.

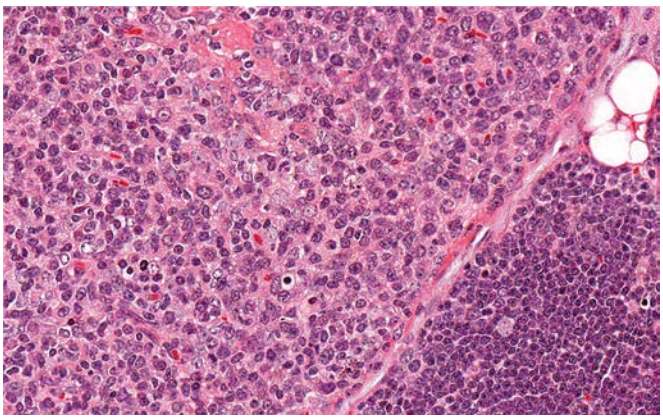


FIGURE 4 Thymus atypical hyperplasia in a C56BL/6 P53+/– mouse. Atypical cells are on the left compared with normal thymus on the right. The atypical lymphocytes are larger with pleomorphic vesicular nuclei and increased eosinophilic cytoplasm.

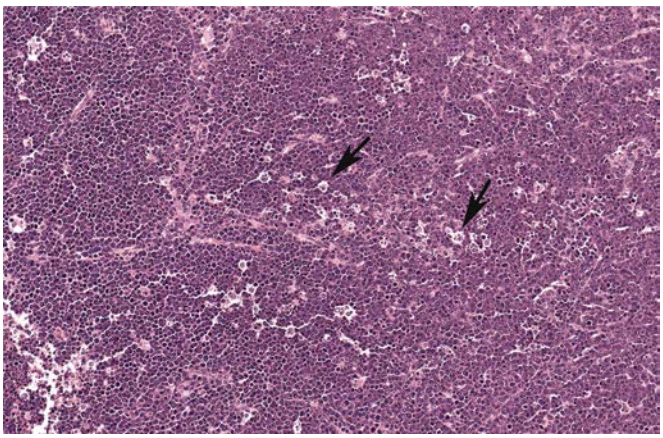


FIGURE 5 Thymic lymphoma in a C56BL/6 P53+/– mouse with scattered apoptotic cells engulfed by tingible body macrophages (arrows). The neoplastic cells are uniform, small and hyperchromatic.



FIGURE 6 Thymic lymphoma in a C56BL/6 P53+/– mouse that has extended beyond the thymic capsule and invaded the surrounding tissue.

References

Dunnick, J.K., Hardisty, J.F., Herbert, R.A., Seely, J.C., Furedi-Machacek, E.M., Foley, J.F., Lacks, G.D., Stasiewicz, S., and French, J.E. 1997. Phenolphthalein induces thymic lymphomas accompanied by loss of the p53 wild type allele in heterozygous p53–deficient (+/–) mice. *Toxicol Pathol* 25:533–540.

National Toxicology Program Technical Report Series No. 465, Toxicology and Carcinogenesis Studies of Phenolphthalein in F344/N Rats and B6C3F1 Mice. https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr465.pdf, last accessed December 05, 2017.

Pearse, G. 2006. Histopathology of the thymus. *Toxicol Pathol* 34:515–547.

Ward, J.M. 2006. Lymphomas and leukemias in mice. *Exp Toxicol Pathol* 57:377–381.

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http://journals.sagepub.com/doi/10.1080/01926230600978458.
https://doi.org/10.1016/j.etp.2006.01.007.

Macrophage hyperplasia is a benign and local increase in the number of macrophages that occurs by proliferation of tissue-resident macrophages within lymphoid and nonlymphoid tissues and in body cavities. A small number of monocytes from circulation (histiocytes) may also enter tissues and body cavities but generally contribute little to local macrophage hyperplasia. Hyperplasia of macrophages generally also results in a change of phenotype to activated macrophages. Macrophage hyperplasia is a reactive response that occurs in response to ingested and inhaled antigens and from trauma, inflammation, necrosis, or neoplasia. Tissue-resident macrophages occur throughout the body, and hyperplasia of these macrophages have previously been designated by tissue-specific terms such as histiocytic hyperplasia and sinus histiocytosis (lymph node sinuses), increased tingible body macrophages (lymph node germinal centers), alveolar histiocytosis (lung), microgliosis (brain), Kupffer cell hyperplasia (liver), osteoclast proliferation (bone),

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and generically as histiocyte aggregates, histiocyte infiltrates, or sometimes incorrectly as granulomatous inflammation.

Synonym(s): **Histiocytic hyperplasia**; **sinus histiocytosis**; **increased tingible body macrophages**; **alveolar histiocytosis**; **microgliosis**; **histiocytic aggregates**; **histiocytic infiltrates**.

References

Davies, L.C., Jenkins, S.J., Allen, J.E., and Taylor, P.R. 2013. Tissue-resident macrophages. *Nat Immunol* 14:986–995.

Haldar, M. and Murphy, K.M. 2014. Origin, development, and homeostasis of tissue-resident macrophages. *Immunol Rev* 262:25–35.

Links

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4045180/
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4203404/

Microgliosis (brain), see the preferred term **Macrophage hyperplasia**.

Mucosa-associated lymphoid tissue (MALT) follicle-associated epithelial (FAE) goblet cell hyperplasia is an increase in goblet cells in the follicle-associated epithelium relative to controls. Usually associated with damage and other changes to the follicle-associated epithelium or underlying lymphoid tissue. This change has been reported after inhalation exposure to acetaldehyde in the nasal-associated lymphoid tissue of rats. The FAE normally contain few goblet cells, and the number relative to epithelial cells appears to vary between species and the MALT examined. Therefore, quantitative assessment of goblet cells may be required, and this diagnosis should be made cautiously from a qualitative evaluation.

References

Kuper, C.F. 2006. Histopathology of mucosa-associated lymphoid tissue. *Toxicol Pathol* 34(5):609–615.

Ermund, A., Gustafsson, J.K., Hansson, G.C., and Keita, Å.V. 2013. Mucus properties and goblet cell quantification in mouse, rat and human ileal Peyer's patches. *PLOS ONE* 8(12):e83688.

Links

http://journals.sagepub.com/doi/full/10.1080/01926230600867735
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0083688

Mucosa-associated lymphoid tissue lymphoma is a B-cell tumor originating from the marginal zone of mucosa-associated lymphoid tissue (MALT) that occurs at sites of MALT and in extranodal tissues. In laboratory animals MALT lymphomas are rare and mostly occur in the stomach associated with gastric bacterial colonization by *Helicobacter* spp. Gastric MALT lymphomas are generally localized with rare metastases and characterized by a dense infiltrate of small lymphocytes that destroy glands and invade the epithelium and may show plasma cell differentiation. Early gastric MALT lymphomas may completely regress following antimicrobial treatment. In laboratory animals, these tumors are of primary interest as research models of tumor promotion by bacterial microbiota.

Differential diagnoses: Stomach adenocarcinoma; **Lymphoma**; Stomach inflammation.

Synonym(s): **Lymphoma, extranodal marginal zone B cell**.

Reference

Kuper, C.F. 2006. Histopathology of mucosa-associated lymphoid tissue. *Toxicol Pathol* 34:609–615.

Link

https://www.ncbi.nlm.nih.gov/pubmed/17067946

Pleomorphic lymphoma, see the preferred term **Lymphoma follicular center cell**.

Pleomorphic mixed cell lymphoma, see the preferred term **Lymphoma follicular center cell**.

Reticulum cell sarcoma, see the preferred term **Lymphoma follicular center cell**.

Sinus histiocytosis, see the preferred term **Macrophage hyperplasia**.

Splenic red pulp nodular hyperplasia is generally found in older rats, particularly the Fisher 344 strain, and usually presents as a solitary nodular mass composed of relatively normal-appearing red pulp with sinusoids, hematopoietic cells, and often hemosiderin, but lacking normal white pulp/lymphoid structures. It is considered most likely to be a hamartoma or congenital malformation. A finding known as nodular hyperplasia is occasionally observed in old dogs as a spontaneous finding. The latter is distinct from the red pulp nodular hyperplasia found in rats in that it can contain both red and white pulp elements. A variant consists of a benign proliferation of fibrohistiocytic cells.

Differential diagnosis: **Follicular center cell lymphoma**.

Reference

Suttie, A.W. 2006. Histopathology of the spleen. *Toxicol Pathol* 34:466–503.

Link

https://doi.org/10.1080/01926230600867750

Splenic red pulp stromal hyperplasia is a rare finding in rodents and is characterized by an increase in the number of splenic red pulp stromal cells, usually with a corresponding contraction and loss of the red pulp venous sinuses with a corresponding decrease in vascularity. Stromal hyperplasia is typically a focal lesion primarily affecting the red pulp, but there may be infiltration into the periarteriolar lymphatic sheaths and marginal zones. Occasionally, there may be corresponding atrophy of the white pulp. Red pulp sinuses may be obliterated or replaced by capillaries, and there may be mature adipocytes within the lesion. In response to congestion, systemic tumor growth, or treatment with a hematotoxic compound, the stromal cells increase either their contractile

properties or their production of extracellular fibers. Thus there may be increased collagen and expression of smooth muscle actin within the hyperplastic stroma. The stromal cells can be derived from any mesenchymal cell compartment, including fibroblasts, myofibroblasts, and smooth muscle cells. Cells have a low mitotic index, and this lesion is not considered to be preneoplastic. The specific causes are unknown, but this finding has been associated with chronic red pulp congestion and treatment with hematotoxic compounds.

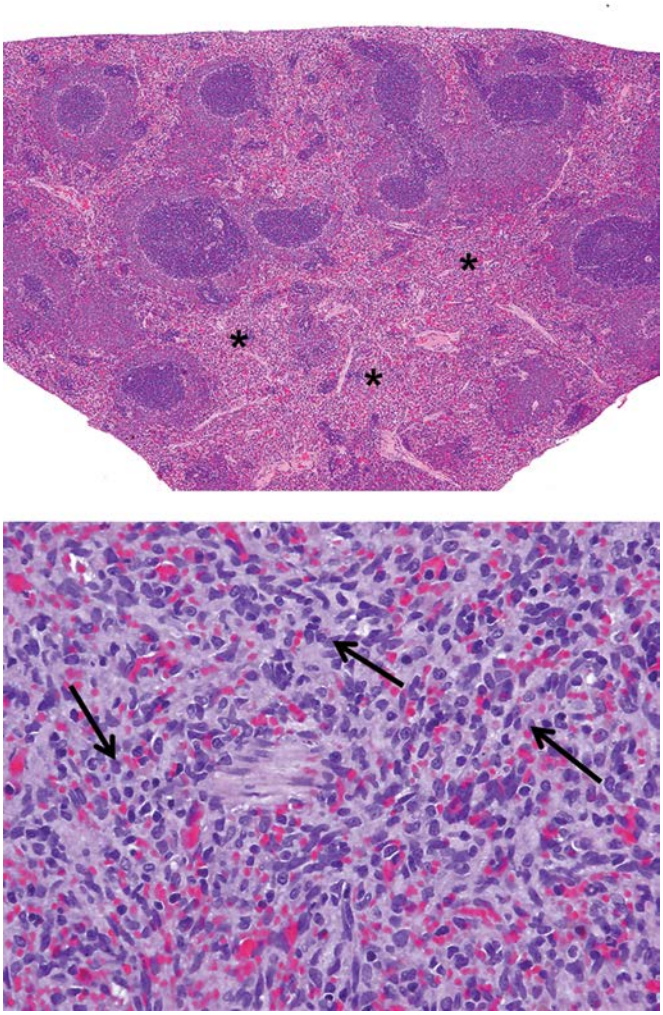


FIGURE 7 Splenic red pulp stromal hyperplasia. At higher magnification, arrows demonstrate hyperplastic red pulp stromal cells.

Reference

Suttie, A.W. 2006. Histopathology of the spleen. *Toxicol Pathol* 34:466–503.

Link

https://doi.org/10.1080/01926230600867750

Thymic epithelial hyperplasia is characterized by tubules or cords with cuboidal to columnar epithelium. Some secretory (goblet) cells may be also be present with pale, eosinophilic proteinaceous fluid within some tubules. Although epithelial cells exist throughout the thymus, they are most prominent in the medullary region, and this is where epithelial hyperplasia typically occurs. Epithelial hyperplasia may be focal or diffuse and is a common age-related finding associated with thymic involution. The degree may vary among different species and strains of rodent, and is more common in rats. This lesion can also be treatment related. As an example, a 2-year rat feed study with the herbicide imazamethabenz-methyl showed a statistically significant increased incidence of thymic epithelial hyperplasia in females at the highest dose of 4000 ppm. Cynomolgus monkeys administered a recombinant derivative of human epidermal growth factor showed pronounced dose-related thymic cortical and medullary epithelial hypertrophy and hyperplasia, although this lesion was not restricted to the thymus.

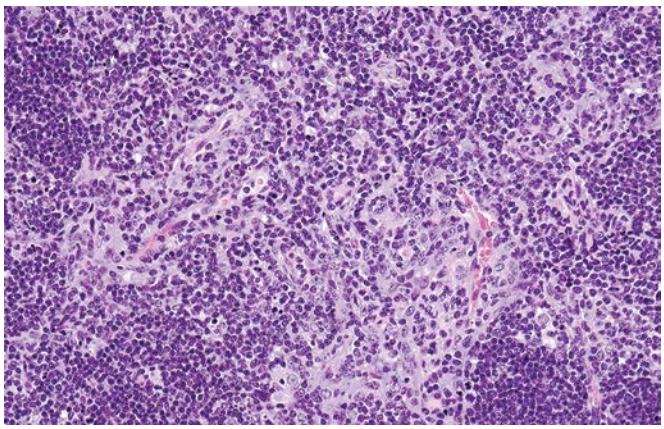


FIGURE 8 Thymic epithelial hyperplasia in a B6C3F1 mouse associated with age-related involution.

References

Hess, F.G., Harris, J.E., Pendine, K., and Ponnock, K. 2001. Imidazolinones, toxicity to laboratory animals (Chapter 74). In: Krieger, R. (ed.) *Handbook of Pesticide Toxicology*, Vol. 2, 2nd ed. San Diego, CA: Academic Press, pp. 1649–1650.

Reindel, J.F., Gough, A.W., Pilcher, G.D., Bobrowki, W.F., Sobocinski, G.P., and De La Iglesia, F.A. 2001. Systemic proliferative changes and clinical signs in cynomolgus monkeys administered a recombinant derivative of human epidermal growth factor. *Toxicol Pathol* 29(2):159–173.

Link

https://www.ncbi.nlm.nih.gov/pubmed/11421483

Thymoma, benign is a neoplasm of the thymus that is characterized by the presence of a neoplastic epithelial component, with or without neoplastic lymphocytes. A lymphoid cell neoplasm originating in the thymus would be diagnosed as a thymic lymphoma. The epithelial component of a benign thymoma may be a minor feature of the neoplasm or comprise a majority of the tumor mass. The lymphocyte component is variable and may be related to the production of trophic factors produced by the neoplastic epithelial cells. Grossly, this tumor is typically firm and encapsulated with a smooth surface and located in the anterior mediastinum. Large thymomas may compress adjacent structures such as the trachea and esophagus. Histologically, thymomas can exhibit a variety of growth patterns. There may be neoplastic but

well-formed tubular epithelial structures of varying size with scant intertubular stroma, well-formed tubular patterns with central areas of squamous differentiation, large areas of squamous cell differentiation with keratin formation, or nodules of nonkeratinized squamous epithelium. If the neoplastic cell component is composed of only lymphocytes, then a diagnosis of thymic lymphoma should be considered if there is no splenic involvement.

Differential diagnoses: **Thymoma, malignant**; Thymic lymphoma.

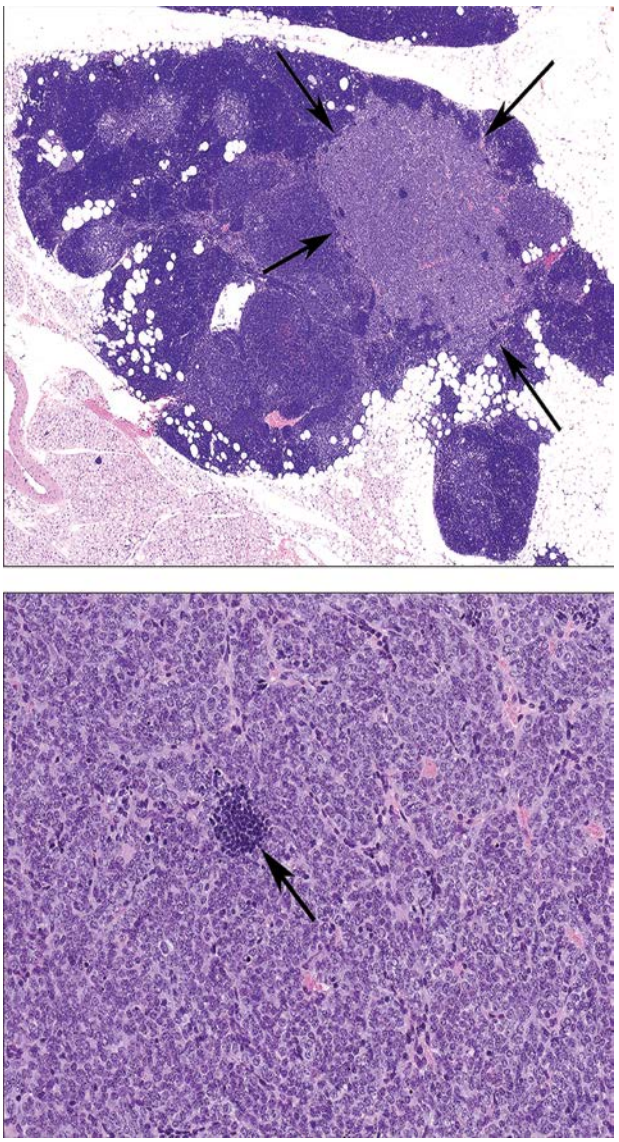


FIGURE 9 Example of a benign thymoma (outlined by arrows) in a 2-year-old B6C3F1 mouse with concurrent age-related involution. At higher magnification, there is a focus of trapped normal thymocytes (arrow). In this example, the neoplastic cell component is epithelial with only a scant fibrovascular stroma.

Reference

Stefanski, S.A., Elwell, M.R., and Stromberg, P.C. 1990. Spleen, lymph nodes and thymus. In: Boorman, G.A., Eustis, S.L., Elwell, M.R., Montgomery, C.A., MacKenzie, W.F. (eds.) *Pathology of the Fischer Rat, Reference and Atlas*. San Diego, CA: Academic Press, p. 392.

Thymoma, malignant may in some ways be morphologically similar to its benign counterpart, but may extend through the capsule and into the adjacent surrounding tissue. This extension through the capsule is what distinguishes the malignant neoplasm from its benign counterpart. Importantly, the term "malignant thymoma" can only be used when there is an epithelial component. A thymic neoplasm composed of only neoplastic lymphocytes should be called "lymphoma, malignant." Thymic epithelial cells are primarily involved in malignant thymomas, generally greater than 80%, and squamous differentiation is often present. However, there may also be a mixture of epithelial cells and lymphocytes. Increased cellular atypia and nuclear polymorphism may also be features. The epithelium may be poorly differentiated and may even resemble a poorly differentiated carcinoma with sheets of pleomorphic epithelioid cells and poorly formed tubules. In the absence of a lymphocytic component, the location of a malignant thymoma

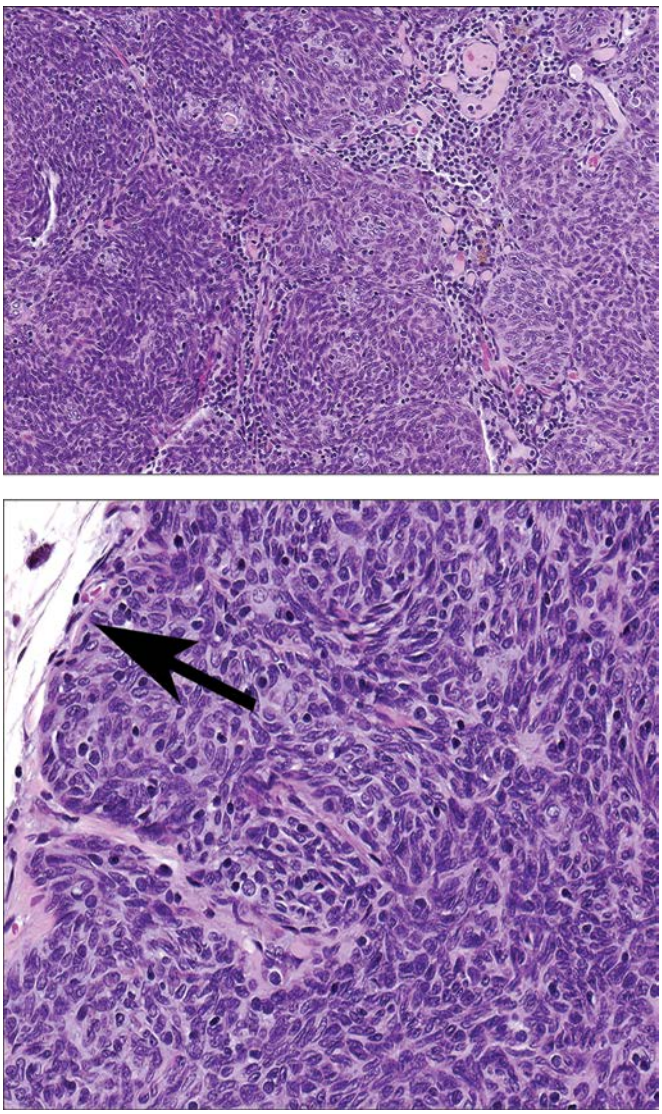


FIGURE 9 Malignant thymoma in a rat with swirls and packets of neoplastic epithelioid cells exhibiting cellular atypia and nuclear polymorphism. At higher magnification, capsular invasion is clearly evident (arrow).

within the thoracic cavity is what can help to distinguish this neoplasm from a squamous cell carcinoma.

Differential diagnosis: **Thymoma, benign**.

Reference

Frith, C.H., Ward, J.M., Harleman, J.H., Stromberg, P.C., Halm, S., Inoue, T., and Wright, J.A. 2001. Hematopoietic system. In: Mohr, U. (ed.) *International Classification of Rodent Tumors, The Mouse*. WHO International Agency for Research and Cancer. Berlin, Heidelberg: Springer-Verlag, pp. 436–437.

NERVOUS SYSTEM

Astrocytoma is a glial tumor of astrocytic origin originating from the neuroepithelial/ectoderm. In toxicologic pathology these tumors are all considered malignant and are further classified as **Astrocytoma, malignant (low grade)** and **Astrocytoma, malignant (high grade)**.

Astrocytoma, malignant (high grade) is a glial neoplasm of neoplastic astrocytes originating from the neuroectoderm. Astrocytes are star-shaped glial cells in the brain and spinal cord that perform many functions, including biochemical support of the endothelial cells that form the blood-brain barrier, supply of nutrients to the nervous tissue, maintenance of extracellular ion balance, and they play a role in the repair and scarring process of the brain and spinal cord following traumatic injuries. Astrocytomas are the most common of all rodent brain tumors. The World Health Organization (WHO) International Histological Classification of Tumors of Domestic Animals classifies astrocytomas as low-grade (well-differentiated), medium-grade (anaplastic), and high-grade astrocytoma (glioblastoma). In toxicologic pathology, astrocytomas are generally noted as malignant, low- or high- grade. Anti-GFAP (glial fibrillary acidic protein) immunohistochemical stains are used to help diagnose tissues of astrocytic origin. The malignant astrocytes in rats and mice do not stain for GFAP, although scavenging reactive astrocytes (gemistocytes), as well as normal astrocytes remain GFAP positive. When gliosis is noted, it is important to comment on whether it is a secondary/reactive response or a proliferative lesion with the biological spectrum extending from hyperplasia to neoplasia. Malignant astrocytomas are highly infiltrative, poorly demarcated, densely cellular, and often multicentric within the brain. Within the tumor parenchyma, hemorrhage and necrosis are common in rats. Characteristic features include invasion along the infiltrating edge into perivascular spaces (Virchow-Robin spaces) and meninges, and pseudopalisading of neoplastic cells around necrotic areas. It is common for the neoplastic cells to surround neurons (satellitosis) and blood vessels. Neoplastic cells are polymorphic, with indistinct cell borders and variably shaped nuclei (round to fusiform). In domestic animals, high-grade astrocytomas are also known as glioblastomas.

Differential diagnoses: **Astrocytoma**; **Astrocytoma, malignant (low grade)**; **Glioblastoma multiforme**.

Synonym(s): **Glioblastoma**; **glioma, astrocytic, malignant**.

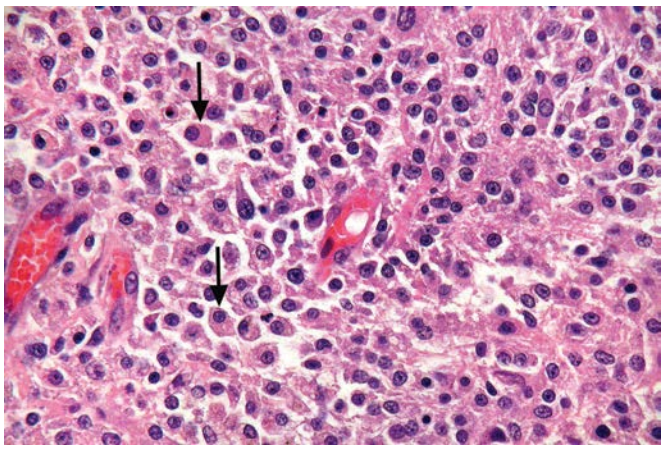


FIGURE 1 Astrocytoma, malignant (high grade). Neoplastic polygonal to spindled cells with mild anisokaryosis and occasional mitotic figures. Cells with enlarged cytoplasm (arrows) likely represent reactive astrocytes (gemistocytes) rather than neoplastic cells. Brain. Rat. H&E. (Copyright 2018 Klaus Weber, AnaPath GmbH, Switzerland.)

Reference

Kaufmann, W. et al. 2012. Proliferative and non-proliferative lesions of the rat and mouse central and peripheral nervous systems. *Toxicol Pathol* 40:87S–157S.

Link

www.ncbi.nlm.nih.gov/pubmed/22637737

Astrocytoma, malignant (low grade) is a glial tumor originating from the neuroectoderm. Astrocytes are star-shaped glial cells in the brain and spinal cord that perform many functions, including biochemical support of the endothelial cells that form the blood-brain barrier, supply of nutrients to the nervous tissue, maintenance of extracellular ion balance, and that play a role in the repair and scarring process of the brain and spinal cord following traumatic injuries. Astrocytomas are the most common of all rodent brain tumors. The World Health Organization (WHO) International Histological Classification of Tumors of Domestic Animals classifies astrocytomas as low-grade (well-differentiated), medium-grade (anaplastic), and high-grade (glioblastoma). In toxicologic pathology, astrocytomas are generally noted as malignant, low-, or high- grade. In rats, low-grade astrocytomas can generally be subclassified as protoplasmic or fibrillary, although this subclassification is not routinely noted in toxicologic pathology. Anti-GFAP (glial fibrillary acidic protein) immunohistochemical stains are used to help diagnose tissues of astrocytic origin. The malignant astrocytes in rats and mice do not stain for GFAP, although scavenging reactive astrocytes (gemistocytes) as well as normal astrocytes remain GFAP positive. When gliosis is noted, it is important to comment on whether it is a secondary/reactive response or a proliferative lesion with the biological spectrum extending from hyperplasia to neoplasia. Low-grade astrocytomas are poorly demarcated, diffusely infiltrative, with low to moderate cellularity, but usually focal within the brain. Within the tumor parenchyma (in mice), a monomorphic population of neoplastic astrocytes are well differentiated, with indistinct

cell borders and moderate eosinophilic cytoplasm containing round or oval nuclei.

Differential diagnoses: **Astrocytosis**; **Astrocytoma, malignant (high grade)**; **Glioma, mixed, low grade**.

Synonym(s): **Astrocytoma, benign**; **astrocytoma, low grade**; **glioma, astrocytic, benign**.

Reference

Kaufmann, W. et al. 2012. Proliferative and non-proliferative lesions of the rat and mouse central and peripheral nervous systems. *Toxicol Pathol* 40:87S–157S.

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www.ncbi.nlm.nih.gov/pubmed/22637737

Astrocytosis is the proliferation of astrocytes in response to injury or tissue defects in the central nervous system (CNS). Wound repair and scar formation in the CNS occur via astrocyte proliferation rather than by fibrosis. Astrocytosis is a type of **gliosis (Gliosis, astrocytosis)**. **Astrocytes** are support cells within the CNS and are far more numerous than neurons. Astrocytes have numerous cell processes, giving them a star-shaped appearance (hence the name astrocytes). The cell processes of astrocytes often end in expansions called end feet. These **astrocytic end feet** surround parenchymal capillaries and completely line the interface of the CNS with other tissues. Astrocytes process waste products from cellular metabolism or toxins in order to protect the neurons. They also take up electrolytes released by neurons during transmission of a nerve impulse and metabolize and recycle many neurotransmitters. Astrocytes are involved in cell-cell communication and monitor and sense the extracellular matrix of the CNS. Reactive astrocytes have a distinctive appearance characterized by large oval nuclei and abundant, clearly visible pale cytoplasm, often with swollen cell processes. This is in contrast to resident, nonreactive astrocytes where the cytoplasm is usually not readily apparent. **Gemistocytes** are reactive astrocytes with abundant pale cytoplasm and eccentric nuclei. Glial fibrillary acidic protein (GFAP) is an intermediate filament protein that helps maintain cytoskeletal integrity and shape. GFAP is found in many cell types, but in the CNS is most prominent in astrocytes and ependymal cells. Immunohistochemical reactions for GFAP are used to identify astrocytes in the CNS. Further discussion is found under the definition of GFAP.

Differential diagnoses: **Gliosis, NOS**; **Astrocytoma, malignant, low grade**.

Synonym(s): **Astrogliosis**; **gemistocytic astrocytes**; **gemistocytosis**; **glial hyperplasia**; **glial hypertrophy**; **gliosis, astrocytic**; **reactive astroglia**.

Reference

Kaufmann, W. et al. 2012. Proliferative and non-proliferative lesions of the rat and mouse central and peripheral nervous systems. *Toxicol Pathol* 40:87S–157S.

Link

www.ncbi.nlm.nih.gov/pubmed/22637737

Astrogliosis, see the preferred terms **Astrocytosis** and **Gliosis.**

Cerebellar neuroblastoma, see the preferred term **Medulloblastoma.**

Chemodectoma, see the preferred term **Paraganglioma.**

Cholesteatoma, see the preferred term **Cholesterol clefts.**

Cholesterol clefts are due to the extracellular accumulation of lipoprotein byproducts left at the site of hemorrhage or necrosis. In paraffin-embedded histologic sections, the resultant crystals are dissolved during processing, leaving empty rhomboid-shaped spaces within a cellular mass or granuloma. This can result in a tumor-like mass occurring most commonly within the choroid plexus of the brain that is composed of inflamed fibrovascular tissue with the presence of cholesterol clefts. Development of the mass likely involves chronic or repeated episodes of congestion and hemorrhage. Masses of large size may result in obstructive hydrocephalus and may compress adjacent parenchyma. These are seen rarely in rodents but may occur in large animals.

Synonym(s): **Cholesteatoma**; **cholesterol granuloma**.

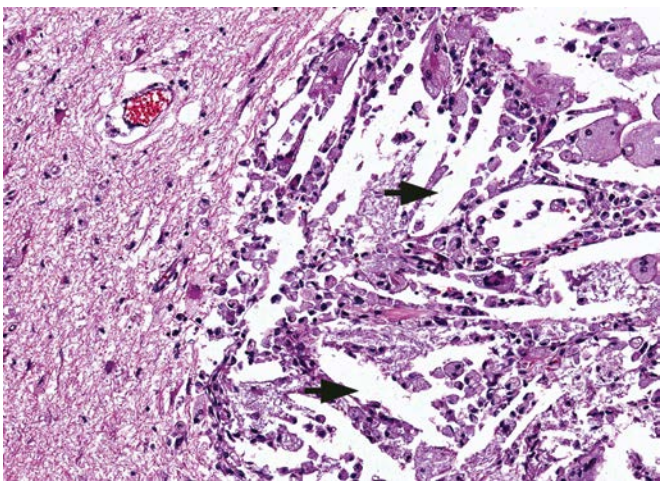


FIGURE 2 Broad linear cholesterol clefts (arrows) within the infiltrates of Gitter cell macrophages are empty spaces left after cholesterol crystals were removed during histologic processing. Brain. Dog. H&E.

Reference

Kaufmann, W. et al. 2012. Proliferative and non-proliferative lesions of the rat and mouse central and peripheral nervous systems. *Toxicol Pathol* 40:87S–157S.

Link

www.ncbi.nlm.nih.gov/pubmed/22637737

Cholesterol granuloma, see the preferred term **Cholesterol clefts.**

Choroid plexus carcinoma is a malignant neoplasm originating from the epithelial cells of the choroid plexus of the brain. Choroid plexus carcinomas are rare in rats and mice. These

neoplasms are usually located in proximity to the anatomic locations of the choroid plexus, and commonly invade the adjacent brain parenchyma. These neoplasms contain poorl to well-developed papillary formations in an arboriform pattern. Pseudostratification of the epithelial layers is frequent with atypical and pleomorphic epithelial cells lining a fibrovascular stroma. In rats, the epithelial cells express transthyretin.

Differential diagnoses: **Choroid plexus papilloma**; **Ependymoma, malignant**.

Synonym(s): None.

Reference

Kaufmann, W. et al. 2012. Proliferative and non-proliferative lesions of the rat and mouse central and peripheral nervous systems. *Toxicol Pathol* 40:87S–157S.

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www.ncbi.nlm.nih.gov/pubmed/22637737

Choroid plexus papilloma is a benign tumor originating from the epithelial cells of the choroid plexus. The choroid plexus is a plexus of cells that produces the cerebrospinal fluid in the ventricles of the brain. Choroid plexus papillomas are rare in rats and mice. These tumors are usually located in proximity to the anatomic locations of the choroid plexus. Choroid plexus papillomas are composed of intricate papillary fronds lining meager fibrovascular stroma. Papillary fronds are composed of a single layer of well developed, cuboidal to columnar epithelial cells containing eosinophilic cytoplasm with round to oval nuclei. Pseudostratification of the epithelial layers is absent, as are mitotic cells. In rats, the epithelial cells express transthyretin and show positive immunoreactivity with cytokeratin antibodies.

Differential diagnoses: **Choroid plexus carcinoma**; **Ependymoma, benign**.

Synonym(s): None.

Reference

Kaufmann, W. et al. 2012. Proliferative and non-proliferative lesions of the rat and mouse central and peripheral nervous systems. *Toxicol Pathol* 40:87S–157S.

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www.ncbi.nlm.nih.gov/pubmed/22637737

Craniopharyngioma is a rare epithelial neoplasm of the sellar region of the brain, presumably derived from remnants of Rathke's pouch. Craniopharyngiomas have been reported in humans, domestic animals, and laboratory animals including rats. Several neoplasms originally reported as craniopharyngioma in dogs have been more recently reclassified as suprasellar germ cell tumors. The sellar region in the basal aspect of the cranial cavity is the recess in which rests the pituitary gland. Craniopharyngiomas may grow to compress the overlying brain and may infiltrate the skull, brain, or pituitary gland. The neoplasm is characterized by stratified squamous epithelium lacking keratohyalin granules with solid and/or cystic areas created by robust hyperkeratosis/parakeratosis.

Differential diagnoses: **Squamous cell carcinoma**; **Zymbal's gland carcinoma**; Rathke's cyst; Epidermoid cyst; Aberrant craniopharyngeal structures; **Teratoma**.

References

Heinrichs, M. and Ernst, H. 2016. Spontaneous malignant craniopharyngioma in an aged Wistar rat. *J Toxicol Pathol* 29(3):195–199.

Weber, K. et al. 2011. Classification of neural tumors in laboratory rodents, emphasizing the rat. *Toxicol Pathol* 39:129–151.

Links

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4963616/#

http://journals.sagepub.com/doi/pdf/10.1177/0192623310392249

Ependymoma, see the preferred term **Ependymoma, benign.**

Ependymoma, anaplastic, see the preferred term **Ependymoma, malignant**.

Ependymoma, benign is a tumor arising from ependymal cells lining the ventricular system of the brain and the central canal of the spinal cord. Ependymomas are rare tumors in rats. These tumors are usually located within proximity to the anatomic locations of the ventricle, aqueduct, and/or the central canal of the spinal cord. The tumors are composed of polygonal ependymal cells with indistinct cytoplasm and cell borders, containing round to oval, hyperchromatic nuclei. Cells are often arranged in rows and rosettes (luminal and perivascular). Cilia and basal bodies (blepharoblasts) are often present in well-differentiated ependymomas. Blepharoblasts are positive for PTAH stain. Ependymomas in rats may include glial elements. Positive immunoreactivity is noted with antibodies to L-glutamate/L-aspartate transporter (GLAST) in both rats and mice.

Differential diagnoses: **Ependymoma, malignant**; **Choroid plexus papilloma**; **Medulloblastoma**.

Synonym(s): None.

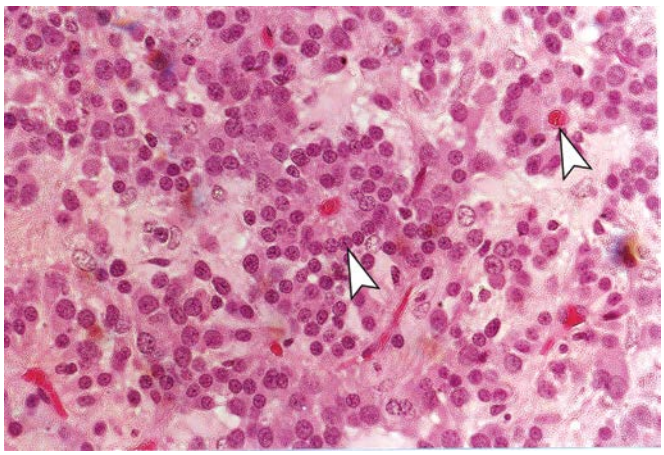


FIGURE 3 Ependymoma, benign. Polygonal to elongate neoplastic cells sometimes arranged in perivascular rosettes (arrowheads). While histologically benign, these neoplasms may grow to compromise the ventricular system. Brain. Rat. H&E. (Copyright 2018 Klaus Weber, AnaPath GmbH, Switzerland.)

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Reference

Kaufmann, W. et al. 2012. Proliferative and non-proliferative lesions of the rat and mouse central and peripheral nervous systems. *Toxicol Pathol* 40:87S–157S.

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www.ncbi.nlm.nih.gov/pubmed/22637737

Ependymoma, malignant is a neoplasm arising from ependymal cells lining the ventricular system of the brain and the central canal of the spinal cord. Ependymomas are rare neoplasms in rats. These neoplasms are usually located within proximity to the anatomic locations of the ventricle, aqueduct, and/or the central canal of the spinal cord with extension into the adjacent brain parenchyma. The neoplasms are composed of atypical pleomorphic neoplastic ependymal cells with high mitotic activity. Cells may be arranged in rows and rosettes (luminal and perivascular). Foci of necrosis, multinucleated giant cells, and glial elements are often present. Positive immunoreactivity is noted with antibodies to L-glutamate/L-aspartate transporter (GLAST) in both rats and mice.

Differential diagnoses: **Ependymoma, benign**; **Oligodendroglioma, malignant**.

Synonym(s): **Ependymoma, anaplastic**.

Reference

Kaufmann, W. et al. 2012. Proliferative and non-proliferative lesions of the rat and mouse central and peripheral nervous systems. *Toxicol Pathol* 40:87S–157S.

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www.ncbi.nlm.nih.gov/pubmed/22637737

Esthesioneuroblastoma, see the preferred term **Neuroepithelial carcinoma**.

Esthesioneuroepithelioma, see the preferred term **Neuroepithelial carcinoma**.

Gangliocytoma or **Ganglioglioma** are subtypes of ganglion cell tumors. See **Ganglion cell tumor** for further information.

Ganglion cell tumor is a tumor of the ganglion cells. A ganglion cell is a neuron the cell body of which is located outside the limits of the brain and spinal cord, hence forming part of the peripheral nervous system. They include gangliogliomas, ganglioneuromas, gangliocytomas, ganglioneuroblastomas. Ganglioneuromas are rare tumors of the autonomic nervous system and are composed of both neuronal (ganglion cells) and peripheral glial cells (Schwann cells and satellite) within a neurofibrillary matrix. Ganglioneuroblastoma is the malignant counterpart to ganglioneuroma.

Differential diagnoses: Pheochromcytoma; Neuroblastoma; **Neurofibroma** (if ganglion cells within the lesion are sparse).

Synonym(s): **Ganglioneuroma**; **ganglioneuroblastoma**.

References

Reznik, G., Ward, J.M., and Reznik-Schuller, H. 1980. Ganglioneuromas in the adrenal medulla of F344 rats. *Vet Pathol* 17:614–621.

Weber, K. et al. 2011. classification of neural tumors in laboratory rodents, emphasizing the rat. *Toxicol Pathol* 39:129–151.

Links

http://journals.sagepub.com/doi/abs/10.1177/030098588001700510?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed

http://journals.sagepub.com/doi/pdf/10.1177/0192623310392249

Ganglioneuroma or **Ganglioneuroblastoma** are subtypes of ganglion cell tumors. See **Ganglion cell tumor** for further information.

Gemistocytic astrocytosis, see the preferred term **Astrocytosis**.

Gemistocytosis, see the preferred term **Astrocytosis**.

Glial cell tumor is a synonym for any of the subtypes of gliomas. See the preferred terms **Glioma mixed malignant; Astrocytoma malignant**; **Oligodendroglioma**.

Glial hyperplasia or **Glial hypertrophy**, see the preferred terms **Astrocytosis** or **Gliosis**.

Glial reaction, see the preferred term **Gliosis**.

Glioblastoma (in large animals including dogs and nonhuman primates), see the preferred term **Astrocytosis, malignant, high grade**.

Glioblastoma multiforme (GBM) is a diagnosis that is typical in human neuro-oncology. In veterinary and toxicologic pathology, the malignant mixed (anaplastic) glioma in rodents shares some histological features with the human tumor termed glioblastoma multiforme. However, multinucleated giant cells and endothelial cell proliferation are not rodent features. Some pathologists limit the diagnosis of glioblastoma multiforme to human tumors. Accordingly, the preferred term in toxicologic pathology is **Glioma, mixed, malignant, high grade (rodent)**.

Glioma is a tumor composed of one or more of the glial cell subtypes in the brain. In toxicologic pathology, gliomas are further subclassified according to the type of neoplastic glial cell, such as glioma, astrocytic and glioma, oligodendrocytic, which are synonyms for astrocytoma or oligodendroglioma, respectively. Glioma, mixed, malignant refers to a glioma of multiple cell types. See **Astrocytoma, Oligodendroglioma, Glioma mixed malignant**, or **Glioblastoma multiforme**.

Glioma, anaplastic (rodent), see the preferred term **Glioma, mixed, malignant high grade (rodent)**.

Glioma, astrocytic (benign or malignant), see the preferred term **Astrocytoma, malignant (low or high grade)**.

Glioma, mixed, malignant (low grade) is a mixed glial neoplasm of both astrocytic and oligodendrocytic origin arising from the neuroectoderm. Low-grade malignant mixed gliomas are often well delineated and focal within the CNS. Mixed gliomas consist of an admixture of neoplastic oligodendrocytes and astrocytes either intermingled in various proportions or present as large regions containing predominantly a single cell type next to each other. In mixed gliomas, each glial cell provides at least 20% of the neoplasm. Compared to astrocytomas and oligodendrogliomas, the neoplastic astrocytes or oligodendrocytes comprise more than 80% of the tumor. The diagnosis is generally driven by the predominant cell type, and the diagnosis of a mixed glioma should be limited to those cases in which there is an approximately equal distribution of both cell types. Vascular endothelial cell hypertrophy and hyperplasia may be present, but necrosis and hemorrhage are usually absent. Neoplastic astrocytes lack immunoreactivity to glial fibrillary acidic protein (GFAP) in rats and mice, although reactive astrocytes as well as normal astrocytes remain GFAP positive. Neoplastic oligodendrocytes stain positively for galactose cerebroside and carbonic anhydrase C.

Differential diagnoses: **Oligodendroglioma, malignant, low grade**; **Astrocytoma, malignant, low grade**; **Glioma, mixed, malignant, high grade**.

Synonym(s): **Oligoastroglioma, benign**.

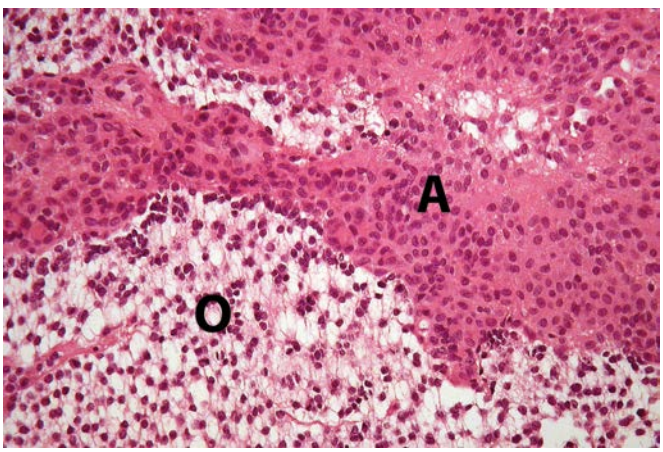


FIGURE 4 Glioma, mixed, malignant (low grade). Neoplastic oligodendrocytes have ample pale/clear cytoplasm (halo formation) and a small round to oval dark nucleus that imparts the so-called "honeycomb" structure. Neoplastic astrocytes have a small, oval, less hyperchromatic nucleus, a moderate amount of eosinophilic cytoplasm, and indistinct cell borders. Brain. Rat. H&E. (Copyright 2018 Klaus Weber, AnaPath GmbH, Switzerland.)

Reference

Kaufmann, W. et al. 2012. Proliferative and non-proliferative lesions of the rat and mouse central and peripheral nervous systems. *Toxicol Pathol* 40:87S–157S.

Link

www.ncbi.nlm.nih.gov/pubmed/22637737

Glioma, mixed, malignant high grade (rodent) is a mixed glial neoplasm of astrocytic and oligodendrocytic origin arising from the neuroectoderm. High-grade malignant mixed gliomas are diffusely infiltrative with indistinct borders and multifocal within the CNS. Like low-grade mixed gliomas, each glial cell type (oligodendrocytes and astrocytes) comprise at least 20% of the neoplasm, and both cell types are intermingled in various proportions, although astrocytic or oligodendrocytic differentiation may not be apparent. Cellular atypia and pleomorphism are common, and tumor giant cells may occasionally be present. The anaplastic features of this glioma in rodents are similar to the human lesion termed glioblastoma multiforme. Marked vascular proliferation, foci of necrosis, edema, and hemorrhage may occur. Neoplastic astrocytes lack glial fibrillary acidic protein (GFAP) labeling in rats and mice. Neoplastic oligodendrocytes stain positively for galactose cerebroside and carbonic anhydrase C.

Differential diagnoses: **Oligodendroglioma, malignant, high grade**; **Astrocytoma, malignant, high grade**; **Glioma, mixed, malignant, low grade**.

Synonym(s): **Glioma, anaplastic** (rodent); **glioblastoma multiforme** (humans).

Reference

Kaufmann, W. et al. 2012. Proliferative and non-proliferative lesions of the rat and mouse central and peripheral nervous systems. *Toxicol Pathol* 40:87S–157S.

Link

www.ncbi.nlm.nih.gov/pubmed/22637737

Glioma, oligodendrocytic, benign, see the preferred term **Oligodendroglioma, malignant, low grade.**

Glioma, oligodendrocytic, malignant, see the preferred term **Oligodendroglioma, malignant, high grade**.

Gliosis (not otherwise specified [NOS]) is increased size (hypertrophy) and/or number (hyperplasia) of glial cells (not neurons) within the central nervous system (CNS) occurring in response to damaged tissue. Gliosis of any glial cell subtype is a common, nonspecific, reactive, and reparative response to injury that may resolve after the injury subsides or remain as an encapsulating astrocytic scar. In response to any type of damage, cell loss, or inflammation within the CNS, glial cells will proliferate. Generally, reactive glial cells involve the resident immune cells (microglia or astrocytes), and less commonly include reactive oligodendroglia (the myelin-forming cells in the CNS). The microscopic characteristics of the cells will usually enable further identification as to the subtype of glial cell involved, either through evaluation of standard H&E-stained sections and/or with immunohistochemical methods to label cellular markers such as glial fibrillary acidic protein (GFAP) for astrocytes and iba-1 for microglia. Astrocytes are the primary glial cells in the CNS, and are large cells with large, oval nuclei, lots of cytoplasm, and numerous cell processes radiating out from the cell body (hence the name astrocytes—resembling stars). Although astrocytes have abundant cytoplasm, when quiescent their cytoplasm is not readily apparent

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in hematoxylin and eosin–stained sections but becomes more evident with GFAP labeling. Microglia are small cells with rod-shaped, often wavy nuclei (hence the synonym "rod cells"), and very little cytoplasm when quiescent. Oligodendroglia have small round nuclei with a thin rim of cytoplasm. In reaction to neuronal loss or damage, oligodendroglia may form a ring around the damaged cell (satellitosis). In the peripheral nervous system (PNS), reactive glial lesions involve Schwann cells, which proliferate to form tubular structures (bands of Bungner) that serve to guide regrowing axons until synaptic connections can be reestablished. "Gliosis," without further qualification, is a nonspecific term. Where possible it is preferred to identify the reactive glial cell type(s) more precisely with terms such as "astrocytosis," "microgliosis," or "oligodendrocyte satellitosis." Each of these terms is a synonym and/or subtype of gliosis.

Differential diagnoses: **Astrocytosis**; **Microgliosis**; **Oligodendrocyte satellitosis**.

Synonym(s): **Astrocytosis**; **astrogliosis**; **gemistocytosis**; **glial hyperplasia**; **glial hypertrophy**; **microgliosis**; **oligodendrocyte satellitosis**.

Reference

Kaufmann, W. et al. 2012. Proliferative and non-proliferative lesions of the rat and mouse central and peripheral nervous systems. *Toxicol Pathol* 40:87S–157S.

Link

www.ncbi.nlm.nih.gov/pubmed/22637737

Gliosis, astrocytic, see the preferred term **Astrocytosis**.

Gliosis, microglial, see the preferred term **Microgliosis**.

Gliosis, oligodendrocytic, see the preferred term **Oligodendrocyte satellitosis**.

Granular cell aggregates are uncommon, non-space–occupying small clusters of cells of uncertain origin with distinct cell boundaries and abundant finely granular cytoplasm, most commonly found as single cells or small clusters of cells within the meninges. Characteristic intracytoplasmic eosinophilic granules stain positively for periodic acid-Schiff (PAS) with diastase resistance and are Alcian blue positive, consistent with ultrastructural evidence for abundant lysosomes. Small round hyperchromatic nuclei are most often centrally located. These granular cell aggregates do not compress adjacent tissues as may be seen with granular cell tumors.

Differential diagnosis: **Granular cell tumor, benign**.

Synonym(s): None.

Reference

Kaufmann, W. et al. 2012. Proliferative and non-proliferative lesions of the rat and mouse central and peripheral nervous systems. *Toxicol Pathol* 40:87S–157S.

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www.ncbi.nlm.nih.gov/pubmed/22637737

Granular cell tumor, benign is a tumor of uncertain origin, but current evidence favors neural crest origin for both rat and human tumors. In rats, the origin is likely an arachnoid cell precursor. Benign granular cell tumors are common in rat chronic studies. Generally, they are compressive but noninvasive micronodular masses confined to the meninges. The tumor is composed of generally homogenous polygonal cells with central to eccentric, round to oval nuclei within a fine vascular stroma. The cytoplasm often contains eosinophilic granules that stain positively with periodic acid-Schiff (PAS) stain. Mitotic figures are generally absent. Other cell types include small round cells with sparsely granular cytoplasm and chromatin-dense nuclei. Mitotic figures are generally absent.

Differential diagnoses: **Granular cell aggregates**; **Granular cell tumor, malignant**.

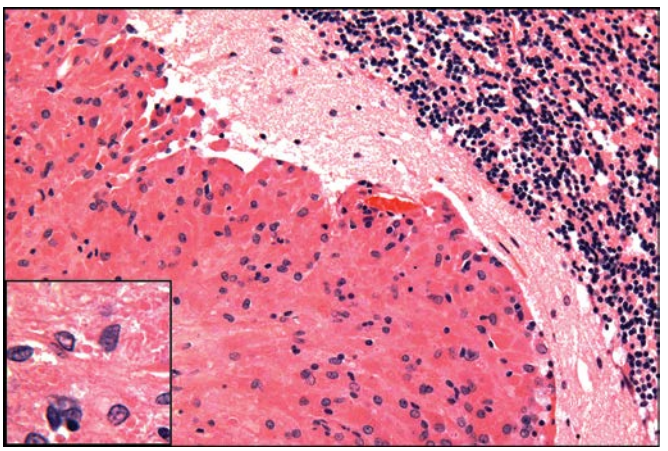


FIGURE 5 Granular cell tumor, benign. A well-demarcated compressive but noninvasive mass composed of densely packed large epithelioid cells with ample cytoplasm densely packed with eosinophilic granules. Brain. Rat. H&E. (Copyright 2018 Klaus Weber, AnaPath GmbH, Switzerland.)

Reference

Kaufmann, W. et al. 2012. Proliferative and non-proliferative lesions of the rat and mouse central and peripheral nervous systems. *Toxicol Pathol* 40:87S–157S.

Link

www.ncbi.nlm.nih.gov/pubmed/22637737

Granular cell tumor, malignant is a tumor of uncertain origin, but current evidence favors neural crest origin for both rat and human tumors. Like their benign counterpart, malignant granular cell tumors are compressive micronodular masses confined to the meninges. However, in addition to compression, there is invasion into the adjacent brain. The neoplasm is supported by a fine fibrovascular stroma and composed of a relatively homogenous population of polygonal cells with a central to eccentric, round to oval nucleus. Mild to moderate anisocytosis and occasional megakaryocytosis may be seen. The cytoplasm often contains eosinophilic granules that stain positively with periodic acid-Schiff (PAS) stain. Other cell types include small round cells with sparsely granular

cytoplasm and chromatin-dense nuclei. Mitotic figures are generally absent.

Differential diagnosis: **Granular cell tumor, benign**.

Reference

Kaufmann, W. et al. 2012. Proliferative and non-proliferative lesions of the rat and mouse central and peripheral nervous systems. *Toxicol Pathol* 40:87S–157S.

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Harmartoma, lipomatous is a benign focal malformation characterized by adipose tissue growing as a disorganized mass. See **Hamartoma** for further information.

Histiocytic sarcoma of the brain, see the preferred term **Reticulosis, malignant**.

Lymphoma of the nervous system, primary, see the preferred term **Reticulosis, malignant**.

Lymphoreticulosis in the brain see the preferred term **Reticulosis, malignant**.

Medulloblastoma is a primitive neuroectodermal tumor (PNET) that originates in the cerebellum and can be locally infiltrative and metastasize within the central nervous system. It is the most common malignant brain tumor in children but rarely reported in preclinical species. The tumor cells are uniform and frequently resemble the granule cell layer of the cerebellar cortex, with small, round or elongated (carrot-shaped) hyperchromatic nuclei, prominent nucleoli, and scant cytoplasm with indistinct cellular margins. The tumor cells can form whorls and pseudorosettes, have bizarre mitotic figures, and exhibit neuronal differentiation.

Synonym(s): **Cerebellar neuroblastoma**; **primitive neuroectodermal tumor (PNET) of cerebellum**.

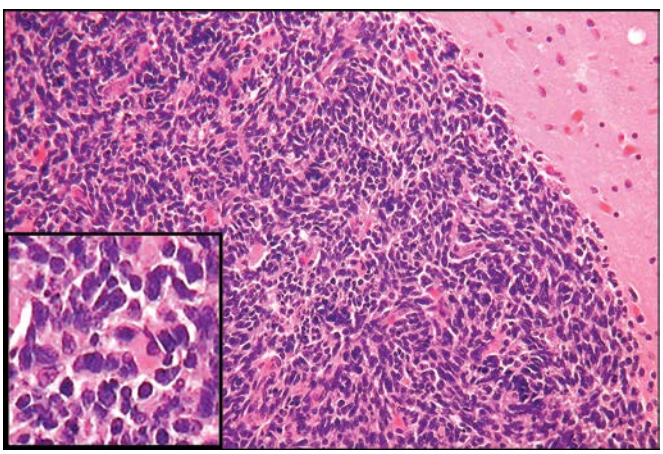


FIGURE 6 Medulloblastoma. A well-demarcated compressive mass composed of densely packed small cells with oval to elongate hyperchromatic nuclei and scant cytoplasm. Brain. Rat. H&E. (Copyright 2018 Klaus Weber, AnaPath GmbH, Switzerland.)

Reference

Kaufmann, W. et al. 2012. Proliferative and non-proliferative lesions of the rat and mouse central and peripheral nervous systems. *Toxicol Pathol* 40:87S–157S.

Link

www.ncbi.nlm.nih.gov/pubmed/22637737

Meningeal sarcoma, see the preferred term **Meningioma, malignant**.

Meningioangiomatosis is a benign proliferative vascular malformation (hamartoma) in the meninges covering the central nervous system (CNS) and often extending perivascularly into the parenchyma of the brain, or along vascular foramina in the skull, often bilaterally distributed along the midline. Grossly this may appear as a plaque-like thickening of the meninges. Microscopically the cells are spindle shaped with occasional polygonal cells, and lack features of neoplasia such as polymorphism or high mitotic rate. The cells may be vimentin positive and some may be α-smooth muscle actin positive.

Differential diagnosis: **Meningioma, benign**.

Synonym(s): None.

Reference

Kaufmann, W. et al. 2012. Proliferative and non-proliferative lesions of the rat and mouse central and peripheral nervous systems. *Toxicol Pathol* 40:87S–157S.

Link

www.ncbi.nlm.nih.gov/pubmed/22637737

Meningioma, benign is a clearly defined, well-demarcated mass within the meninges overlying the brain, spinal cord, or cranial nerves. These masses are well demarcated and often compress, but do not invade adjacent tissue. They may be composed primarily of elongated spindle or fusiform cells (fibroblastic type), or primarily of larger epithelioid cells (meningothelial type), or a mixture of these cells (mixed type). In rats they may also have granular cells. Mitoses are uncommon (low mitotic rate).

Differential diagnoses: **Granular cell tumor, benign**; **Meningioma, malignant**; Meningiomatosis; **Histiocytic sarcoma**; **Reticulosis, malignant**.

Synonym(s): None.

Reference

Kaufmann, W. et al. 2012. Proliferative and non-proliferative lesions of the rat and mouse central and peripheral nervous systems. *Toxicol Pathol* 40:87S–157S.

Link

www.ncbi.nlm.nih.gov/pubmed/22637737

Meningioma, malignant is a poorly circumscribed mass or plaque on the surface of the brain, spinal cord, or cranial nerves that is clearly associated with the meninges. These tumors are highly cellular and invade along the adventitia of blood vessels without clear demarcation between tumor and

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normal tissue. The constituent cells may be fibrous, spindloid, or undifferentiated and may represent the same type of neoplastic cell showing different types of differentiation. This tumor is characterized by bundles of neoplastic cells arranged in interlacing or irregular patterns. The tumor cells are surrounded by variable amounts of collagen. Fibrous and spindloid tumors have elongated nuclei and nucleoli with eosinophilic (fibrous) to basophilic (spindloid) cytoplasm. Undifferentiated sarcomas have pleomorphic cells with bizarre nuclei forming occasional multinuclear giant cells. Mitotic figures are numerous and may be bizarre.

Differential diagnoses: **Meningioma, benign**; **Histiocytic sarcoma**.

Synonym(s): **Meningeal sarcoma**.

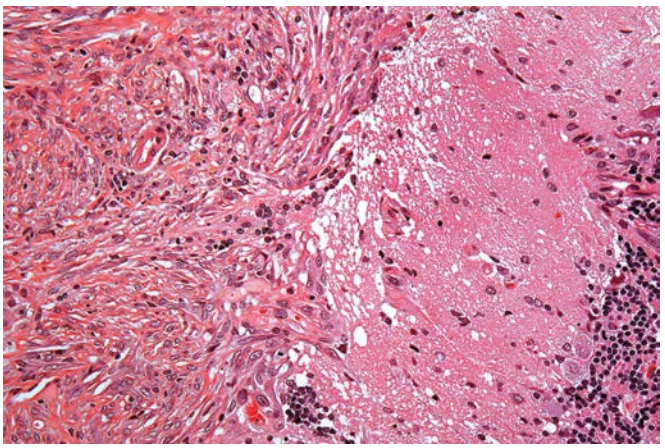


FIGURE 7 Meningioma, malignant. Interweaving bundles of neoplastic spindled cells overlie and infiltrate the cerebellar cortex. Brain. Rat. H&E. (Copyright 2018 Klaus Weber, AnaPath GmbH, Switzerland.)

Reference

Kaufmann, W. et al. 2012. Proliferative and non-proliferative lesions of the rat and mouse central and peripheral nervous systems. *Toxicol Pathol* 40:87S–157S.

Link

www.ncbi.nlm.nih.gov/pubmed/22637737

Microglial cell nodule, see the preferred term **Neuronophagia**.

Microglial cell proliferation, see the preferred term **Microgliosis**.

Microgliomatosis, see the preferred term **Reticulosis, malignant**.

Microgliosis is a focal or multifocal accumulation of microglial cells. Microglia serve as resident macrophages, the primary immune effector cells within the central nervous system (CNS), and are thought to be derived from the monocyte-macrophage cell line. Like monocytes and macrophages in other organs, microglia are involved in immune surveillance, are antigen-presenting cells, secrete cytokines in response to inflammatory stimuli, and maintain homeostasis by phagocytosing and removing cell debris resulting from metabolism or following injury. Microgliosis is a nonspecific reaction to inflammation or injury in the CNS, and in times of high demand, monocytes can be recruited from the peripheral circulation to become tissue microglia. Quiescent microglia are small cells with small, spindle-shaped or wavy nuclei and scant cytoplasm (also called **rod cells**). When actively phagocytic in response to injury, microglia become enlarged with numerous small cytoplasmic vacuoles; these actively phagocytic microglia are called **Gitter cells.**

Differential diagnoses: **Gliosis, not otherwise specified**; **Astrocytosis.**

Synonym(s): **Microglial cell proliferation**; **reactive microglia**; **gitter cells**; **gliosis not otherwise specified**.

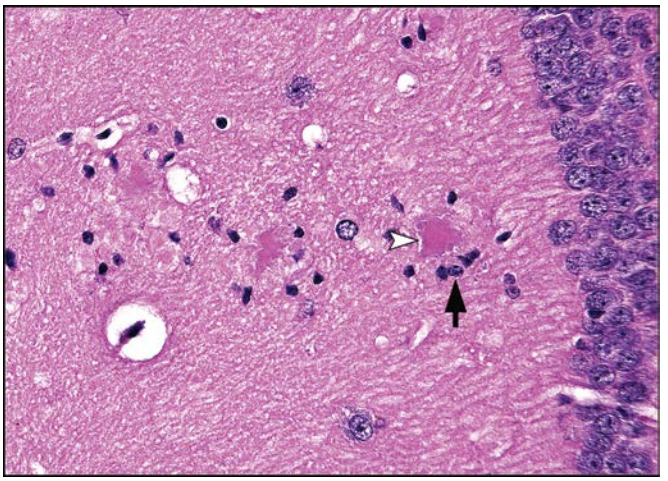


FIGURE 8 Microgliosis. Small, dark, oval to elongated microglial cell nuclei (black arrow) surround irregularly shaped hyaline eosinophilic deposits of β-amyloid (white arrow) in an animal model of human amyloid plaque. Brain. PDAPP mouse. H&E.

Reference

Kaufmann, W. et al. 2012. Proliferative and non-proliferative lesions of the rat and mouse central and peripheral nervous systems. *Toxicol Pathol* 40:87S–157S.

Link

www.ncbi.nlm.nih.gov/pubmed/22637737

Neurilemmoma, see the preferred term **Schwannoma**.

Neurinoma, see the preferred term **Schwannoma**.

Neuroepithelial carcinoma is an uncommon tumor in preclinical species and humans arising from the neuroblasts of the nasal olfactory epithelium. In the nasal cavity, these tumors can attach to the ethmoid turbinates and nasal bones and frequently infiltrate the paranasal sinuses and cribriform plate resulting in intracranial extension to the frontal lobes. The tumor is highly cellular, comprised of cells arranged in islands and clusters separated by fine fibrovascular stroma. Cells can form pseudorosettes

(peritrabecular and perivascular structures) with densely basophilic nuclei with fine chromatin, and a basophilic nucleolus. Tumor cells can express PGP 9.5, CD 56, S-100, NSE, and vimentin. The morphology of this neoplasm is heterogeneous and the histogenic origin is unclear. When it is thought to arise from the basal cells of the olfactory neuroepithelium, it is called an esthesioneuroblastoma or esthesioneuroepithelioma. These tumors have been chemically induced in rats, dogs, and mink, and described in cats, horses, carp, and humans where the tumor is of spontaneous origin. Chemicals that damage the olfactory epithelium directly via inhalation most frequently affect the most rostral olfactory epithelium lining the dorsal medial meatus. Chemicals that require metabolism to a toxic intermediate will usually induce lesions throughout the olfactory epithelium. The development of olfactory tumors induced by chemicals is not related to the route of administration of the chemical but is directly associated with chemical metabolism in nasal basal cells that leads to neoplastic transformation. The mink has been proposed as a model for nasal tumor induction because of its markedly expanded nasal mucosa, and has had 100% incidence of olfactory tumor development following subcutaneous exposure to N′-nitrosonornicotine.

Differential diagnosis: None.

Synonym(s): **Esthesioneuroblastoma**; **esthesioneuroepithelioma**; **olfactory neuroblastoma**; **olfactory neuroepithelioma**; **olfactory carcinoma**.

References

Koppang, N. et al. 1992. A study of tobacco carcinogenesis XCVIII Carcinogenicity of N'-nitrosonornicotine in mink. *Carcinogenesis* 13:1957–1960.

Renne, R. et al. 2009. Proliferative and Nonproliferative lesions of the rat and mouse respiratory tract. *Toxicol Pathol* 37:5S–73S.

Thompson, L.D.R. 2009. Olfactory neuroblastoma. *Head Neck Pathol* 3:252–259.

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https://www.ncbi.nlm.nih.gov/pubmed/1423862
http://tpx.sagepub.com/content/37/7_suppl/5S

Neuroepithelioma, olfactory, see the preferred term **Neuroepithelial carcinoma.**

Neuroma is a nonneoplastic proliferation of Schwann cells around regenerating axons in the peripheral nervous system. Neuromas can form after transection or partial transection of a peripheral nerve or following repetitive trauma to an area. Neuromas can result in severe neuropathic pain, and functional impairment. When peripheral nerves are transected, a variety of techniques has been proposed to prevent the formation of neuromas, with varying success. Animal models have been developed to study the formation and treatment or prevention of neuroma.

Differential diagnosis: **Schwannoma, benign**.

Synonym(s): None.

Reference

Toia, F., Giesen, T., Giovanoli, P., and Calcagi, M. 2015. A systematic review of animal models for experimental neuroma. *J Plast Reconstr Aesthet Surg* 68:1447–1463.

Link

http://www.sciencedirect.com/science/article/pii/S1748681515002417

Neuromyoblastoma, malignant is a tumor of neuronal precursor cells typically found in the ventral cranial cavity near the pituitary gland and adjacent nerves; this tumor is rare in rodents. These tumors are composed of two cell populations (neuroblastic and myoblastic) in varying compositions and proportions. Neuroblastic cells have round to oval nuclei, no nucleolus, poorly defined cytoplasm, and generally lack mitotic figures (neuronal differentiation). Myoblastic cells (muscle differentiation) are pleomorphic with often multiple nuclei with prominent nucleoli, abundant cytoplasm that may contain intracytoplasmic fibers with cross-striations like muscle cells, and may be elongated or round. Mitotic figures can be common and occasionally bizarre.

Differential diagnoses: **Medulloblastoma**; Peripheral nerve sheath tumor, malignant; **Teratoma**.

Synonym(s): None.

Reference

Kaufmann, W. et al. 2012. Proliferative and non-proliferative lesions of the rat and mouse central and peripheral nervous systems. *Toxicol Pathol* 40:87S–157S.

Link

www.ncbi.nlm.nih.gov/pubmed/22637737

Olfactory neuroblastoma, see the preferred term **Neuroepithelial carcinoma.**

Olfactory neuroepithelioma, see the preferred term **Neuroepithelial carcinoma.**

Oligoastroglioma, benign, see the preferred term **Glioma, mixed, malignant (low grade).**

Oligodendrocyte satellitosis represents rings of reactive oligodendroglia near a degenerating neuronal cell body in the central nervous system (CNS). Oligodendroglia are cells that produce myelin within the central nervous system and wrap around axons to insulate and speed the transmission of nerve impulses. Oligodendroglia have a distinct cell morphology consisting of a round central nucleus surrounded by a thin rim (halo) of pale cytoplasm. Satellitosis will develop secondary to primary neuronal degeneration, and clustering of these cells near or around degenerating neurons may serve a supportive or protective function for the adjacent neurons, as oligodendroglia are not generally a reactive cell population. One or two oligodendroglia immediately adjacent to neuronal cell bodies does occur as a normal feature in the CNS, and therefore the diagnosis of satellitosis should be made only after

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careful comparison to the same anatomic area in controls to verify a clear increase in numbers of these perineuronal cells. Oligodendrocyte satellitosis can also be considered a subtype of gliosis. Note that the term "satellitosis" is also used in dermatology to describe lymphocytes surrounding degenerating or necrotic keratinocytes.

Differential diagnosis: None.

Synonym(s): **Reactive oligodendroglia**.

Reference

Kaufmann, W. et al. 2012. Proliferative and non-proliferative lesions of the rat and mouse central and peripheral nervous systems. *Toxicol Pathol* 40:87S–157S.

Link

www.ncbi.nlm.nih.gov/pubmed/22637737

Oligodendroglioma, anaplastic, see the preferred term **Oligodendroglioma, malignant, high grade**.

Oligodendroglioma, benign, see the preferred term **Oligodendroglioma, malignant, low grade**.

Oligodendroglioma, malignant, high grade are well-circumscribed tumors extending over multiple areas of the brain or spinal cord that can infiltrate the meninges. These tumors are highly cellular, with often focal to diffuse areas of atypical pleomorphic cells, with variable nuclei and increased mitotic index. Some cells may have typical oligodendrocyte morphology with round central nuclei surrounded by a halo of pale cytoplasm, and distinct cell borders. This tumor is often accompanied by vascular proliferation at the periphery with characteristic atypical capillary endothelial hyperplasia, and frequent foci of necrosis with cysts and hemorrhage/hemosiderin.

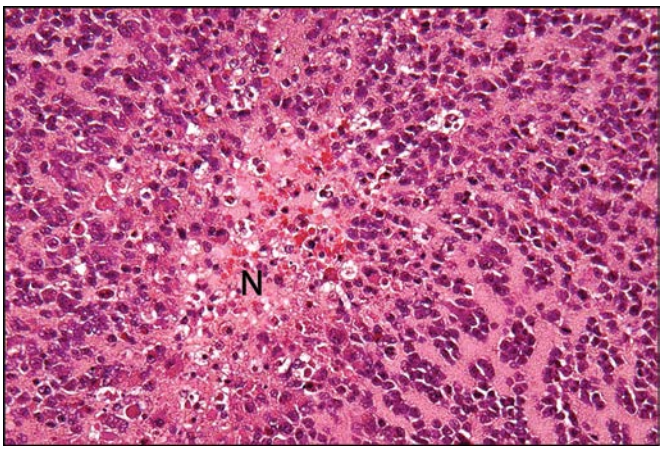


FIGURE 9 Oligodendroglioma, malignant, high grade. The neoplasm consists of small cells with small, dark, oval nuclei and scant cytoplasm with indistinct borders. The pericellular clear halos that impart the typical honeycomb appearance in more well-differentiated oligodendroglial neoplasms are not apparent. Cells may be arranged in haphazard short rows. A focus of necrosis (N) is located centrally in this field. Brain. Rat. H&E. (Copyright 2018 Klaus Weber, AnaPath GmbH, Switzerland.)

Differential diagnoses: **Oligodendroglioma, malignant, low grade**; **Ependymoma, malignant**; **Glioma, mixed, malignant, high grade**.

Synonym(s): **Glioma, oligodendrocytic, malignant**; **oligodendroglioma, anaplastic**.

Reference

Kaufmann, W. et al. 2012. Proliferative and non-proliferative lesions of the rat and mouse central and peripheral nervous systems. *Toxicol Pathol* 40:87S–157S.

Link

www.ncbi.nlm.nih.gov/pubmed/22637737

Oligodendroglioma, malignant, low grade are well-circumscribed tumors occurring in one area of the brain and composed of sheets and rows of cells with typical oligodendrocyte morphology. The cells have round central nuclei, surrounded by a halo of pale cytoplasm, and distinct cell borders. This tumor may be accompanied by vascular proliferation, especially at the periphery, with some atypical capillary endothelial hyperplasia, and necrosis or cystic areas with hemorrhage/hemosiderin.

Differential diagnoses: **Oligodendroglioma, malignant, high grade**; **Ependymoma, benign**; **Glioma, mixed, malignant, low grade**.

Synonym(s): **Glioma, oligodendrocytic, benign**; **oligodendroglioma, benign**.

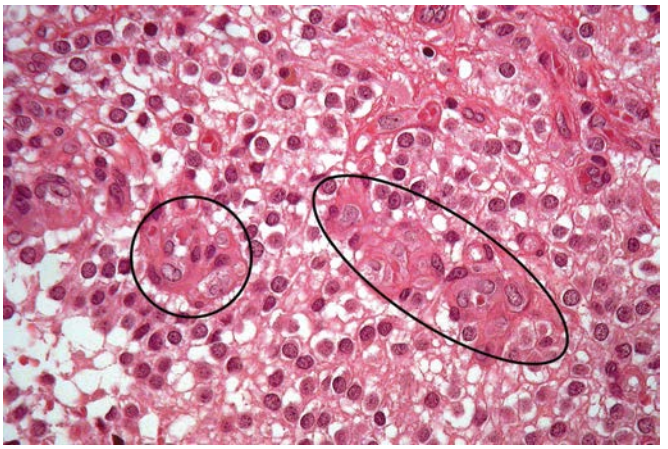


FIGURE 10 Oligodendroglioma, malignant, low grade. Densely cellular mass composed of cells with uniformly sized round nuclei and a small halo of clear to lightly eosinophilic cytoplasm that imparts the typical "honeycomb" structure. Capillary strands (garlands) are encircled. Brain. Rat. H&E. (Copyright 2018 Klaus Weber, AnaPath GmbH, Switzerland.)

Reference

Kaufmann, W. et al. 2012. Proliferative and non-proliferative lesions of the rat and mouse central and peripheral nervous systems. *Toxicol Pathol* 40:87S–157S.

Link

www.ncbi.nlm.nih.gov/pubmed/22637737

Paraganglioma is a rare neuroendocrine tumor originating from paraganglia derived from embryonic neural crest origin and are usually associated with the sympathetic nervous system such as the carotid and aortic bodies. Paragangliomas have been reported in chronic carcinogenicity studies in F-344 rats. Paragangliomas are generally well-circumscribed polypoid masses composed of round to oval cells arranged in nests (Zellballen) separated by fibrovascular trabeculae that stain positively with reticulin stains and negatively with chromaffin. The cells contain neurosecretory granules and may be argyrophilic.

Differential diagnosis: **Pheochromocytoma**.

Synonym(s): **Chemodectoma, glomus tumor**.

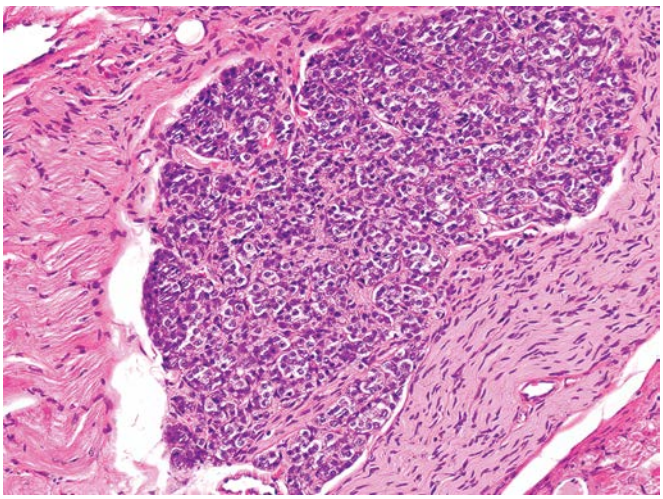


FIGURE 11 Paraganglioma, heart. Well-circumscribed mass composed of densely packed small round to oval cells arranged in small nests supported by fine fibrovascular stroma. Heart. Rat. H&E. (Copyright 2018 Klaus Weber, AnaPath GmbH, Switzerland.)

Reference

Weber, K. et al. 2011. Classification of neural tumors in laboratory rodents, emphasizing the rat. *Toxicol Pathol* 39:129–151.

Link

http://journals.sagepub.com/doi/pdf/10.1177/0192623310392249

Pineal parenchymal tumors are primary pineal gland tumors that are very uncommon in humans and animals. According to the human classification, these tumors are classified as pineal parenchymal tumors, but other pineal tumors can have a germinal, glial, or another origin. In addition, a papillary tumor of the pineal region that is thought to originate from the specialized ependymal cells of the subcommissural organ has been reported in a beagle dog. Pinealomas are benign pineal gland tumors (terminology used in rats) but are also denominated pineocytomas. Transformation of pineocytomas to a less differentiated tumor is denominated pineoblastoma. Pineocytomas have densely packed, large, pale cells with large nuclei containing multifocal condensations of chromatin in addition to other small, dark cells resembling lymphocytes arranged in clusters. These tumors are positive for desmoplakin 2, synaptophysin, and cytokeratin AE1/AE3.

Synonym(s): **Pinealoma**; **pineocytoma**; **pineoblastoma**.

Reference

Tihan, T. 2016. Pineal parenchymal tumors. In: Adesina, A., Tihan, T., Fuller, C., Poussaint, T. (eds.) *Atlas of Pediatric Brain Tumors*. Cham: Springer.

Link

https://link.springer.com/chapter/10.1007/978-3-319-33432-5_34

Pinealoma, see the preferred term **Pineal parenchymal tumor**.

Pineoblastoma, see the preferred term **Pineal parenchymal tumor**.

Pineocytoma, see the preferred term **Pineal parenchymal tumor**.

Primary lymphoma of the nervous system, see the preferred term **Reticulosis, malignant.**

Primitive neuroectodermal tumor (PNET) of the cerebellum, see the preferred term **Medulloblastoma**.

Protoplasmic astrocytoma, see the preferred term **Astrocytoma**.

Reactive astroglia, see the preferred term **Astrocytosis**.

Reactive microglia, see the preferred terms **Microgliosis** or **Gliosis**.

Reactive oligodendroglia, see the preferred term **Oligodendroglial satellitosis**, or **Satellitosis**.

Reticulosis, malignant is a malignant neoplasm of uncertain origin that has a mixed component of mononuclear and glial cells and infiltrates the meninges and the perivascular and periventricular areas in the brain. It has been called malignant reticulosis because the tumors cells do not resemble differentiated lymphocytes or gliomas; however, immunohistochemical stains for lymphocytes and monocytes (CD3, CD45RA, CD68 [ED1], F4/80) in humans and animals have demonstrated a leukocytic origin. This tumor is composed of pleomorphic lymphoid to histiocytic cells with pleomorphic nuclei that are resting within a stroma rich in reticulin fibers. Multinucleated giant cells and mitotic figures are common.

Differential diagnoses: **Astrocytoma, malignant, high grade**; **Histiocytic sarcoma**; **Granulomatous inflammation**.

Synonym(s): **Lymphoreticulosis**; **microgliomatosis**; **primary lymphoma of the nervous system**; **primary histiocytic sarcoma of the brain**.

Reference

Kaufmann, W. et al. 2012. Proliferative and non-proliferative lesions of the rat and mouse central and peripheral nervous systems. *Toxicol Pathol* 40:87S–157S.

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Schwann cell hyperplasia is proliferation of the glial cells that ensheath axons with myelin in the peripheral nervous system. Reactive Schwann cell proliferation occurs in the context of peripheral nerve regeneration following axon degeneration or transection (Wallerian degeneration). Distal to the transection or area of degeneration the axon degenerates and Schwann cells proliferate to form cell columns (bands of Bungner) that will eventually receive the regenerated axon sprouts, guiding the sprouts to the synapse site and reforming the myelin sheath. In a different context, hyperplasia of Schwann cells resulting in space-occupying lesions has been induced by treatments such as intraventricular infusion of nerve growth factor and in neurofibromatosis type-2 (NF2) transgenic mice. The NF2 transgenic mice also develop schwannomas.

Differential diagnosis: **Schwannoma, benign**.

Synonym(s): None.

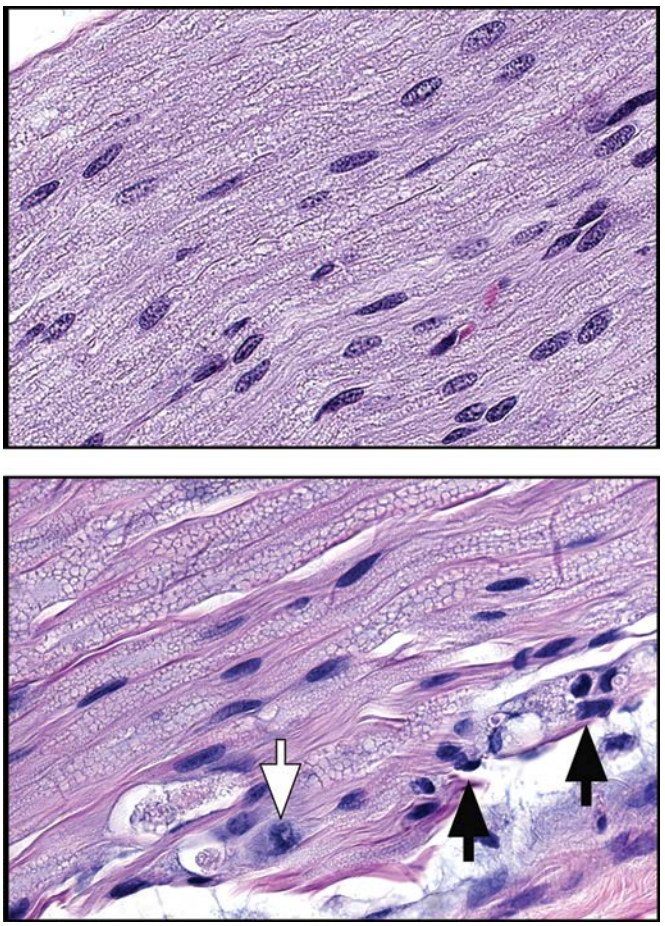


FIGURE 12 Schwann cell hyperplasia. Top: Normal region of peripheral nerve composed of myelinated axons and scattered oval to elongate dark Schwann cell nuclei. Bottom: Around or adjacent to small dilated spaces containing fragments of degenerating axons (digestion chambers) are increased numbers of Schwann cell nuclei that are smaller and more hyperchromatic (black arrows) and display occasional mitotic figures (white arrow). Sciatic nerve. Rat. H&E. (Copyright 2018 Pfizer.)

References

Giovannini, M. et al. 1999. Schwann cell hyperplasia and tumors in transgenic mice expressing a naturally occurring mutant NF2 protein. *Genes Dev* 13:978–986.

Winkler, J. et al. 1997. Reversible Schwann cell hyperplasia and sprouting of sensory and sympathetic neurites after intraventricular administration of nerve growth factor. *Ann Neurol* 41(1):82–93.

Links

http://onlinelibrary.wiley.com/doi/10.1002/ana.410410114/abstract
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC316642/

Schwannoma, benign are neoplasms derived from Schwann cells, which are glial cells that wrap around the nerve fiber in the peripheral nervous system and form the myelin sheaths of peripheral axons. These tumors can form in any organ containing peripheral nerves. In the rat, these are most commonly found in the heart, near the ear pinna, in the eye, or in the mandibular salivary gland. These tumors are of neuroectodermal origin with mesenchymal features. Benign schwannomas grow by expansion rather than infiltration and frequently are unaccompanied by clinical signs. Tumor cells have elongated cytoplasm with indistinct cell borders that form nuclear palisades (Antoni A pattern). Portions of the neoplasm may also be sparsely cellular with a clear matrix (Antoni B pattern) that may contain cystic cavities.

Differential diagnoses: **Fibroma**; **Leiomyoma**; **Schwannoma, malignant**; **Neuroma**.

Synonym(s): **Neurilemmoma**; **neurinoma**.

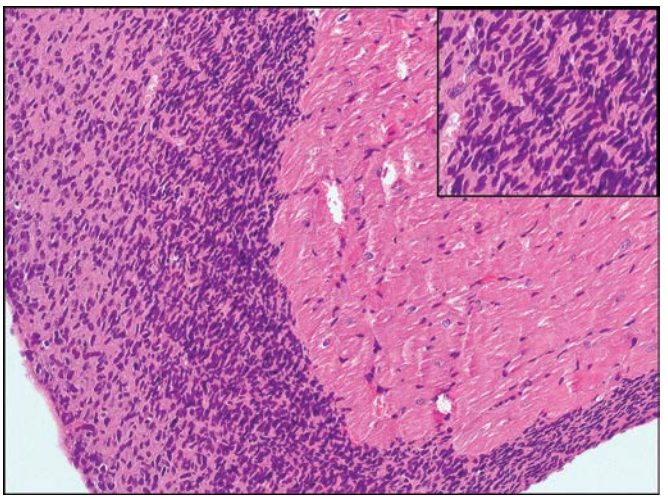


FIGURE 13 Schwannoma, benign. A thick layer of densely packed, small, spindled cells with thin, elongated, dark nuclei and scant cytoplasm. Palisades of neoplastic cells are depicted in the inset. Heart. Rat. H&E. (Copyright 2018 Klaus Weber, AnaPath GmbH, Switzerland.)

Reference

Kaufmann, W. et al. 2012. Proliferative and non-proliferative lesions of the rat and mouse central and peripheral nervous systems. *Toxicol Pathol* 40:87S–157S.

Link

www.ncbi.nlm.nih.gov/pubmed/22637737

Schwannoma, malignant are neoplasms derived from Schwann cells, which are glial cells that wrap around the nerve fiber in the peripheral nervous system and form the myelin sheaths of peripheral axons. These tumors can form

in any organ containing peripheral nerves. In the rat, these are most commonly found in the heart, near the ear pinna, in the eye, or in the mandibular salivary gland. These tumors are of neuroectodermal in origin with mesenchymal features. The malignant versions of these tumors are unencapsulated and expansive with compression of adjacent structures. There is a high mitotic rate with cellular atypia, including atypical mitotic figures and locally invasive growth and/or metastases. Tumor cells have elongated cytoplasm with indistinct cell borders that form nuclear palisades (Antoni A pattern). Portions of the neoplasm may also be sparsely cellular with a clear matrix (Antoni B pattern) and may contain cystic cavities.

Differential diagnoses: **Fibroma**; **Leiomyoma**; **Schwannoma, malignant**; **Neuroma**.

Synonym(s): **Neurilemmoma**; **neurinoma**.

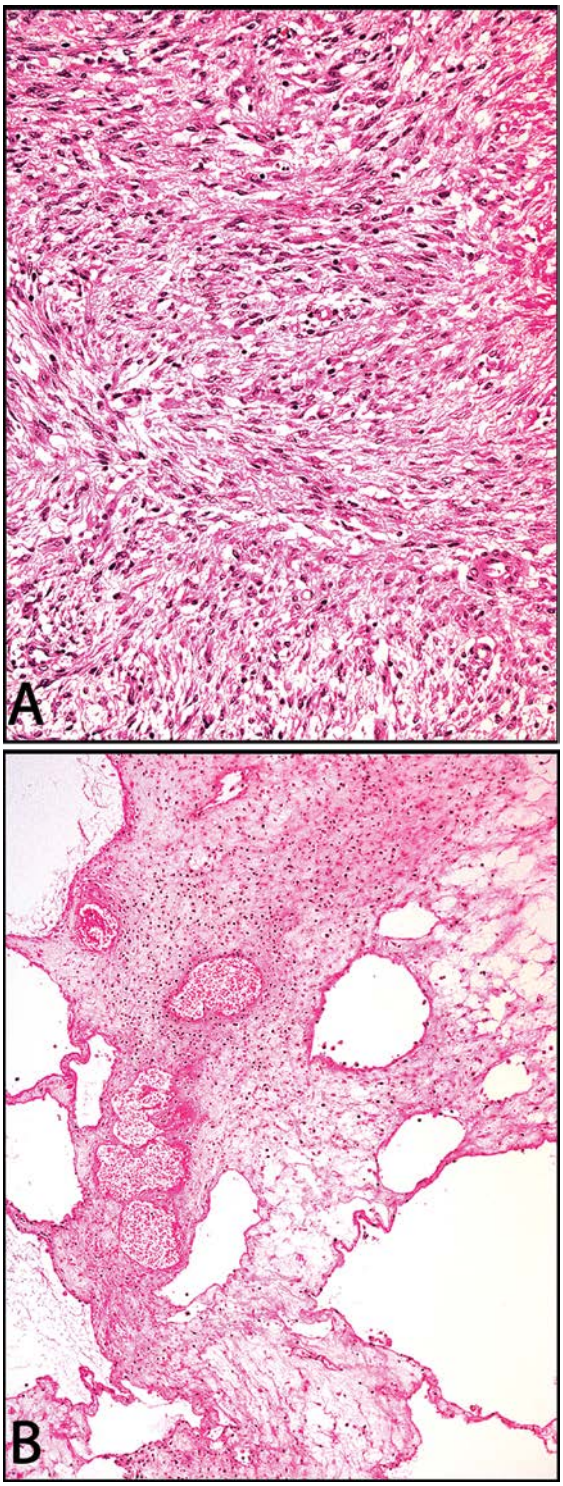


FIGURE 14 Schwannoma, malignant. (A) Antoni type A pattern with densely packed spindled cells forming interweaving herringbone swarms. (B) Antoni type B pattern with cysts and loosely cellular myxoid areas. Rat. H&E. (Copyright 2018 Klaus Weber, AnaPath GmbH, Switzerland.)

Reference

Kaufmann, W. et al. 2012. Proliferative and non-proliferative lesions of the rat and mouse central and peripheral nervous systems. *Toxicol Pathol* 40:87S–157S.

Link

www.ncbi.nlm.nih.gov/pubmed/22637737

REPRODUCTIVE SYSTEM AND MAMMARY GLAND: FEMALE

Adenomyosis is an infrequent, non-neoplastic change in the uterine myometrium which is characterized by normal-appearing endometrial epithelial and stromal structures within the myometrium. The endometrial structures remain confined to the myometrium and subserosa. Adenomyosis may occur spontaneously or in response to endocrine disruption after xenobiotic treatment in neonates or adults. It is a more frequent spontaneous change in some strains of mice but is observed in multiple laboratory species including the rat, dog, and monkey. Adenomyosis or endometriosis is reported with an incidence of up to approximately 30% in colonies of rhesus and cynomolgus macaques.

Differential diagnoses: **Endometriosis**; **Endometrial adenoma**; **Endometrial adenocarcinoma**.

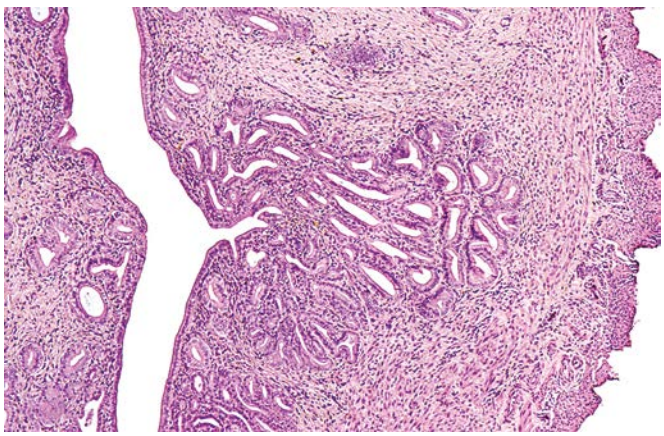


FIGURE 1 Adenomyosis, extension of glands into myometrium, uterus, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Dixon D. et al. 2014.)

References

Cline, J. et al. 2008. Selected background findings and interpretation of common lesions in the female reproductive system in macaques. *Toxicol Pathol* 36(7):142s–163s.

Dixon, D. et al. 2014. Nonproliferative and proliferative lesions of the rat and mouse female reproductive system. *J Toxicol Pathol* 27(3–4 Suppl):1S–107S.

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Links

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3070965/
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/
http://www.goreni.org/

Arrhenoblastoma, see the preferred term **Sertoli cell tumor, malignant**.

Cervical carcinoma in situ, see the preferred term **Cervical intraepithelial neoplasia**.

Cervical epithelial dysplasia, see the preferred term **Cervical intraepithelial neoplasia**.

Cervical intraepithelial neoplasia is a papillomavirus-associated lesion in nonhuman primates (and women) characterized by foci of epithelial dysplasia and formation of epithelial pearls within areas of expanded basal epithelium. Affected epithelial cells are dysplastic with loss of polarity and perinuclear vacuolation. Nuclei may have atypical mitoses. Cervical intraepithelial neoplasms do not breach the basement membrane and invade the underlying stroma. The lesions may extend into the vagina with comparable morphology.

Synonym(s): **Cervical epithelial dysplasia**; **cervical carcinoma in situ**.

References

Dixon, D. et al. 2014. Nonproliferative and proliferative lesions of the rat and mouse female reproductive system. *J Toxicol Pathol* 27(3–4 Suppl):1S–107S.

Wood, C. et al. 2004. Cervical and vaginal epithelial neoplasms in cynomolgus monkeys. *Vet Pathol* 41(2):108–115.

Links

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/
http://journals.sagepub.com/doi/abs/10.1354/vp.41-2-108?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed
http://www.goreni.org/

Choriocarcinoma is a rare neoplasm in rodent and nonrodent laboratory animals composed of placental cytotrophoblasts and trophoblastic giant cells or synctiotrophoblasts. Placental cytotrophoblasts are small, round cells. The giant cells are pleomorphic and polyhedral and have single large (trophoblastic giant cell) or multiple (synctiotrophoblast) nuclei. Synctiotrophoblasts have considerable anisocytosis and anisokaryosis. For both trophoblastic and synctiotrophoblast cell types, nucleoli are prominent, and erythrophagocytosis or intracytoplasmic periodic acid-Schiff (PAS)-positive material may be present. Choriocarcinomas are infiltrative and are often associated with hemorrhage and necrosis.

Differential diagnoses: **Yolk sac carcinoma**; **Embryonal carcinoma**.

Synonym(s): **Chorioepithelioma, malignant**.

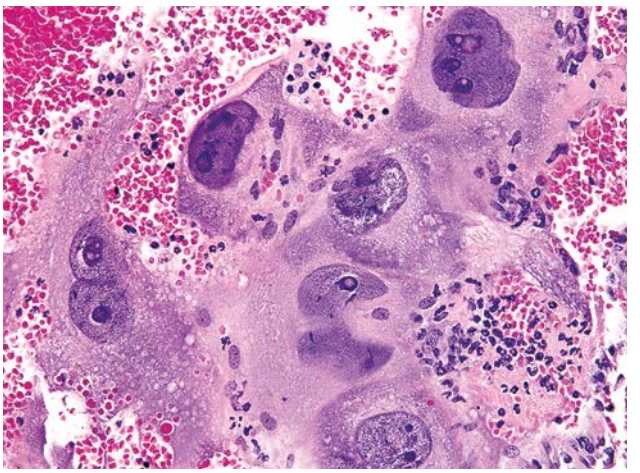


FIGURE 2 Choriocarcinoma, ovary, mouse, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Dixon, D. et al. 2014.)

Reference

Dixon, D. et al. 2014. Nonproliferative and proliferative lesions of the rat and mouse female reproductive system. *J Toxicol Pathol* 27(3–4 Suppl):1S–107S.

Links

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/
http://www.goreni.org/

Chorioepithelioma, malignant, see the preferred term **Choriocarcinoma**.

Clitoral gland adenocarcinoma is a malignant neoplasm of the clitoral gland. The neoplasm can be solid, cystic, and papillary or a mix of multiple types. Often the overlying skin is ulcerated. There is loss of the normal acinar structure and nuclear/cellular atypia is common. Mitoses and local invasion are frequent. Cystic forms usually have intralesional keratin and cell debris. There may be squamous differentiation of neoplastic epithelial cells. Stroma is scant but neoplasms can be surrounded by a thick fibrous capsule, i.e., infiltrated by the neoplastic epithelial cells.

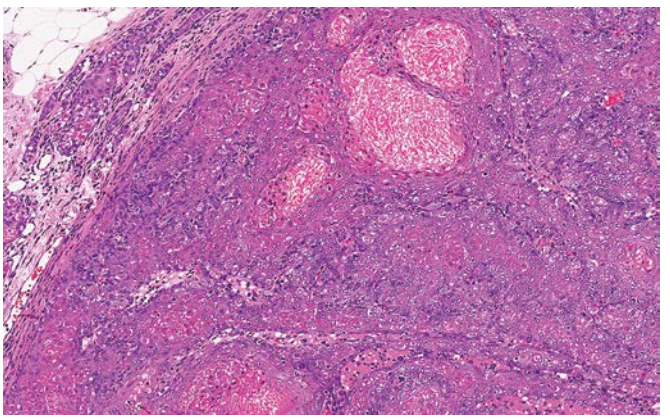


FIGURE 3 Clitoral gland adenocarcinoma, clitoral gland, rat, H&E. (Reproduced with permission of Society of Toxicologic Pathology from Rudmann, D. et al. 2012.)

Reference

Rudmann, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse mammary, Zymbal's, preputial, and clitoral glands. *Toxicol Pathol* 40(6 Suppl):7S–39S.

Links

https://www.ncbi.nlm.nih.gov/pubmed/22949413
http://www.goreni.org/

Clitoral gland adenoma is a benign neoplasm of the clitoral gland. These neoplasms are well circumscribed and usually are of a solid type that mimics the normal clitoral gland organization. There is compression of the adjacent gland and variable amounts of stroma. Cells are well differentiated and there is no local invasion. Mitoses are rare. In some cases, the neoplasms may be cystic with intralesional keratin and cell debris.

Reference

Rudmann, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse mammary, Zymbal's, preputial, and clitoral glands. *Toxicol Pathol* 40(6 Suppl):7S–39S.

Links

https://www.ncbi.nlm.nih.gov/pubmed/22949413
http://www.goreni.org/

Dysgerminoma is a rare ovarian neoplasm in the mouse, and more commonly in older dogs, characterized by effacement of the normal ovarian architecture by a monomorphic, undifferentiated, round cell population. Neoplastic cells have pale or clear cytoplasm and are organized in sheets. These tumors may be observed occasionally as an incidental finding in mouse carcinogenicity studies.

Differential diagnoses: **Yolk sac carcinoma**; **Ovarian cystadenocarcinoma**; **Choriocarcinoma**.

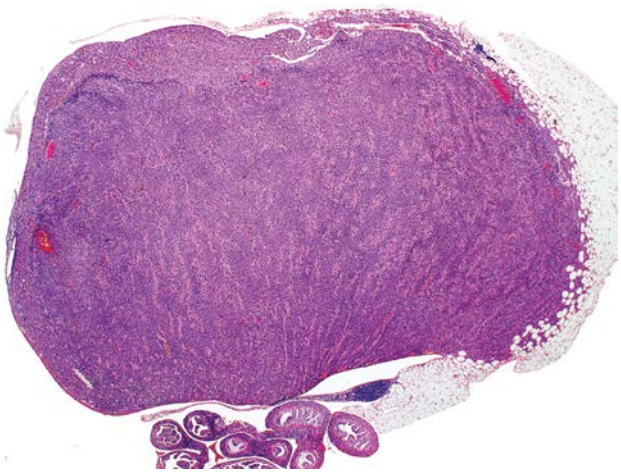


FIGURE 4 Dysgerminoma, ovary, mouse, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Dixon, D. et al. 2014.)

Reference

Dixon, D. et al. 2014. Nonproliferative and proliferative lesions of the rat and mouse female reproductive system. *J Toxicol Pathol* 27(3–4 Suppl):1S–107S.

Links

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/
http://www.goreni.org/

Embryonal carcinoma is a rare uterine tumor that arises from a mixture of pluripotent germ cells, sex-cord stromal cells, and cells of the visceral yolk sac. Neoplastic cells are generally large and undifferentiated and arranged in solid sheets; however acinar, papillary, or tubular structures are observed. The stromal component is minimal, and the neoplasm often has areas of necrosis and hemorrhage.

Reference

Dixon, D. et al. 2014. Nonproliferative and proliferative lesions of the rat and mouse female reproductive system. *J Toxicol Pathol* 27(3–4 Suppl):1S–107S.

Links

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/
http://www.goreni.org/

Endodermal sinus tumor, malignant, see the preferred term **Yolk sac carcinoma**.

Endometrial adenocarcinoma is a rare neoplasm of the uterine endometrium characterized by a malignant population of endometrial glandular epithelial cells that form nests, sheets, or glandular structures. Cells may be well differentiated or atypical and pleomorphic and have a high mitotic index. The neoplasm is locally invasive and may metastasize, and is often associated with considerable inflammation, necrosis, and hemorrhage.

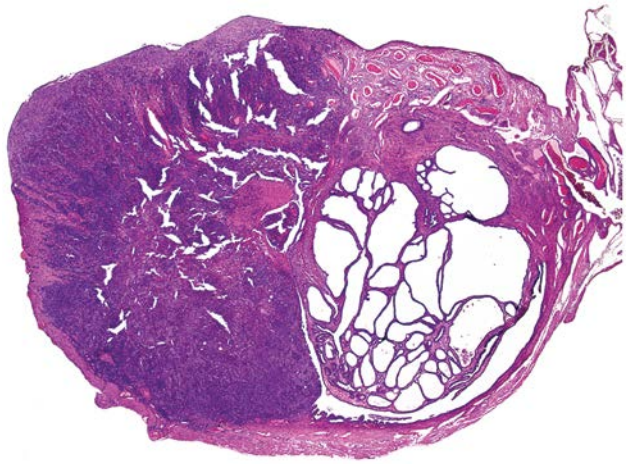


FIGURE 5 Endometrial adenocarcinoma, uterus, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Dixon, D. et al. 2014.)

Reference

Dixon, D. et al. 2014. Nonproliferative and proliferative lesions of the rat and mouse female reproductive system. *J Toxicol Pathol* 27(3–4 Suppl):1S–107S.

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https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/
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Endometrial adenoma is a rare neoplasm of the uterine endometrium characterized by a benign proliferation of the surface epithelium on a broad or narrow base. The epithelium is well differentiated and usually forms glandular to tubular structures which are pseudostratified or stratified (two layers). Mitoses are infrequent, and the glandular structures are restricted to the endometrium proper but may compress the surrounding endometrial stroma and adjacent myometrium. This tumor is differentiated from an endometrial polyp by the lack of a significant stroma component.

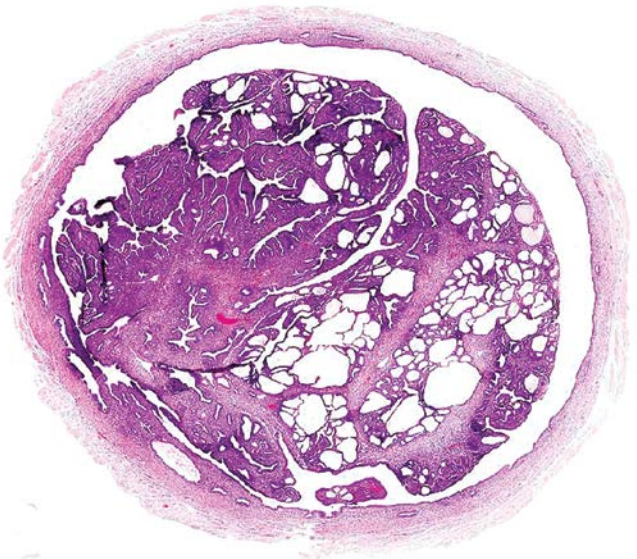


FIGURE 6 Endometrial adenoma, uterus, mouse, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Dixon, D. et al. 2014.)

Reference

Dixon, D. et al. 2014. Nonproliferative and proliferative lesions of the rat and mouse female reproductive system. *J Toxicol Pathol* 27(3–4 Suppl):1S–107S.

Links

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/
http://www.goreni.org/

Endometrial adenomatous hyperplasia, see the preferred term **Endometrial diffuse hyperplasia**.

Endometrial atypical cystic hyperplasia, see the preferred term **Endometrial cystic hyperplasia**.

Endometrial atypical glandular hyperplasia, see the preferred term **Endometrial diffuse hyperplasia**.

Endometrial cystic glandular hyperplasia, see the preferred term **Endometrial cystic hyperplasia**

Endometrial cystic hyperplasia is an endometrial lesion characterized by increased numbers of endometrial gland profiles which have a single layer of epithelial cells with an increased mitotic index. Gland profiles are usually dilated or cystic, and epithelial cells may be atypical. Endometrial epithelium may be thrown into folds. There may be secondary inflammation characterized by mixed inflammatory cell infiltrates, congestion/hemorrhage, and edema. The uterine lumen may contain sloughed degenerate epithelial cells admixed with leukocytes and eosinophilic material. The lesion is a common background finding in aged rodents, especially mice, is frequently observed in rabbits, and is associated with pseudopregnancy in dogs. (See **Pseudopregnancy** for further information.) Prolonged estrogen stimulation secondary to ovarian follicular cysts, or because of estrogenic xenobiotics, may produce cystic glandular hyperplasia.

Differential diagnosis: **Endometrial glandular polyp**.

Synonym(s): **Endometrial atypical cystic hyperplasia**; **endometrial cystic glandular hyperplasia**.

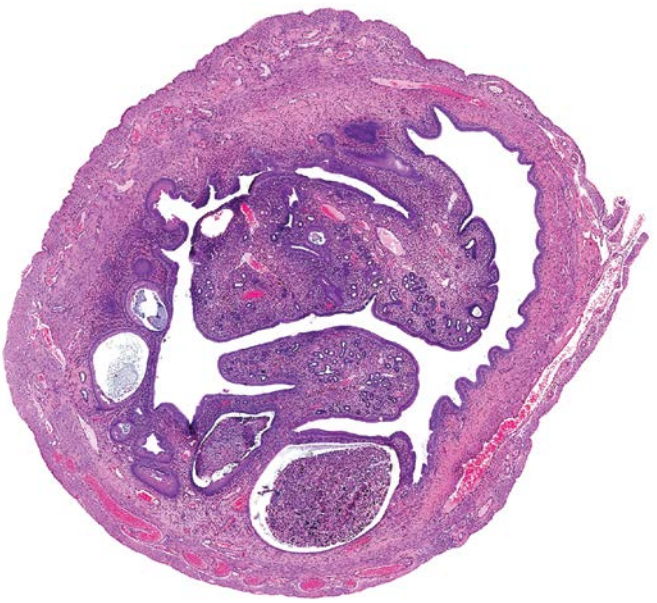


FIGURE 7 Cystic endometrial hyperplasia, uterus, SD rat, H&E. (Images courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

Reference

Dixon, D. et al. 2014. Nonproliferative and proliferative lesions of the rat and mouse female reproductive system. *J Toxicol Pathol* 27(3–4 Suppl):1S–107S.

Links

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/
http://www.goreni.org/

Endometrial diffuse hyperplasia is characterized by an increased number of normal or hypertrophied glands, and/or a hypercellular luminal epithelium comprising the uterine endometrium. An increased number of luminal epithelial cells may result in the endometrium being thrown into folds, and glands may be dilated and fluid filled (see **Endometrial cystic hyperplasia** for further information). Hyperplasia of the stromal elements of the endometrium may also occur (see **Endometrial stromal hyperplasia** for further information).

Synonym(s): **Endometrial glandular hyperplasia**; **endometrial atypical glandular hyperplasia**; **endometrial adenomatous hyperplasia**.

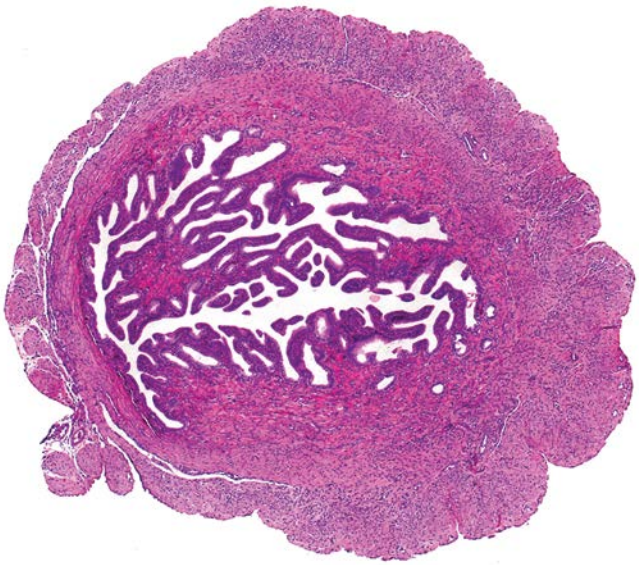


FIGURE 8 Diffuse endometrial hyperplasia, uterus, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Dixon, D. et al. 2014.)

Reference

Dixon, D. et al. 2014. Nonproliferative and proliferative lesions of the rat and mouse female reproductive system. *J Toxicol Pathol* 27(3–4 Suppl):1S–107S.

Links

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/
http://www.goreni.org/

Endometrial focal glandular hyperplasia is characterized by a focus of disorganized, atypical glands within a normal endometrium. Affected glands have an epithelium that may be stratified. Epithelial cells are enlarged, pleomorphic, and have abundant eosinophilic or basophilic cytoplasm and increased mitoses. Focal glandular hyperplasia is a preneoplastic change and is observed in both rats and mice.

Differential diagnoses: **Endometrial stromal polyp**; **Decidualization**; **Endometrial stromal sarcoma**.

Reference

Dixon, D. et al. 2014. Nonproliferative and proliferative lesions of the rat and mouse female reproductive system. *J Toxicol Pathol* 27(3–4 Suppl):1S–107S.

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https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/
http://www.goreni.org/

Endometrial glandular hyperplasia, see the preferred term **Endometrial diffuse hyperplasia**.

Endometrial glandular polyp is a uterine or cervical benign proliferation of normal endometrial glands and the associated fibrovascular stroma that protrudes into the uterine or cervical lumen. Glandular components are prominent or hyperplastic and may be cystic. In some cases, there can be a decidual reaction (see **Decidual reaction** for further information) within the polyp. Frequently, polyps are observed in older rodents, but can occur in dogs and nonhuman primates.

Differential diagnoses: **Endometrial stromal polyp**; **Endometrial adenoma**.

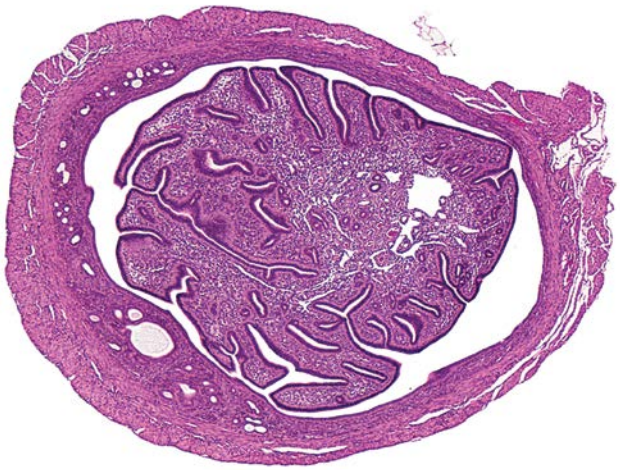


FIGURE 9 Endometrial glandular polyp, uterus, mouse, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Dixon, D. et al. 2014.)

Reference

Dixon, D. et al. 2014. Nonproliferative and proliferative lesions of the rat and mouse female reproductive system. *J Toxicol Pathol* 27(3–4 Suppl):1S–107S.

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https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/
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Endometrial stromal hyperplasia in the uterus has a hypercellular stromal compartment (fibroblasts), with or without an increase in accompanying matrix (collagen). The stromal cells are well differentiated. Endometrial stromal hyperplasia may be observed concurrently with endometrial diffuse hyperplasia. If alone, the hyperplasia may be due to increased androgen levels, or due to the direct stimulation of androgen receptors.

Reference

Dixon, D. et al. 2014. Nonproliferative and proliferative lesions of the rat and mouse female reproductive system. *J Toxicol Pathol* 27(3–4 Suppl):1S–107S.

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https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/
http://www.goreni.org/

Endometrial stromal polyp is a uterine or cervical benign proliferation of the endometrial fibrovascular stroma which

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protrudes into the uterine or cervical lumen but lacks a significant glandular component. The stroma is well differentiated. It is the most common neoplasm of the laboratory rat and mouse, especially in F344/N rats and B6C3F1 mice.

Differential diagnoses: **Endometrial glandular polyp**; **Vaginal polyp**; **Endometrial stromal sarcoma**.

Synonym(s): **Endometrial stromal tumor, benign**.

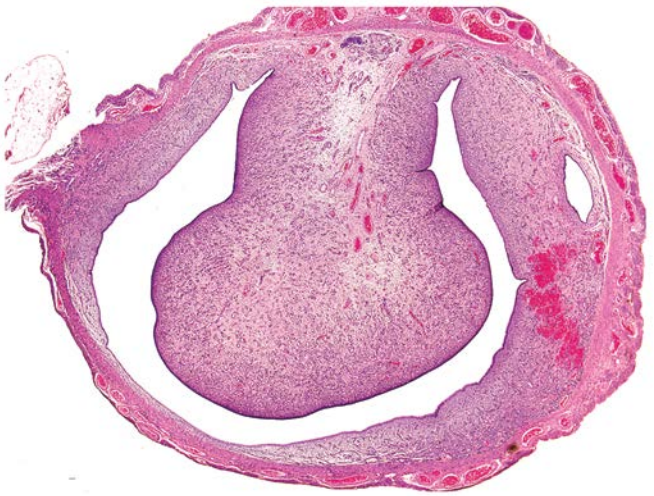


FIGURE 10 Endometrial stromal polyp, uterus, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Dixon, D. et al. 2014.)

Reference

Dixon, D. et al. 2014. Nonproliferative and proliferative lesions of the rat and mouse female reproductive system. *J Toxicol Pathol* 27(3–4 Suppl):1S–107S.

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https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/
http://www.goreni.org/

Endometrial stromal sarcoma is an invasive uterine neoplasm characterized by the proliferation of undifferentiated endometrial stromal cells. Stromal cells may be pleomorphic, exhibit a moderate to high mitotic rate, have small, basophilic nuclei, and have less cytoplasm than normal stromal cells. Endometrial stromal sarcomas may be polypoid in nature, and exhibit necrosis and hemorrhage.

Differential diagnoses: **Female sex organs, leiomyosarcoma**; Endometrial schwannoma.

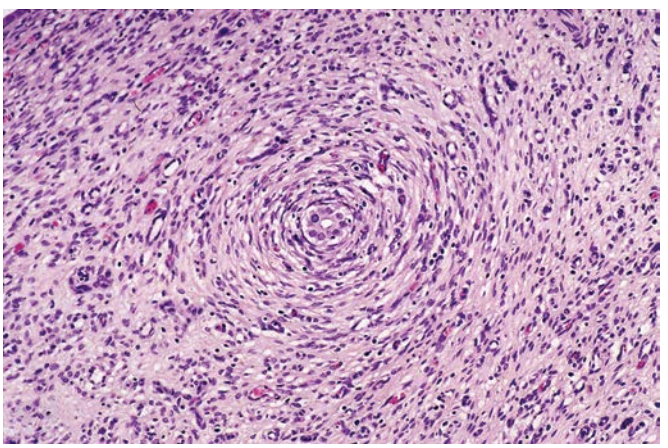


FIGURE 11 Endometrial stromal sarcoma, uterus, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Dixon, D. et al. 2014.)

Reference

Dixon, D. et al. 2014. Nonproliferative and proliferative lesions of the rat and mouse female reproductive system. *J Toxicol Pathol* 27(3–4 Suppl):1S–107S.

Links

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/
http://www.goreni.org/

Endometrial stromal tumor, benign, see the preferred term **Endometrial stromal polyp**.

Endometriosis is a nonneoplastic change in the sexually mature nonhuman (and human) primate uterus, characterized by normal-appearing endometrial epithelial and stromal structures within the myometrium and serosa. The endometrial structures may implant on the serosa surfaces of other abdominal organs. Because of the younger-aged nonhuman primates used in nonclinical toxicology studies, endometriosis is uncommon.

Differential diagnoses: **Adenomyosis**; **Endometrial adenocarcinoma**.

References

Cline, J. et al. 2008. Selected background findings and interpretation of common lesions in the female reproductive system in macaques. *Toxicol Pathol* 36(7):142s–163s.

Dixon, D. et al. 2014. Nonproliferative and proliferative lesions of the rat and mouse female reproductive system. *J Toxicol Pathol* 27(3–4 Suppl):1S–107S.

Links

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3070965/
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/
http://www.goreni.org/

Female sex organs (uterus, oviduct, cervix, vagina) leiomyoma is a well-circumscribed, benign tumor of smooth muscle composed of interlacing bundles of uniform spindle cells, characteristically with blunt-ended nuclei (cigar-shaped), and cytoplasmic myofibrils. They are common spontaneous tumors of the myometrium of rats, mice, guinea pigs, and hamsters, but leiomyomas of the mesovarium in rats have been induced with β_2 adrenergic receptor agonists, and leiomyomas of the uterus have been induced in mice treated with medroxalol hydrochloride, and in mice treated prenatally or neonatally with diethylstilbestrol. Malignant and benign smooth muscle tumors have been reported in the uterus and vagina of beagles treated with estrogenic contraceptive agents. Uterine smooth muscle tumor cells express estrogen receptors and appear to be hormonally responsive.

Differential diagnoses: **Female sex organs, leiomyosarcoma**; **Female sex organs, fibroma**.

Synonym(s): **Myometrial leiomyoma**.

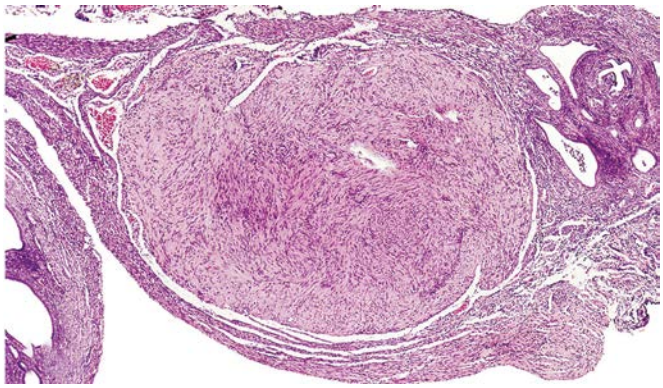


FIGURE 12 Leiomyoma, uterus, mouse, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Dixon, D. et al. 2014.)

Reference

Dixon, D. et al. 2014. Nonproliferative and proliferative lesions of the rat and mouse female reproductive system. *J Toxicol Pathol* 27(3–4 Suppl):1S–107S.

Links

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/
http://www.goreni.org/

Female sex organs (uterus, oviduct, cervix, vagina) leiomyosarcoma is composed of bundles of spindle cells with cellular and nuclear pleomorphism; they are poorly circumscribed and invasive. They arise spontaneously in the myometrium of rats, mice, and hamsters. Malignant and benign smooth muscle tumors have been reported in the uterus and vagina of beagles treated with estrogenic contraceptive agents. Uterine smooth muscle tumor cells express estrogen, progesterone, and androgen receptors, and appear to be hormonally responsive.

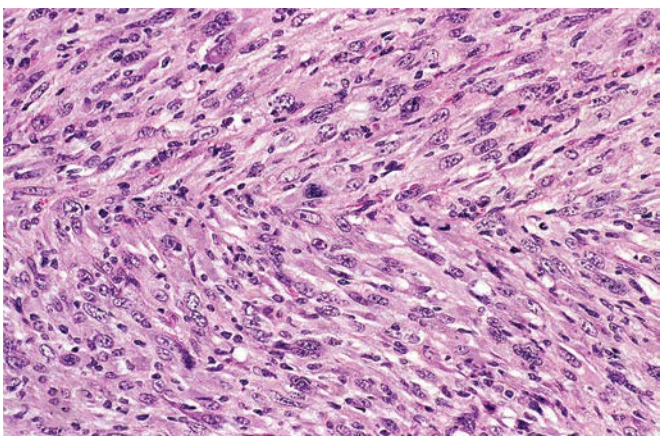


FIGURE 13 Leiomyosarcoma, uterus, mouse, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Dixon, D. et al. 2014.)

Differential diagnoses: **Female sex organs, leiomyoma**; **Endometrial stromal sarcoma**; **Female sex organs, histiocytic sarcoma**; **Female sex organs, fibrosarcoma**.

Reference

Dixon, D. et al. 2014. Nonproliferative and proliferative lesions of the rat and mouse female reproductive system. *J Toxicol Pathol* 27(3–4 Suppl):1S–107S.

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https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/
http://www.goreni.org/

Female sex organs (uterus, oviduct, cervix, vagina), fibroma is a well-circumscribed, benign tumor composed of well-differentiated fibroblasts. Neoplastic cells are composed of uniform spindle cells embedded in an eosinophilic collagen matrix. There is compression of the surrounding tissue, and often these neoplasms are only modestly cellular.

Reference

Dixon, D. et al. 2014. Nonproliferative and proliferative lesions of the rat and mouse female reproductive system. *J Toxicol Pathol* 27(3–4 Suppl):1S–107S.

Links

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/
http://www.goreni.org/

Female sex organs (uterus, oviduct, cervix, vagina), fibrosarcoma is a locally invasive, malignant tumor composed of pleomorphic spindle cells. Neoplastic cells have frequent mitoses and are associated with variable amounts of extracellular collagen. Necrosis and hemorrhage may be observed.

Reference

Dixon, D. et al. 2014. Nonproliferative and proliferative lesions of the rat and mouse female reproductive system. *J Toxicol Pathol* 27(3–4 Suppl):1S–107S.

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https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/
http://www.goreni.org/

Luteoma is a type of sex cord stromal tumor or ovarian tumor comprising neoplastic populations of granulosa cells, theca cells, their luteinized derivatives, and fibroblasts. Luteomas are composed predominantly of highly luteinized cells with abundant pale or vacuolated cytoplasm, and distinct cell boundaries. In rats and mice, the size of the proliferative lesion is larger than that of three corpora lutea. Although proliferative lesions of the sex cord stroma are one of the most common types of proliferative lesions in laboratory animal species, luteomas are uncommon. Malignant luteomas have not been reported. Luteoma in the nonhuman primate (NHP) express calretinin, CKs, GATA-4, neuron-specific enolase (NSE), protein gene product 9.5 (PGP 9.5),

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and vimentin but not Inhibin-A. Luteomas may produce androgens or estrogens.

Differential diagnoses: **Ovarian granulosa cell tumor, benign**; **Thecal cell tumor, benign**; **Sex cord stromal tumor**; **Corpora lutea hypertrophy**.

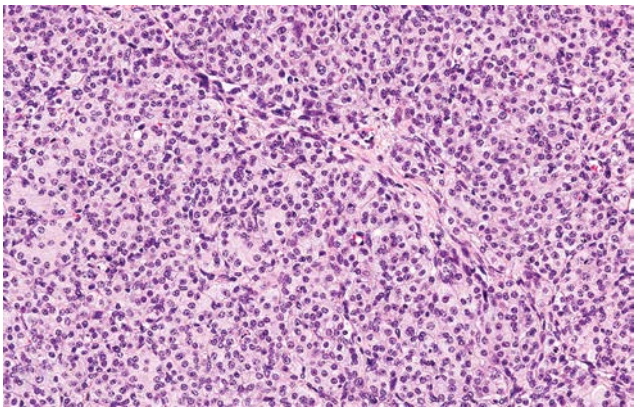


FIGURE 14 Luteoma, benign, ovary, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Dixon et al., 2014.)

Reference

Dixon, D. et al. 2014. Nonproliferative and proliferative lesions of the rat and mouse female reproductive system. *J Toxicol Pathol* 27(3–4 Suppl):1S–107S.

Links

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/
http://www.goreni.org/

Mammary adenosquamous carcinoma is a neoplasm in mice characterized by a mixed glandular and squamous phenotype. Squamous regions compose at least 25% of the neoplasm and neoplastic cells are generally well differentiated, with intracytoplasmic keratin and keratin pearl formation. Glandular portions are composed of round to polygonal epithelial cells and blend with the squamous areas. Cellular and nuclear atypia and mitoses are present. While neoplasms may be well circumscribed, both epithelial and squamous components metastasize.

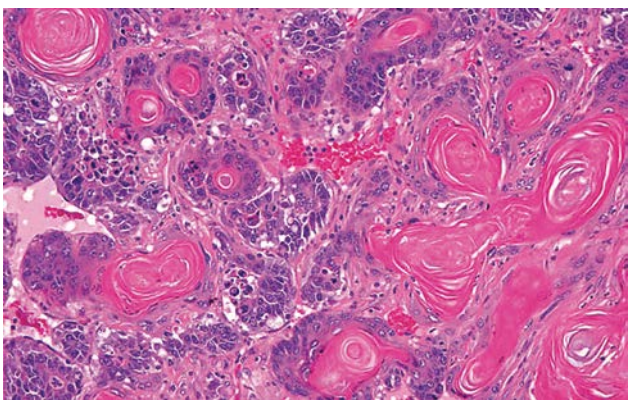


FIGURE 15 Adenosquamous carcinoma, mammary gland, rat, H&E. (Reproduced with permission of Society of Toxicologic Pathology from Rudmann, D. et al. 2012.)

Reference

Rudmann, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse mammary, Zymbal's, preputial, and clitoral glands. *Toxicol Pathol* 40(6 Suppl):7S–39S.

Links

https://www.ncbi.nlm.nih.gov/pubmed/22949413
http://www.goreni.org/

Mammary carcinosarcoma, see the preferred term **Mammary tumor, mixed**.

Mammary gland adenocarcinoma is a malignant neoplasm of the mammary gland characterized by an infiltrative mass with epithelial pleomorphism and atypia. Adenocarcinoma may form solid, cystic, papillary, tubular, or undifferentiated structures and cells have considerable cellular and nuclear pleomorphism, frequent mitoses, and invade adjacent tissues. These neoplasms can occur in all laboratory species. In laboratory rats, adenocarcinomas are uncommon spontaneous tumors. In laboratory beagles, lobular adenocarcinoma occurs spontaneously in females greater than 5 years of age, while the ductal carcinoma is the most frequent histology in laboratory macaques. Tumors in dogs and macaques may be both locally invasive and metastatic.

Differential diagnosis: **Mammary gland adenocarcinoma arising in fibroadenoma**.

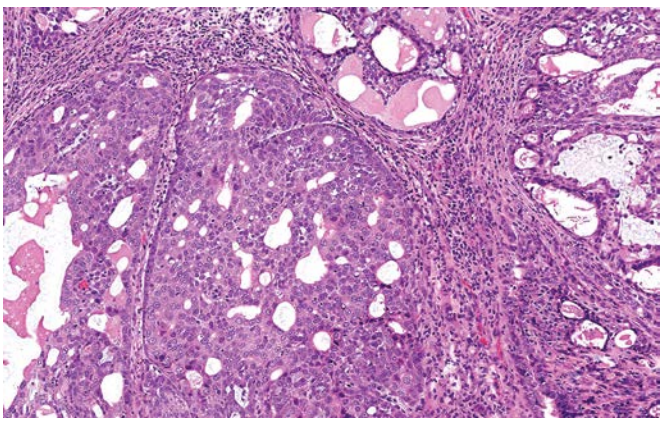


FIGURE 16 Adenocarcinoma, mammary gland, female rat, H&E. (Reproduced with permission of Society of Toxicologic Pathology from Rudmann, D. et al. 2012.)

Reference

Rudmann, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse mammary, Zymbal's, preputial, and clitoral glands. *Toxicol Pathol* 40(6 Suppl):7S–39S.

Links

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http://www.goreni.org/

Mammary gland adenocarcinoma arising in fibroadenoma is an uncommon, rat-specific neoplasm characterized

by focal areas of adenocarcinomatous change within a fibroadenoma (see **Mammary gland fibroadenoma** for further information). The adenocarcinoma (see **Mammary gland adenoma** and **Mammary gland adenocarcinoma** for further information) can present as a single subtype (e.g., alveolar) or have a mixed phenotype (e.g., alveolar, cystic, or papillary). Neoplastic cells are atypical and pleomorphic, may have numerous mitoses, and may invade the adjacent stroma. The fibroadenoma is considered the primary neoplasm. The histologic characteristics of the fibroadenoma can vary in terms of the proportion that is epithelial versus connective tissue; however, both the epithelial and fibrous collagenous connective tissue components are well differentiated.

Differential diagnosis: **Mammary gland adenocarcinoma**.

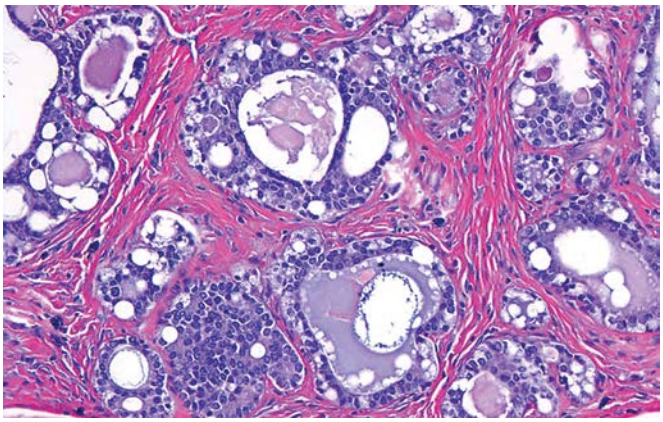


FIGURE 17 Nests of malignant epithelial cells embedded in a fibroadenoma, mammary gland, female rat, H&E. (Reproduced with permission of Society of Toxicologic Pathology from Rudmann, D. et al. 2012.)

Reference

Rudmann, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse mammary, Zymbal's, preputial, and clitoral glands. *Toxicol Pathol* 40(6 Suppl):7S–39S.

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https://www.ncbi.nlm.nih.gov/pubmed/22949413
http://www.goreni.org/

Mammary gland adenoma is a benign neoplasm of the mammary gland characterized by a well-demarcated and compressive area composed of dense, generally well-differentiated alveolar and tubular epithelium. The neoplasms may form solid, cystic, papillary, tubular, or undifferentiated structures but are well-demarcated tumors composed of differentiated epithelial cells. These neoplasms can occur in all laboratory species. In laboratory rats, adenomas are uncommon spontaneous tumors; fibroadenoma is the most frequent tumor observed.

Differential diagnoses: **Mammary tumor, mixed**; **Mammary gland hyperplasia with atypia**.

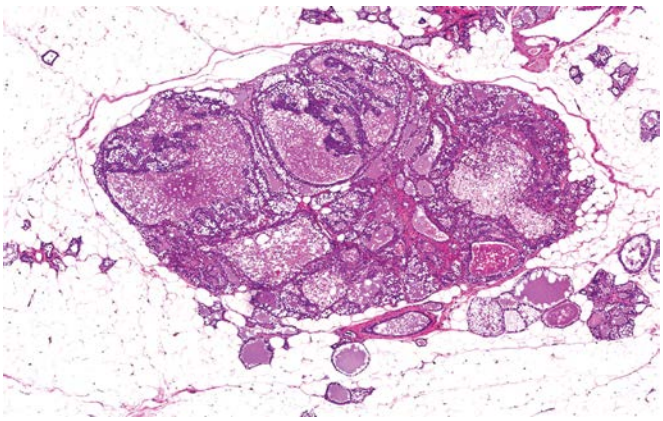


FIGURE 18 Mammary gland adenoma, female rat, H&E. (Reproduced with permission of Society of Toxicologic Pathology from Rudmann, D. et al. 2012.)

Reference

Rudmann, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse mammary, Zymbal's, preputial, and clitoral glands. *Toxicol Pathol* 40(6 Suppl):7S–39S.

Links

https://www.ncbi.nlm.nih.gov/pubmed/22949413
http://www.goreni.org/

Mammary gland ductal hyperplasia in females is characterized by extralobular ducts that have a stratified (usually three or more layers) epithelium. Epithelial cells are well differentiated and have increased vacuolation and/or cytoplasmic volume. The cytoplasm may be basophilic, and mitoses apparent. Ductal hyperplasia has been reported in rhesus monkeys administered sex steroids, and similar changes have been observed in dogs and rodents. In rodents, the change is observed in carcinogenicity studies either spontaneously or as a xenobiotic effect, but both are diagnosed as focal hyperplasia.

Differential diagnosis: **Mammary gland hyperplasia, focal with atypia**.

Reference

Rudmann, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse mammary, Zymbal's, preputial, and clitoral glands. *Toxicol Pathol* 40(6 Suppl):7S–39S.

Links

https://www.ncbi.nlm.nih.gov/pubmed/22949413
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Mammary gland fibroadenoma is a benign neoplasm composed of a mixture of predominantly fibrous connective tissue with variable numbers of epithelial cells, forming ducts or acini. The fibrous connective tissue predominates over the epithelial component and varies in level of cellularity. Both the epithelial and fibrous connective tissue components are well differentiated and delineated from normal mammary gland. Mitoses are rare.

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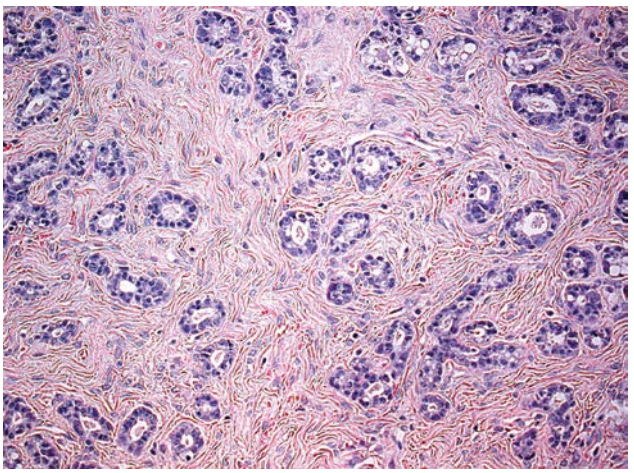


FIGURE 19 Fibroadenoma, mammary gland, female rat, H&E. (Reproduced with permission of Society of Toxicologic Pathology from Rudmann, D. et al. 2012.)

Reference

Rudmann, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse mammary, Zymbal's, preputial, and clitoral glands. *Toxicol Pathol* 40(6 Suppl):7S–39S.

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https://www.ncbi.nlm.nih.gov/pubmed/22949413
http://www.goreni.org/

Mammary gland hyperplasia, focal with atypia is the focal and irregular proliferation of mammary gland ductal or alveolar epithelium. It can occur within an area of lobuloalveolar hyperplasia or within otherwise normal mammary glands. Epithelial cells have some level of atypia with basophilic or eosinophilic cytoplasm and anisokaryosis and hyperchromatic or vesicular nuclear chromatin. Epithelial cells may be organized in solid nests or form papillary structures.

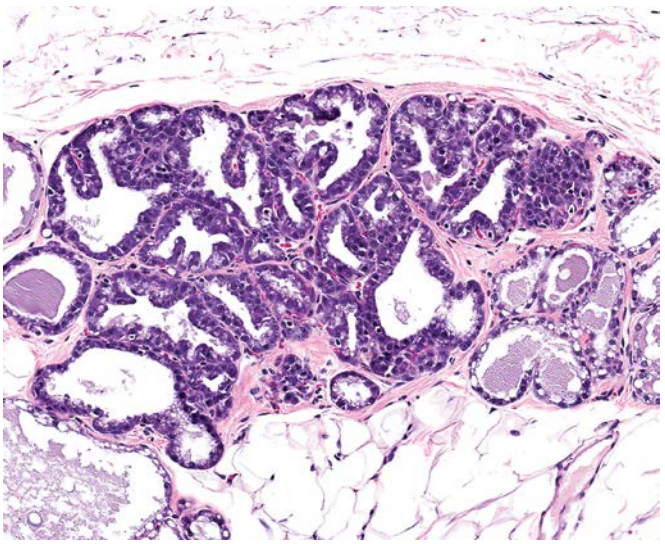


FIGURE 20 Atypical hyperplasia, mammary gland, female rat, H&E. (Reproduced with permission of Society of Toxicologic Pathology from Rudmann, D. et al. 2012.)

Reference

Rudmann, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse mammary, Zymbal's, preputial, and clitoral glands. *Toxicol Pathol* 40(6 Suppl):7S–39S.

Links

https://www.ncbi.nlm.nih.gov/pubmed/22949413
http://www.goreni.org/

Mammary gland hyperplasia, lobuloalveolar, see the preferred term **Mammary gland lobular hyperplasia**.

Mammary gland hyperplastic alveolar nodule (HAN) is a form of mammary lobular hyperplasia that occurs in high incidence in mice harboring mouse mammary tumor virus (MMTV). HAN are composed of groups of alveoli lined by small basophilic epithelial cells with mitotic and secretory activity, and cellular atypia. HAN is the primary lesion that precedes and gives rise to mammary tumors in mice infected with MMTV and are thus considered preneoplastic and have a high risk of malignant transformation. HAN can develop spontaneously but at a lower incidence than in MMTV infected mice.

Reference

Rudmann, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse mammary, Zymbal's, preputial, and clitoral glands. *Toxicol Pathol* 40(6 Suppl):7S–39S.

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https://www.ncbi.nlm.nih.gov/pubmed/22949413
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Mammary gland lobular hyperplasia is characterized by epithelial proliferation in the intralobular ductules (acini) of the mammary gland. Lobular hyperplasia may be focal or diffuse and may occur with or without cellular atypia. Lobular

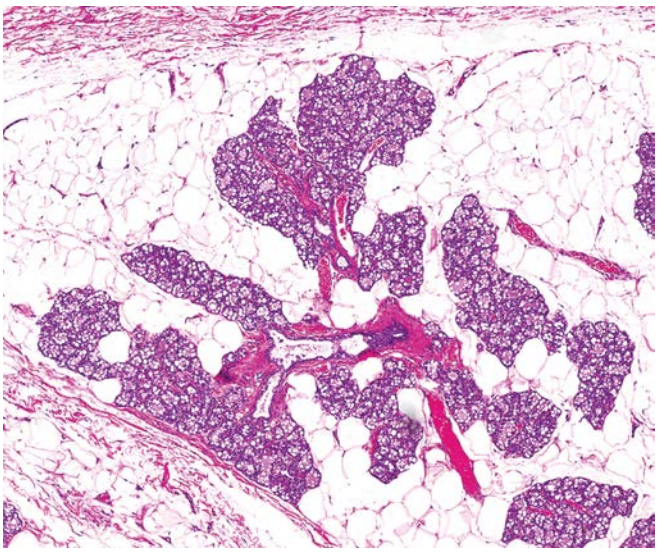


FIGURE 21 Mammary gland lobular hyperplasia, female rat, H&E. (Reproduced with permission of Society of Toxicologic Pathology from Rudmann, D. et al. 2012.)

hyperplasia is a common form of mammary gland hyperplasia observed in rodents and beagles. Diffuse hyperplasia is usually physiologic and is prominent in late gestation and during lactation (see **Pseudopregnancy** for further information). Lobular alveolar hyperplasia may result from xenobiotics that increase prolactin in female rats. It has been induced in dogs and rhesus macaques treated with oral contraceptive steroids, and in dogs treated with progesterone.

Synonym(s): **Mammary gland hyperplasia, lobuloalveolar**; **mammary gland pseudopregnancy**.

References

Lucas, J. et al. 2007. The rat mammary gland: Morphologic changes as an indicator of systemic hormonal perturbations induced by xenobiotics. *Toxicol Pathol* 35(2):199–207.

Rudmann, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse mammary, Zymbal's, preputial, and clitoral glands. *Toxicol Pathol* 40(6 Suppl):7S–39S.

Links

http://journals.sagepub.com/doi/full/10.1080/01926230601156260
https://www.ncbi.nlm.nih.gov/pubmed/22949413
http://www.goreni.org/

Mammary gland pseudopregnancy, see the preferred term **Mammary gland lobular hyperplasia**.

Mammary tumor, mixed is a neoplasm of the dog mammary gland that is composed of at least one epithelial and one mesenchymal (myoepithelial) component, with fibrous stroma and foci of cartilage, bone, and/or adipose tissue. In benign tumors, both components lack features of malignancy; in malignant tumors, at least one component exhibits features of malignancy. In dogs, the most common presentation of the malignant mixed tumor is a carcinoma and osteosarcoma. Benign mixed mammary tumor is common in dogs but uncommon in other laboratory species.

Synonym(s): **Mammary carcinosarcoma**.

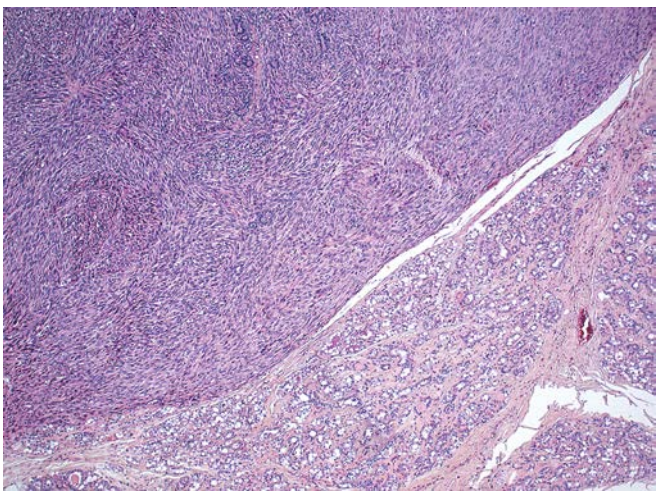


FIGURE 22 Mixed mammary gland tumor, sarcomatous and adenocarcinomatous areas intermixed, female rat, H&E. (Reproduced with permission of Society of Toxicologic Pathology from Rudmann, D. et al. 2012.)

References

Goldschmidt, M. et al. 2011. Classification and grading of canine mammary tumors. *Vet Pathol* 48(1):117–131.

Rudmann, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse mammary, Zymbal's, preputial, and clitoral glands. *Toxicol Pathol* 40(6 Suppl):7S–39S.

Links

http://journals.sagepub.com/doi/full/10.1177/0300985810393258
https://www.ncbi.nlm.nih.gov/pubmed/22949413
http://www.goreni.org/

Mesovarial leiomyoma is a benign neoplasm of smooth muscle located in the mesovarium. Leiomyomas of the mesovarium are morphologically similar to those of other parts of the female reproductive tract. They are typically well-circumscribed, benign tumors of smooth muscle, and are composed of interlacing bundles of uniform spindle cells, characteristically with blunt ended nuclei (cigar-shaped) and cytoplasmic myofibrils. Leiomyoma of the mesovarium is a rare spontaneous tumor in laboratory species that has been induced with β_2 adrenergic receptor agonists in rats but not mice, and was prevented by coadministration of propranolol.

Differential diagnosis: **Mesovarial smooth muscle hyperplasia**.

Reference

Dixon, D. et al. 2014. Nonproliferative and proliferative lesions of the rat and mouse female reproductive system. *J Toxicol Pathol* 27(3–4 Suppl):1S–107S.

Links

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/
http://www.goreni.org/

Mesovarial smooth muscle hyperplasia is characterized by irregular areas of parallel-arranged, smooth muscle fiber proliferation within the mesovarium, suspensory ligaments, or ovarian hilus. Mesovarial smooth muscle hyperplasia has been induced with β_2 adrenergic receptor agonists in rats but not in mice and was prevented by coadministration of propranolol.

Differential diagnosis: **Mesovarial leiomyoma**.

Reference

Dixon, D. et al. 2014. Nonproliferative and proliferative lesions of the rat and mouse female reproductive system. *J Toxicol Pathol* 27(3–4 Suppl):1S–107S.

Links

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/
http://www.goreni.org/

Mullerian tumor, mixed, benign is most commonly observed in the uterus or ovary and believed to arise from the pluripotent cells of the Mullerian ducts, which can give rise to cells of both epithelial and stromal types. The tumor is rare in domestic and laboratory animals. The benign tumor is

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composed of an admixture of well-differentiated benign epithelial and benign mesenchymal elements. The mesenchymal component can display a variety of patterns that have been referred to as homologous (i.e., has differentiation toward cell types normally present in the uterus such as fibrous tissue, smooth muscle, or endometrial stroma-like tissue) or heterologous (i.e., contains areas with cell types not normally present in the uterus such as striated muscle, cartilage, bone, and/or adipose tissue).

Differential diagnoses: **Teratoma**; **Endometrial adenoma**.

Reference

Dixon, D. et al. 2014. Nonproliferative and proliferative lesions of the rat and mouse female reproductive system. *J Toxicol Pathol* 27(3–4 Suppl):1S–107S.

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https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/
http://www.goreni.org/

Mullerian tumor, mixed, malignant is less common than its benign counterpart in the uterus or ovary, and is believed to arise from the pluripotent cells of the Mullerian ducts, which can give rise to cells of both epithelial and stromal types. The neoplasm is characterized by an admixture of malignant epithelial and mesenchymal elements. The mesenchymal component displays a variety of patterns that have been referred to as homologous (i.e., has differentiation toward cell types normally present in the uterus such as fibrous tissue, smooth muscle, or endometrial stroma-like tissue) or heterologous (i.e., contains areas with cell types not normally present in the uterus such as striated muscle, cartilage, bone, and/or adipose tissue).

Synonym(s): **Uterus/ovary benign mixed mesodermal tumor**; **uterus/ovary carcinosarcoma (for homologous malignant tumors)**; **uterus/ovary mixed mesodermal tumor (for heterologous neoplasms)**.

Reference

Dixon, D. et al. 2014. Nonproliferative and proliferative lesions of the rat and mouse female reproductive system. *J Toxicol Pathol* 27(3–4 Suppl):1S–107S.

Links

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/
http://www.goreni.org/

Myometrial hyperplasia is a focal or diffuse lesion within the myometrium of the uterus consisting of irregular zones of hypercellularity of well-differentiated smooth muscle cells with an increased nucleus:cell ratio but without nuclear atypia. Collagen may be interspersed between smooth muscle cells. This is an uncommon lesion in rats and mice but is a common structural variation in humans and not reported in the nonhuman primate.

Differential diagnosis: **Myometrial leiomyoma**.

Reference

Dixon, D. et al. 2014. Nonproliferative and proliferative lesions of the rat and mouse female reproductive system. *J Toxicol Pathol* 27(3–4 Suppl):1S–107S.

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https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/
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Myometrial leiomyoma, see the preferred term **Female sex organ, leiomyoma**

Ovarian cystadenocarcinoma is an infiltrative, malignant neoplasm of the surface epithelium of the ovary. The neoplasm is composed of pleomorphic cuboidal or low columnar epithelial cells organized in solid or cystic masses. Mitoses are common. While also derived from the surface epithelium like the tubulostromal carcinoma, tumor stroma for a cystadenocarcinoma is sparse and tubules are less differentiated.

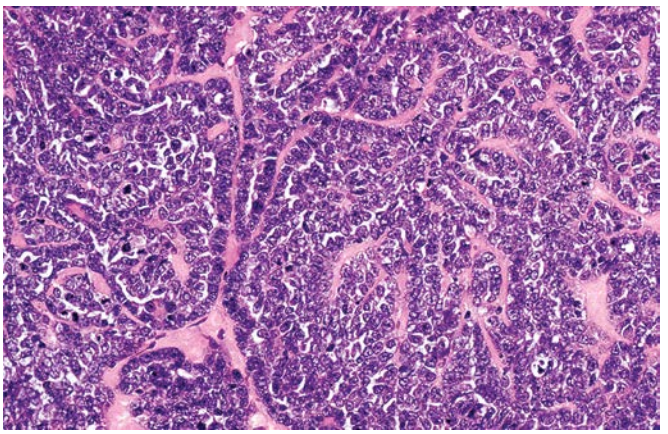


FIGURE 23 Cystadenocarcinoma, ovary, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Dixon, D. et al. 2014.)

Reference

Dixon, D. et al. 2014. Nonproliferative and proliferative lesions of the rat and mouse female reproductive system. *J Toxicol Pathol* 27(3–4 Suppl):1S–107S.

Links

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/
http://www.goreni.org/

Ovarian cystadenoma is a benign neoplasm derived from the surface epithelium of the ovary that is composed of well-differentiated cuboidal or low columnar epithelial cells. The neoplasm is organized in solid or cystic masses. Necrosis and hemorrhage are not common and there is no local invasion. Mitoses are rare.



FIGURE 24 Cystadenoma, ovary, mouse, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Dixon, D. et al. 2014.)

Reference

Dixon, D. et al. 2014. Nonproliferative and proliferative lesions of the rat and mouse female reproductive system. *J Toxicol Pathol* 27(3–4 Suppl):1S–107S.

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https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/
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Ovarian epithelial hyperplasia, see the preferred term **Ovarian tubulostromal hyperplasia**.

Ovarian granulosa cell hyperplasia is a proliferative change of granulosa cells (one type of sex cord stromal cells) in the ovarian follicle consisting of cystic or solid groups of sex cord stromal cells in which >70% of the cells comprising the lesion are granulosa cells. Granulosa cell hyperplasia may be associated with increased serum levels of estrogen and has been induced by selective estrogen receptor modulators.

Differential diagnoses: Vaginal granulosa cell tumor; **Luteoma**.

References

Dixon, D. et al. 2014. Nonproliferative and proliferative lesions of the rat and mouse female reproductive system. *J Toxicol Pathol* 27(3–4 Suppl):1S–107S.

Long, G. et al. 2001. Proliferative lesions of ovarian granulosa cells and reversible hormonal changes induced in rats by a selective estrogen receptor modulator. *Toxicol Pathol* 29(6):719–726.

Links

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/
http://journals.sagepub.com/doi/abs/10.1080/019262301753386031?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed
http://www.goreni.org/

Ovarian granulosa cell tumor, benign is a proliferative change of granulosa cells (one type of sex cord stromal cell) in the ovarian follicle consisting of a compressive, cystic, or solid group of well-differentiated sex cord stromal cells in which >70% of the cells comprising the lesion are granulosa cells. Granulosa cell tumors may secrete estrogens or androgens and have been reported in rats treated with selective estrogen receptor modulators. Granulosa cell tumors are the most common sex cord stromal tumors in domestic animals; they are common in rodents, particularly certain strains of mice, and have also been reported in dogs and primates. They have been induced by xenobiotics (e.g., in mice with diethylstilbestrol [DES], dimethylbenzanthracene) and irradiation.

Differential diagnoses: **Ovarian granulosa cell hyperplasia**; Luteal cell tumor, benign.

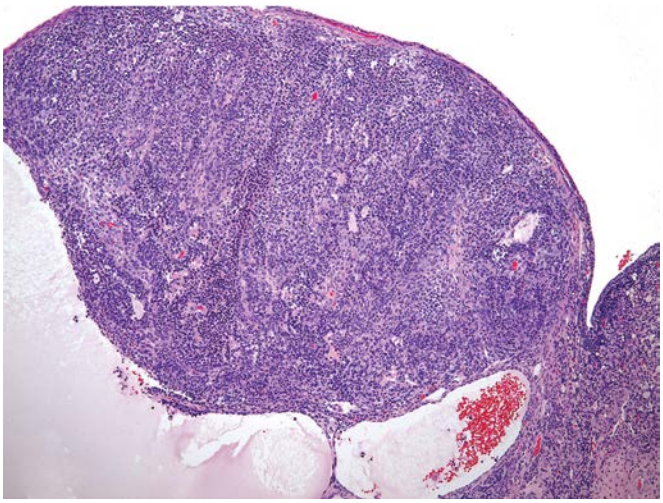


FIGURE 25 Granulosa cell hyperplasia, ovary, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Dixon, D. et al. 2014.)

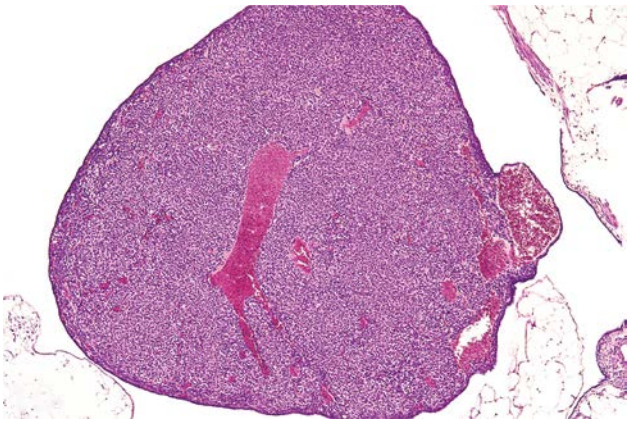


FIGURE 26 Granulosa cell tumor, benign, ovary, mouse, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Dixon, D. et al. 2014.)

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Reference

Dixon, D. et al. 2014. Nonproliferative and proliferative lesions of the rat and mouse female reproductive system. *J Toxicol Pathol* 27(3–4 Suppl):1S–107S.

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https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/
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Ovarian granulosa cell tumor, malignant is a proliferative change of granulosa cells (one type of sex cord stromal cell) in the ovarian follicle consisting of a compressive, cystic, or solid group of poorly differentiated sex cord stromal cells in which >70% of the cells comprising the lesion are granulosa cells. There is either local invasion and/or distant metastases and mitoses are frequent. Granulosa cell tumors may secrete estrogens or androgens, and have been reported in rats treated with selective estrogen receptor modulators. Granulosa cell tumors are the most common sex cord stromal tumors in domestic animals; they are common in rodents, particularly certain strains of mice, and have also been reported in dogs and primates. They have been induced by xenobiotics (e.g., in mice with diethylstilbestrol [DES], dimethylbenzanthracene) and irradiation.

Differential diagnoses: **Ovarian granulosa cell hyperplasia**; **Luteoma**.

Reference

Dixon, D. et al. 2014. Nonproliferative and proliferative lesions of the rat and mouse female reproductive system. *J Toxicol Pathol* 27(3–4 Suppl):1S–107S.

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https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/
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Ovarian Sertoli cell tumor, benign is a neoplasm characterized by a cluster of well-differentiated Sertoli cells that has a size greater than that of a corpus luteum (CL) and is encapsulated and compresses the adjacent parenchyma. See **Ovarian sex cord stromal tumor** and **Testicular Sertoli cell tumor** for further information.

Differential diagnoses: **Sertoli cell hyperplasia**; **Ovarian granulosa cell tumor, benign**; **Thecal cell tumor, benign**.

Reference

Dixon, D. et al. 2014. Nonproliferative and proliferative lesions of the rat and mouse female reproductive system. *J Toxicol Pathol* 27(3–4 Suppl):1S–107S.

Links

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/
http://www.goreni.org/

Ovarian Sertoli cell tumor, malignant is a locally invasive malignant neoplasm characterized by poorly differentiated Sertoli cells organized in nests or sheets that are often interwoven and palisading. Neoplastic Sertoli cells have a high mitotic index and considerable atypia. There may be neoplasm-associated hemorrhage and necrosis. Stroma is delicate and scant.

Synonym(s): **Arrhenoblastoma**.

Reference

Dixon, D. et al. 2014. Nonproliferative and proliferative lesions of the rat and mouse female reproductive system. *J Toxicol Pathol* 27(3–4 Suppl):1S–107S.

Links

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/
http://www.goreni.org/

Ovarian tubulostromal adenoma is a benign neoplasm of the surface epithelium of the ovary, is larger than a corpus luteum (CL), and compresses adjacent ovarian parenchyma. The neoplasm is composed of fine tubules lined by cuboidal cells with slight pleomorphism and atypia. The neoplasm is supported by a variable amount of stroma, which may include nests of luteinized sex cord and stromal cells. There

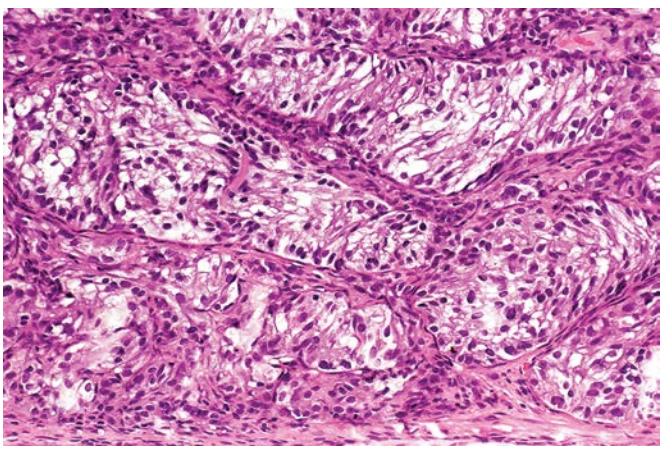


FIGURE 27 Sertoli cell tumor, benign, ovary, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Dixon, D. et al. 2014.)

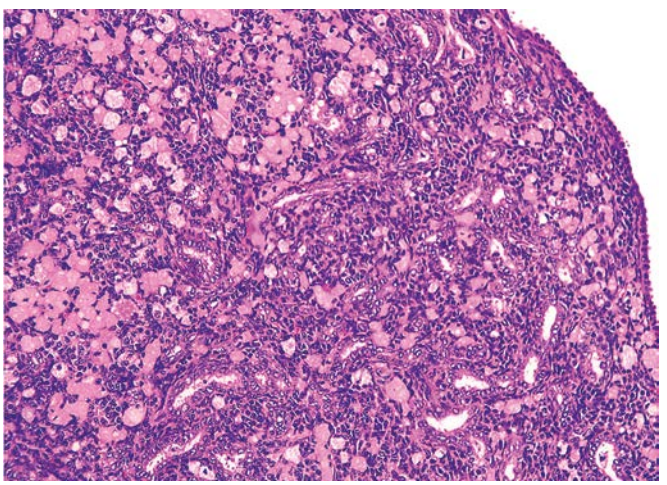


FIGURE 28 Adenoma, tubulostromal, ovary, mouse, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Dixon, D. et al. 2014.)

may be local invasion but it is normally limited to the ovarian bursa.

Differential diagnosis: **Ovarian tubulostromal hyperplasia**.

Reference

Dixon, D. et al. 2014. Nonproliferative and proliferative lesions of the rat and mouse female reproductive system. *J Toxicol Pathol* 27(3–4 Suppl):1S–107S.

Links

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/
http://www.goreni.org/

Ovarian tubulostromal carcinoma is a malignant neoplasm of the surface epithelium of the ovary, is larger than a corpus luteum (CL), and compresses adjacent ovarian parenchyma. The malignant neoplasm is composed of fine tubules lined by cuboidal cells with pleomorphism and atypia. The neoplasm is supported by a variable amount of stroma, which may include nests of luteinized sex cord and stromal cells. There is local invasion beyond the ovarian bursa, and often the presence of metastases.

Reference

Dixon, D. et al. 2014. Nonproliferative and proliferative lesions of the rat and mouse female reproductive system. *J Toxicol Pathol* 27(3–4 Suppl):1S–107S.

Links

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/
http://www.goreni.org/

Ovarian tubulostromal hyperplasia is characterized by expansion of well-differentiated ovarian surface epithelium. The epithelium forms delicate tubules infiltrating the ovary along with a variable amount of stroma. The lesion is often diffuse, but noncompressive; if focal, the proliferative focus is smaller than a corpus luteum (CL). In mice, it may circumscribe the ovary. There is minimal or no cellular atypia. Ovarian tubulostromal hyperplasia is distinguished from sex cord stromal hyperplasia based on the connection with the surface epithelium, and the predominantly tubular growth pattern.

Differential diagnoses: **Ovarian tubulostromal adenoma**; **Ovarian cystadenoma**.

Synonym(s): **Ovarian epithelial hyperplasia**.

Reference

Dixon, D. et al. 2014. Nonproliferative and proliferative lesions of the rat and mouse female reproductive system. *J Toxicol Pathol* 27(3–4 Suppl):1S–107S.

Links

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/
http://www.goreni.org/

Sertoli cell hyperplasia is an increased number of Sertoli cells in the ovary; if focal, the increased cellularity is an area smaller than a large corpus luteum, and if diffuse does not enlarge the ovary. In areas of hyperplasia, Sertoli cells form focal nests or seminiferous-like tubules. Sertoli cell hyperplasia may be seen during reproductive senescence in rodents.

Differential diagnosis: **Sex cord mixed stromal hyperplasia**.

Reference

Dixon, D. et al. 2014. Nonproliferative and proliferative lesions of the rat and mouse female reproductive system. *J Toxicol Pathol* 27(3–4 Suppl):1S–107S.

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Sex cord mixed stromal hyperplasia is characterized by increased ovarian stromal and sex cord cells with minimal or no compression of surrounding ovarian tissue. The

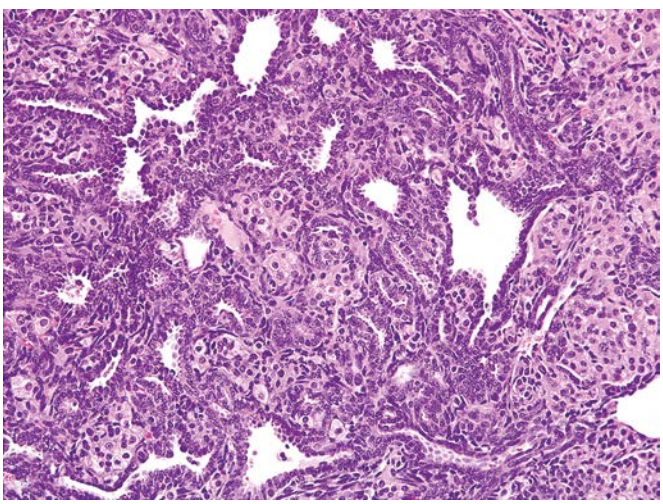


FIGURE 29 Hyperplasia, tubulostromal, ovary, mouse, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Dixon, D. et al. 2014.)

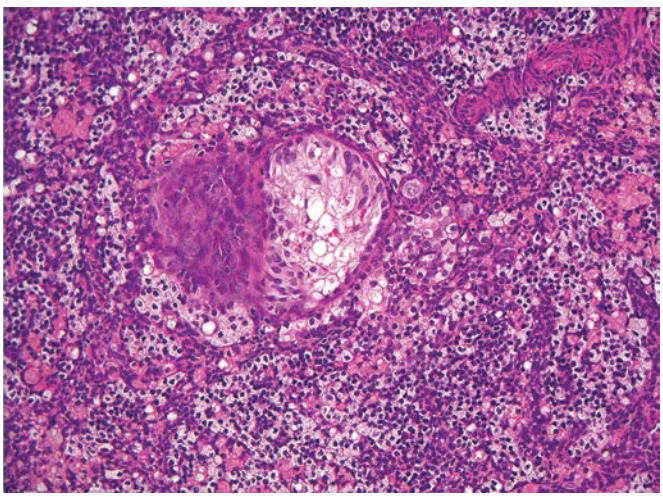


FIGURE 30 Sex cord mixed stromal hyperplasia, ovary, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Dixon, D. et al. 2014.)

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increased number of cells represents an admixture of theca, luteal, granulosa and/or Sertoli cells, with no single cell type predominating. Focal lesions are smaller than a large corpus luteum; diffuse lesions are nondiscrete and smaller than the size of a normal ovary. In the female rat and mouse, stromal sex cord hyperplasia is common during reproductive senescence.

Differential diagnosis: **Sex cord stromal tumor, benign**.

Reference

Dixon, D. et al. 2014. Nonproliferative and proliferative lesions of the rat and mouse female reproductive system. *J Toxicol Pathol* 27(3–4 Suppl):1S–107S.

Links

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/
http://www.goreni.org/

Sex cord stromal tumor, benign is a group of neoplasms that originate from the hormone-producing gonadal stromal cells. In the ovary, these can include estrogen-producing granulosa and Sertoli cells, androgen-producing theca and Leydig cells, progesterone-producing luteal cells, and/or fusiform thecal cells. While sex cord stromal tumors are not always associated with increased hormone production, it is a common feature that distinguishes this tumor type from the epithelial-origin ovarian neoplasms. Benign sex cord stromal tumors are composed of a mixed cell population with variable degrees of differentiation and a low mitotic index that may be compressive but do not demonstrate appreciable necrosis and do not invade or metastasize. Most sex cord stromal tumors have some mixed cell components, but a benchmark of 70% predominance is used to distinguish specific tumor types. Types of benign sex cord stromal tumors include gonadal stromal tumor, benign; granulosa-theca cell tumor, benign; and luteoma, benign.

Differential diagnosis: **Sex cord mixed stromal hyperplasia**.

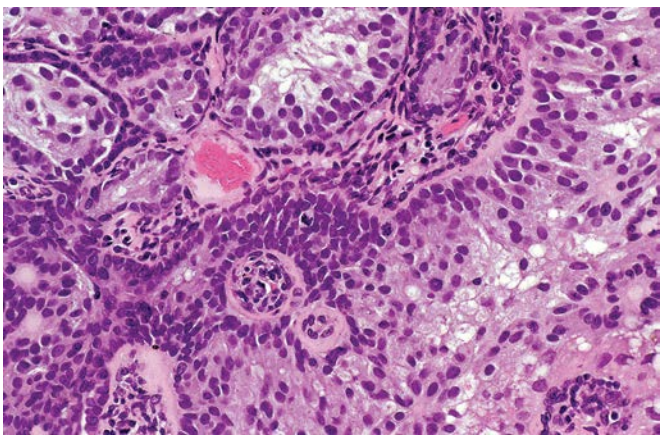


FIGURE 31 Sex cord mixed tumor, ovary, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Dixon, D. et al. 2014.)

Reference

Dixon, D. et al. 2014. Nonproliferative and proliferative lesions of the rat and mouse female reproductive system. *J Toxicol Pathol* 27(3–4 Suppl):1S–107S.

Links

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/
http://www.goreni.org/

Sex cord stromal tumor, malignant is a group of neoplasms that originate from the hormone-producing gonadal stromal cells. In the ovary, these can include estrogen-producing granulosa and Sertoli cells, androgen-producing theca and Leydig cells, progesterone-producing luteal cells, and/or fusiform thecal cells. While sex cord stromal tumors are not always associated with increased hormone production, it is a common feature that distinguishes this tumor type from the epithelial-origin ovarian neoplasms. Malignant tumors have necrosis, local invasion, and/or metastases and may be composed of a mixed cell population with variable degrees of differentiation. Most sex cord stromal tumors have some mixed cell components, but a benchmark of 70% predominance is used to distinguish specific tumor types. Types of malignant sex cord stromal tumors include gonadal stromal tumor, malignant; granulosa-theca cell tumor, malignant; and mixed tumor, malignant.

Reference

Dixon, D. et al. 2014. Nonproliferative and proliferative lesions of the rat and mouse female reproductive system. *J Toxicol Pathol* 27(3–4 Suppl):1S–107S.

Links

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/
http://www.goreni.org/

Theca cell hyperplasia is an increased number of thecal cells in the ovary; if focal, the increased cellularity is an area smaller than a large corpus luteum, and if diffuse does not enlarge the ovary. In areas of hyperplasia, theca cells may be fusiform or plump and vacuolated, and may be associated with increased androgen production. Theca cell hyperplasia may be seen during reproductive senescence.

Differential diagnosis: **Theca cell tumor, benign**.

Reference

Dixon, D. et al. 2014. Nonproliferative and proliferative lesions of the rat and mouse female reproductive system. *J Toxicol Pathol* 27(3–4 Suppl):1S–107S.

Links

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/
http://www.goreni.org/

Theca cell tumor, benign is a sex cord stromal tumor in which the predominant cell type is the theca cell. This neoplasm may produce androgenic steroid hormones. Benign theca cell tumors are characterized by a size greater than a

corpus luteum (CL), encapsulation, and compression of adjacent parenchyma.

Differential diagnosis: **Theca cell hyperplasia**.

Synonym(s): **Thecoma**.

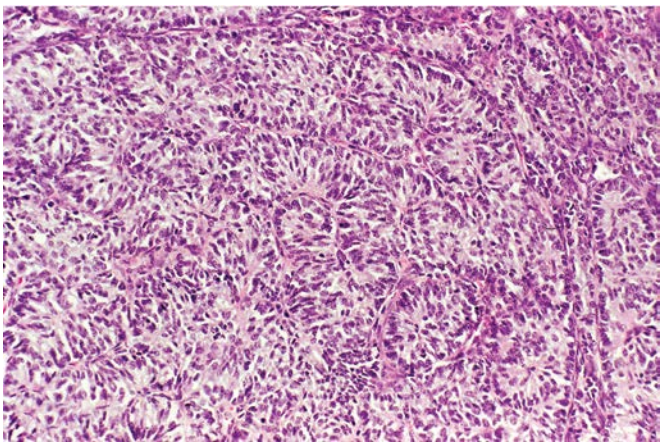


FIGURE 32 Theca cell tumor, benign, ovary, mouse, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Dixon, D. et al. 2014.)

Reference

Dixon, D. et al. 2014. Nonproliferative and proliferative lesions of the rat and mouse female reproductive system. *J Toxicol Pathol* 27(3–4 Suppl):1S–107S.

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https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/
http://www.goreni.org/l

Theca cell tumor, malignant is a sex cord stromal tumor in which the predominant cell type is the theca cell. This neoplasm may produce androgenic steroid hormones. Features indicative of malignancy include increased mitoses and cellular atypia, local invasion, hemorrhage, necrosis, and metastases.

Synonym(s): **Thecoma, malignant**.

Reference

Dixon, D. et al. 2014. Nonproliferative and proliferative lesions of the rat and mouse female reproductive system. *J Toxicol Pathol* 27(3–4 Suppl):1S–107S.

Links

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/
http://www.goreni.org/

Thecoma, see the preferred term **Theca cell tumor, benign**.

Thecoma, malignant, see the preferred term **Theca cell tumor, malignant**.

Uterine angiomatous hyperplasia is a nonneoplastic alteration of the uterine endometrium or myometrium characterized by a well-demarcated, noncompressive focus that contains a higher number of capillaries or other vascular spaces which are often blood-filled and lined by normal appearing endothelial cells. These changes have been reported in mice treated with peroxisome proliferator-activated receptor (PPAR) agonists.

Synonym(s): **Uterine stromal angiomatous hyperplasia**.

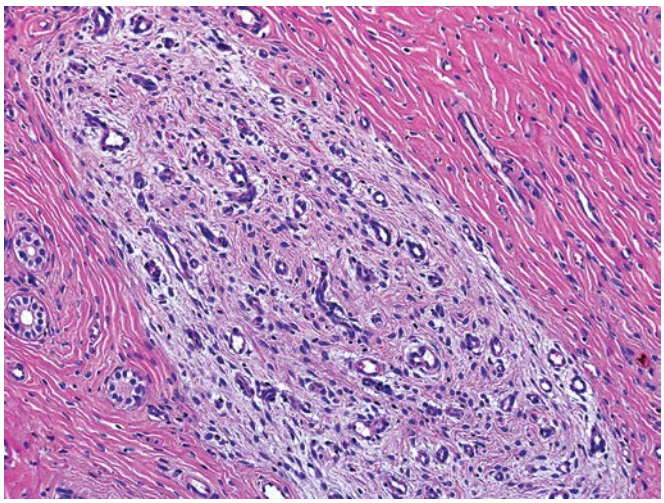


FIGURE 33 Angiomatous hyperplasia, proliferation of small vessels in endometrial stroma, uterus, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Dixon, D. et al. 2014.)

References

Dixon, D. et al. 2014. Nonproliferative and proliferative lesions of the rat and mouse female reproductive system. *J Toxicol Pathol* 27(3–4 Suppl):1S–107S.

Hardisty, J. et al. 2007. Histopathology of hemangiosarcomas in mice and hamsters and liposarcomas/fibrosarcomas in rats associated with PPAR agonists. *Toxicol Pathol* 35(7):928–941.

Links

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2366205/
http://www.goreni.org/

Uterine sarcoma is a malignant neoplasm of the myometrium (see **Female sex organs, leiomyosarcoma** for further information) or of the endometrial stroma (see **Endometrial stromal sarcoma** for further information). Uterine sarcomas appear as poorly demarcated, infiltrative masses composed of irregular fascicles of fusiform to anaplastic mesenchymal cells. Features of malignancy used to differentiate from a benign mesenchymal tumor, such as a uterine leiomyoma, include degree of infiltration, relative cell density, prominence of mitoses, and nuclear atypia. Sarcomas originating from smooth muscle cells may have giant cells with multiple irregular nuclei. Both benign and malignant tumors of the uterine wall may be large to multinodular and may have areas of hemorrhage or necrosis.

A2

Reference

Dixon, D. et al. 2014. Nonproliferative and proliferative lesions of the rat and mouse female reproductive system. *J Toxicol Pathol* 27(3–4 Suppl):1S–107S.

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https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/
http://www.goreni.org/

Uterine stromal angiomatous hyperplasia, see the preferred term **Uterine angiomatous hyperplasia**.

Uterus/ovary benign mixed mesodermal tumor, see the preferred term **Mullerian tumor, mixed**.

Uterus/ovary carcinosarcoma (for homologous malignant tumors), see the preferred term **Mullerian tumor, mixed**.

Uterus/ovary mixed mesodermal tumor (for heterologous neoplasms), see the preferred term **Mullerian tumor, mixed**.

Vaginal carcinoma is an exophytic epithelial growth with squamous cell differentiation over a thin fibrovascular core that invades the submucosa, has a more disorganized growth pattern, numerous mitoses, and more cellular atypia than the vaginal papilloma.

Reference

Dixon, D. et al. 2014. Nonproliferative and proliferative lesions of the rat and mouse female reproductive system. *J Toxicol Pathol* 27(3–4 Suppl):1S–107S.

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https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/
http://www.goreni.org/

Vaginal granular cell tumor is an expansile cluster of a uniform population of neoplastic cells with small basophilic nuclei and abundant granular eosinophilic cytoplasm that are periodic acid-Schiff (PAS)-positive and diastase resistant, sometimes admixed with smaller cells containing small, dark, uniform nuclei and relatively few cytoplasmic granules. Variable amounts of interstitial collagen are also observed. By transmission electron microscopy, the granules appear to be secondary lysosomes. Benign tumors are well circumscribed, while malignant tumors are larger and more pleomorphic, and may have areas of necrosis. In the female rodent reproductive tract, granular cell tumors occur in the endometrium or in wall of the cervix and vagina. In the rodent reproductive tract, cells comprising a granular cell tumor may be of Schwann cell, smooth muscle cell, and/or endometrial gland epithelial cell origin, but a definitive parental cell type has not yet been identified. Granular cell lesions are spontaneous findings in the reproductive tract of aging female rodents, but increases have been reported in mice treated with estrogenic substances.

Differential diagnosis: Vaginal granular cell hyperplasia.

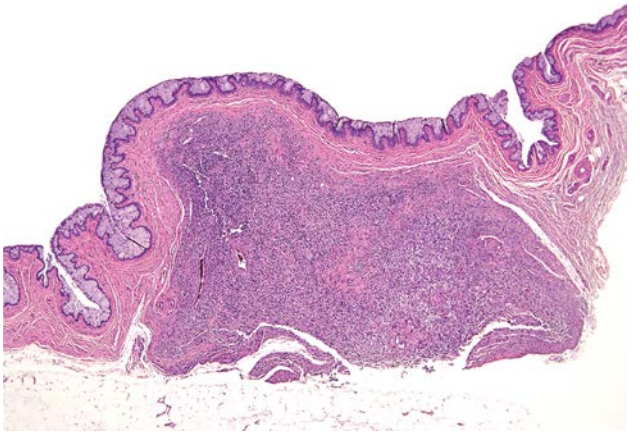


FIGURE 34 Granular cell tumor, benign, vagina, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Dixon, D. et al. 2014.)

Reference

Dixon, D. et al. 2014. Nonproliferative and proliferative lesions of the rat and mouse female reproductive system. *J Toxicol Pathol* 27(3–4 Suppl):1S–107S.

Links

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/
http://www.goreni.org/

Vaginal papilloma is an exophytic epithelial growth with squamous cell differentiation over a thin fibrovascular core. The cells are well-differentiated without atypia or local invasion, but the papilloma mass is often associated with inflammation secondary to trauma. The papilloma is distinguished from the vaginal polyp based on epithelial rather than stromal predominance for the mass.

Differential diagnosis: **Vaginal polyp**.

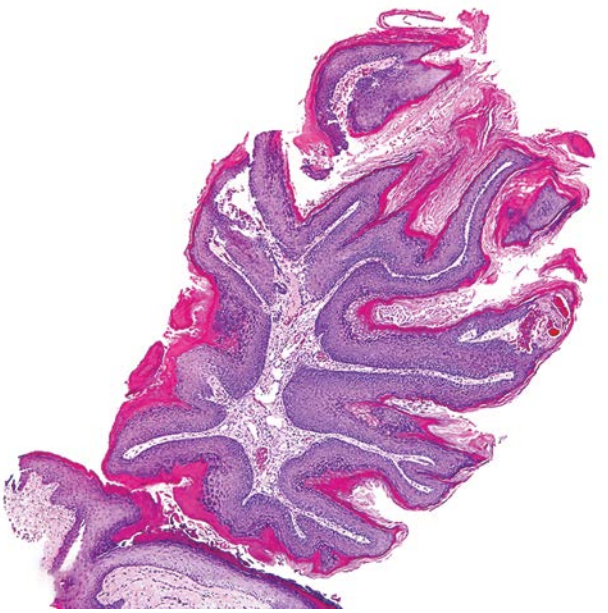


FIGURE 35 Papilloma, vaginal, mouse, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Dixon, D. et al. 2014.)

Reference

Dixon, D. et al. 2014. Nonproliferative and proliferative lesions of the rat and mouse female reproductive system. *J Toxicol Pathol* 27(3–4 Suppl):1S–107S.

Links

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/
http://www.goreni.org/

Vaginal polyp is an exophytic, benign, well-differentiated mass lesion of the vaginal mucosa and submucosa, often attached to the adjacent normal mucosa by a thin fibrovascular stalk. Vaginal polyps typically have a well-differentiated, stratified squamous epithelium over a dense fibrovascular to fibromuscular stroma; they may be single or multiple. Stromal edema or infarction may be present, and there may be areas of squamous hyperplasia and/or hyperkeratosis of the epithelium.

Differential diagnosis: **Vaginal papilloma**.

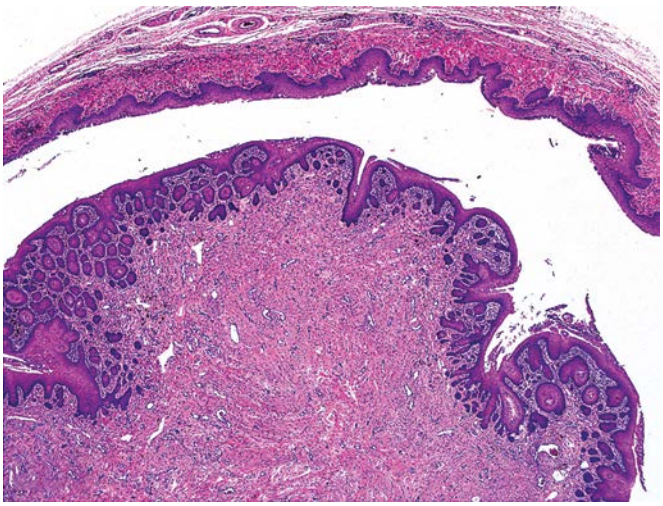


FIGURE 36 Polyp with epithelial hyperplasia, vagina, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Dixon, D. et al. 2014.)

Reference

Dixon, D. et al. 2014. Nonproliferative and proliferative lesions of the rat and mouse female reproductive system. *J Toxicol Pathol* 27(3–4 Suppl):1S–107S.

Links

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/
http://www.goreni.org/

Yolk sac carcinoma is a malignancy derived from endodermal sinus germ cells which form two distinct layers characteristic of the parietal and visceral layers of the yolk sac. Parietal layer cells are cuboidal and may form nests or rosettes. The neoplastic parietal layer cells contain periodic acid-Schiff (PAS)-positive cytoplasmic droplets and produce an abundant PAS-positive matrix. The neoplasm is typically laminin-positive when immunohistochemistry (IHC) is performed. The visceral layer cells are large cylindrical cells with a papillary growth pattern and endoderm-lined mesenchyme. Giant endodermal cells may surround blood-filled spaces. Yolk sac tumors are typically laminin-positive by IHC. The yolk sac carcinoma can be differentiated from the choriocarcinoma, ovarian cystadenocarcinoma, and endometrial carcinoma based on the presence of the PAS-positive matrix and granules. The embryonal carcinoma will also have well-differentiated tissue belonging to 1 or 2 germ cell layers, but otherwise resembles the yolk sac tumor.

Differential diagnoses: **Choriocarcinoma**; **Ovarian cystadenocarcinoma**; **Endometrial adenocarcinoma**.

Synonym(s): **Yolk sac tumor**; **endodermal sinus tumor, malignant**.

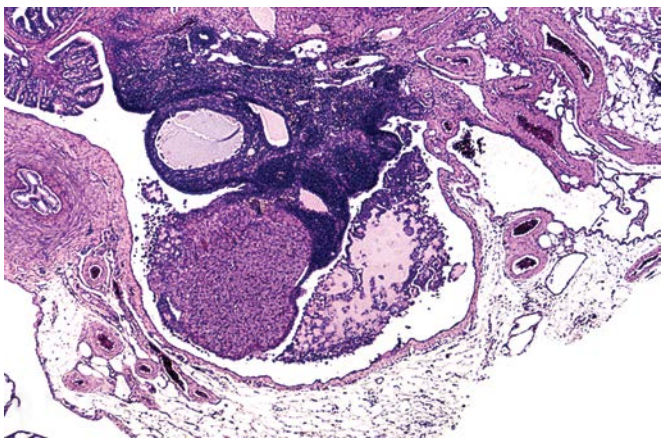


FIGURE 37 Yolk sac carcinoma, ovary, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Dixon, D. et al. 2014).

Reference

Dixon, D. et al. 2014. Nonproliferative and proliferative lesions of the rat and mouse female reproductive system. *J Toxicol Pathol* 27(3–4 Suppl):1S–107S.

Links

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/
http://www.goreni.org/

Yolk sac tumor, see the preferred term **Yolk sac carcinoma**.

REPRODUCTIVE SYSTEM AND MAMMARY GLAND: MALE

Abrikosoff tumor, see the preferred term **Accessory male sex organs, granular cell tumor, benign**.

Accessory male sex organs, adaptive hyperplasia, see the preferred term **Accessory male sex organs, hyperplasia, functional**.

Accessory male sex organs, adenocarcinoma (prostate, seminal vesicle, coagulating gland) is an uncommon spontaneous neoplasm in the seminal vesicle and prostate, and rare in the coagulative gland of rodents. These neoplasms are more

A2

common and well characterized in Nkx3.1+/–, Nkx3.1–/–, PTEN+/–, p27–/–, p53–/–, and hybrid crosses of genetically engineered mouse models of prostate cancer. Neoplastic cells are organized in pseudolobules separated by fibrous septa, are pleomorphic and/or anaplastic with basophilic nuclei, have numerous mitotic figures, and contain abundant eosinophilic cytoplasm. Pseudolobules may be cribriform, comedo-type, or solid subtypes. Frequently, there is focal necrosis, mixed inflammatory cell infiltrates, hemorrhage, squamous metaplasia, and both local invasion and metastases to regional lymph nodes, lung, and kidney. In the coagulating gland, cribriform adenocarcinoma may lack local invasion, but neoplastic cells have marked cellular and nuclear polymorphism. Adenocarcinomas are commonly induced in seminal vesicles and prostate following administration of carcinogenic xenobiotics.

Differential diagnoses: **Accessory male sex organs, adenoma**; **Granular cell tumor, benign**; **Granular cell tumor, malignant**.

Synonym(s): **Prostatic adenocarcinoma**.

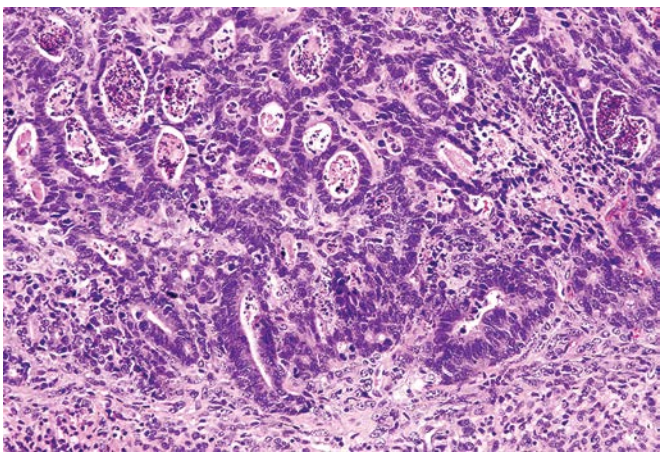


FIGURE 1 Prostatic carcinoma, mouse, H&E. (Reproduced with permission of Society of Toxicologic Pathology from Creasy, D. et al. 2012. Toxicol Pathol 40(6 Suppl):40S–121S.)

References

Creasy, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse male reproductive system. *Toxicol Pathol* 40(6 Suppl):40S–121S.

Park, J.H. et al. 2002. Prostatic intraepithelial neoplasia in genetically engineered mice. *Am J Pathol* 161(2):727–735.

Shappell, S.B. et al. 2004. Prostate pathology of genetically engineered mice: Definitions and classification. The consensus report from the Bar Harbor meeting of the Mouse Models of Human Cancer Consortium Prostate Pathology Committee. *Cancer Res* 15;64(6):2270–2305.

Links

https://www.ncbi.nlm.nih.gov/pubmed/22949412
http://www.goreni.org/
https://www.ncbi.nlm.nih.gov/pubmed/12163397
https://www.ncbi.nlm.nih.gov/pubmed/15026373

Accessory male sex organs, adenoma (prostate, seminal vesicle, coagulating gland) is an uncommon spontaneous neoplasm in the seminal vesicle and prostate, and rare in the coagulative gland of rodents. These neoplasms are more common and well characterized in Nkx3.1+/–, Nkx3.1–/–, PTEN+/–, p27–/–, p53–/–, and hybrid crosses of genetically engineered mouse models of prostate cancer. Data from mouse models of prostate cancer indicate that there is a morphologic continuum from focal atypical hyperplasia to benign adenoma and to adenocarcinoma. In the prostate, adenomas generally involve more than one acinus, and partially or completely obliterate the acinar lumen, encapsulated in the seminal vesicle. Cells are arranged in papillary, cribriform, comedo, or microglandular patterns and have mild cellular atypia, cellular crowding, and loss of polarity and distortion of the architecture.

Differential diagnoses: **Accessory male sex organs, atypical hyperplasia**; **Accessory male sex organs, granular cell tumor, benign**; **Accessory male sex organs, adenocarcinoma**.

Synonym(s): **Prostatic adenoma**.



FIGURE 2 Prostatic adenoma, rat, H&E. (Reproduced with permission of Society of Toxicologic Pathology from Creasy, D. et al. 2012. Toxicol Pathol 40(6 Suppl):40S–121S.)

References

Creasy, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse male reproductive system. *Toxicol Pathol* 40(6 Suppl):40S–121S.

Park, J.H. et al. 2002. Prostatic intraepithelial neoplasia in genetically engineered mice. *Am J Pathol* 161(2):727–735.

Shappell, S.B. et al. 2004. Prostate pathology of genetically engineered mice: Definitions and classification. The consensus report from the Bar Harbor meeting of the Mouse Models of Human Cancer Consortium Prostate Pathology Committee. *Cancer Res* 15;64(6):2270–2305.

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https://www.ncbi.nlm.nih.gov/pubmed/22949412
http://www.goreni.org/
https://www.ncbi.nlm.nih.gov/pubmed/12163397
https://www.ncbi.nlm.nih.gov/pubmed/15026373

Accessory male sex organs, adenomatous hyperplasia, see the preferred term **Accessory male sex organs, atypical hyperplasia**.

Accessory male sex organs, atypical hyperplasia (prostate, seminal vesicle, coagulating gland) is the focal or multifocal proliferation of the glandular epithelium in the ventral prostate, dorsolateral prostate, seminal vesicle, or coagulating gland. Microscopically foci are composed of multilayered but otherwise normal epithelium affecting a few adjacent acini of otherwise normal glands. Occurring spontaneously in rats and mice, the lesion is more common and well characterized in Nkx3.1+/−, Nkx3.1−/−, PTEN+/−, p27−/−, p53−/−, and hybrid crosses of genetically engineered mouse models of prostate cancer. Citral, phenylephrine, cadmium, and testosterone or a combination of cyproterone acetate, testosterone propionate, and *N*-methyl-*N*-nitrosourea cause atypical hyperplasia of the prostate in rats. Atypical hyperplasia is not necessarily a precursor to carcinoma but may be classified as preneoplastic if accompanied by an increased incidence of accessory sex gland tumors, or evidence of progression.

Differential diagnoses: **Accessory male sex organs reactive, hyperplasia**; **Accessory male sex organs, adenoma**.

Synonym(s): **Accessory male sex organs, focal hyperplasia**; **prostatic intraepithelial neoplasia**; **accessory male sex organs, adenomatous hyperplasia**; **accessory male sex organs, dysplasia**.

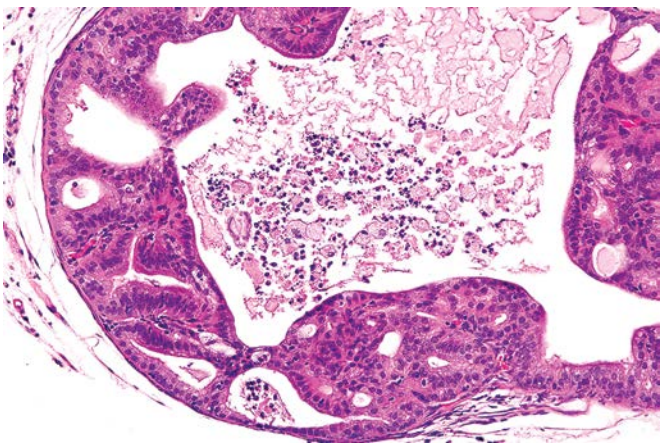


FIGURE 3 Atypical hyperplasia, prostate, mouse, H&E. (Reproduced with permission of Society of Toxicologic Pathology from Creasy, D. et al. 2012. Toxicol Pathol 40(6 Suppl): 40S–121S.)

References

Creasy, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse male reproductive system. *Toxicol Pathol* 40(6 Suppl):40S–121S.

Mahapokai, W., Van Sluijs, F.J., and Schalken, J.A. 2000. Models for studying benign prostatic hyperplasia. *Prostate Cancer Prostatic Dis* 3(1):28–33.

Park, J.H. et al. 2002. Prostatic intraepithelial neoplasia in genetically engineered mice. *Am J Pathol* 161(2):727–735.

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https://www.ncbi.nlm.nih.gov/pubmed/22949412
http://www.goreni.org/
https://www.ncbi.nlm.nih.gov/pubmed/12163397
https://www.ncbi.nlm.nih.gov/pubmed/12497158

Accessory male sex organs, benign myoblastoma, see the preferred term **Accessory male sex organs, granular cell tumor, benign**

Accessory male sex organs, carcinosarcoma (prostate, seminal vesicle, coagulating gland) is a rare, locally invasive neoplasm composed of spindle cells, pleomorphic cells, and/or homogenous large polygonal, epithelial-like cells within an adenocarcinoma. Neoplastic cells stain positive for cytokeratin 8 or other keratins, and vimentin or other mesenchymal cell markers, and develop from cells that transform during the epithelial–mesenchymal transition in late-stage adenocarcinomas. The neoplasm is described in genetically engineered mouse models of prostate cancer, and in rats treated with trifluridine.

Differential diagnoses: **Accessory male sex organs, adenocarcinoma**; **Accessory male sex organs, sarcoma**.

Synonym(s): **Prostatic carcinosarcoma**; **prostatic poorly-differentiated adenocarcinoma**; **prostatic sarcomatoid carcinoma**; **prostatic epithelial mesenchymal tumor**.

Reference

Creasy, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse male reproductive system. *Toxicol Pathol* 40(6 Suppl):40S–121S.

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https://www.ncbi.nlm.nih.gov/pubmed/22949412
http://www.goreni.org/

Accessory male sex organs, dysplasia, see the preferred term **Accessory male sex organs, atypical hyperplasia**.

Accessory male sex organs, focal hyperplasia, see the preferred term **Accessory male sex organs, atypical hyperplasia**.

Accessory male sex organs, granular cell tumor, benign (prostate, seminal vesicle, coagulating gland) is a spontaneous tumor that occurs in the rat and mouse, and is more common in females than males. The cell of origin is unknown but may be the Schwann or mesenchymal cell. Tumors are well circumscribed and solid, and grow by expansion, which causes compression/atrophy of surrounding tissue. The macroscopic appearance is that of a pink or pale yellow-gray mass. Microscopically, cells are large, round to oval, with large pale nuclei. Eosinophilic granules are noted in the cytoplasm. Special stains may be used to confirm the diagnosis, including periodic acid-Schiff (PAS), neuron specific enolase (NSE), S-100, and peripheral myelin protein stains.

Differential diagnoses: **Accessory male sex organs, granular cell tumor malignant**; Accessory male sex organs, cellular pleomorphism.

Synonym(s): **Abrikosoff tumor**; **Accessory male sex organs, benign myoblastoma**.

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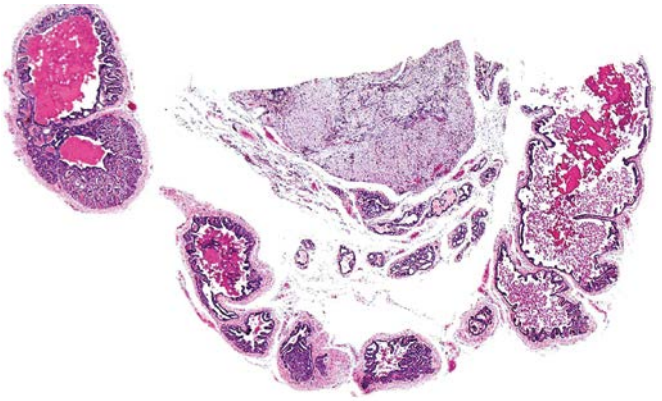


FIGURE 4 Granular cell tumor, seminal vesicle, mouse, H&E. (Reproduced with permission of Society of Toxicologic Pathology from Creasy, D. et al. 2012. Toxicol Pathol 40(6 Suppl):40S–121S.)

Reference

Creasy, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse male reproductive system. *Toxicol Pathol* 40(6 Suppl):40S–121S.

Links

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http://www.goreni.org/

Accessory male sex organs, granular cell tumor, malignant (prostate, seminal vesicle, coagulating gland) is a rare, spontaneous tumor in the rat and mouse, which may originate from the Schwann or mesenchymal cell. It is typically restricted to the primary site, with no regional or distant metastasis. The macroscopic appearance is that of a solid mass. Microscopic features are similar to the benign granular cell tumor, except for increased pleomorphism, decreased cytoplasmic granularity, and an increased nuclear-to-cytoplasmic ratio. There is a low mitotic index. Areas of necrosis are frequently present. Special stains may be used to confirm the diagnosis, including periodic acid-Schiff (PAS), which is only weakly positive, and S-100 stains.

Differential diagnoses: **Accessory male sex organs, granular cell tumor, benign**; **Accessory male sex organs, adenocarcinoma**.

Reference

Creasy, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse male reproductive system. *Toxicol Pathol* 40(6 Suppl):40S–121S.

Links

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Accessory male sex organs, hyperplasia, functional (prostate, coagulating gland, seminal vesicle) occurs in response to increased demand, and consists of epithelial hypertrophy and hyperplasia. Microscopically, there is multifocal or diffuse thickening of the epithelium with cell crowding. Cells are cuboidal to columnar, and may exhibit luminal in-folding. There is no cellular atypia or obliteration of acinar lumens. Functional hyperplasia can be challenging to identify since the tissue appears relatively normal; there is just an increased amount. Increased organ weights and grossly observable enlargement is generally noted with the diffuse change. In the rat ventral prostate, it is more commonly multifocal in distribution, is often accompanied by decreased secretion, and may be a spontaneous background finding. Diffuse functional hyperplasia occurs most commonly following exogenous androgen administration.

Differential diagnoses: **Accessory male sex organs, atypical hyperplasia**; **Accessory male sex organs, reactive hyperplasia**; **Accessory male sex organs, adenoma**.

Synonym(s): **Accessory male sex organs, adaptive hyperplasia**; **accessory male sex organs, simple hyperplasia**.

Reference

Creasy, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse male reproductive system. *Toxicol Pathol* 40(6 Suppl):40S–121S.

Links

https://www.ncbi.nlm.nih.gov/pubmed/22949412
http://www.goreni.org/

Accessory male sex organs, mesenchymal proliferative lesion (prostate, seminal vesicle, coagulating gland) is a primarily spontaneous subepithelial collection of large epithelial cells with peripheral fibrocyte- or smooth muscle-like spindle cells and mononuclear cells in the prostate, seminal vesicles, and coagulating gland. Epithelial cells appear typical but may have periodic acid-Schiff (PAS)-positive eosinophilic granules, and eccentric nuclei with prominent nucleoli. Mesenchymal proliferative lesion has been regarded as a benign tumor based on the potential to be locally invasive. Because of morphologic similarities to the uterine decidual reaction, some consider the lesion to be a decidual-like reaction. Mesenchymal proliferative lesions have been observed predominantly in Swiss Webster, NMRI, and CD1 mouse strains. Lesions of similar morphology have been described in uterus and urinary bladder.

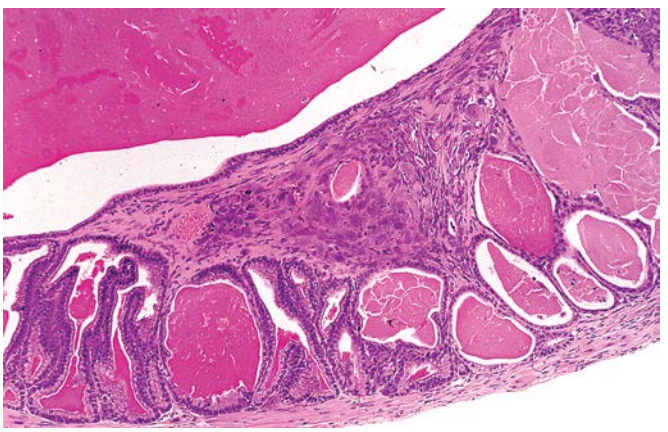


FIGURE 5 Mesenchymal proliferative lesion, epithelioid cells surrounded by spindle cells, seminal vesicle, mouse, H&E. (Reproduced with permission of Society of Toxicologic Pathology from Creasy, D. et al. 2012. Toxicol Pathol 40(6 Suppl):40S–121S.)

Differential diagnosis: **Accessory male sex organs, carcinosarcoma**.

Synonym(s): **Accessory male sex organs, vegetative lesion**; **accessory male sex organs, mesenchymal tumor**; **decidual-like reaction**.

Reference

Creasy, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse male reproductive system. *Toxicol Pathol* 40(6 Suppl):40S–121S.

Links

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Accessory male sex organs, mesenchymal tumor; see the preferred term **Accessory male sex organs, mesenchymal proliferative lesion**.

Accessory male sex organs, reactive hyperplasia (prostate, seminal vesicle, coagulating gland) commonly accompanies inflammatory lesions resulting from urogenital infections. It is particularly common in mice and often located in the dorsolateral lobes. Accompanying suppurative inflammation is the most reliable differential diagnostic criterion to distinguish reactive hyperplasia from preneoplastic focal hyperplasia. The lesion may be focal, multifocal, or diffuse, and squamous metaplasia may also be present. Hyperplastic cells are cuboidal to columnar with increased cytoplasmic basophilia, and sometimes, atypia and pseudoglandular structures. In more severe urogenital infections, the seminal vesicle epithelium may become hyperplastic. Hyperplasia of the accessory sex glands is not often seen as a response to inflammation in the dog or monkey.

Reference

Creasy, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse male reproductive system. *Toxicol Pathol* 40(6 Suppl):40S–121S.

Links

https://www.ncbi.nlm.nih.gov/pubmed/22949412
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Accessory male sex organs, simple hyperplasia, see the preferred term **Accessory male sex organs, hyperplasia, functional**.

Accessory male sex organs, squamous cell carcinoma (prostate, seminal vesicle, coagulating gland) is a malignant tumor derived from squamous epithelial cells. Diagnostic criteria include presence of epidermoid cells that are arranged in cords, sheets, or irregular nests with or without keratinization and with evidence of invasion and metastasis. In rodents, the squamous cell carcinoma is induced by numerous carcinogens and ionizing radiation. In both the coagulating gland and prostate, the tumor may have an adenosquamous morphology with tubular and glandular structures in addition to extensive squamous differentiation. Although prostatic adenocarcinomas are very common in the human and in other mammalian species, squamous cell carcinomas are very rare (0.5–1% of all carcinomas) in humans.

References

Bosland, M.C. 1987. Adenocarcinoma, prostate, rat. In: Jones, T.C., Mohr U., Hunt, R.D. (eds.) *Monographs on Pathology of the Laboratory Animals, Genital System*. Berlin, Heidelberg, New York, Tokyo: Springer, pp. 252–260.
Creasy, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse male reproductive system. *Toxicol Pathol* 40(6 Suppl):40S–121S.
Malik, R.D. et al. 2011. Squamous cell carcinoma of the prostate. *Urology* 13:56–60.

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http://www.goreni.org/
https://www.ncbi.nlm.nih.gov/pubmed/21826130

Accessory male sex organs, squamous cell papilloma (prostate, seminal vesicle, coagulating gland) is a very rare spontaneous benign tumor which arises from the metaplastic acinar epithelium. The neoplasm is characterized by papillary protrusion of the mucosa into the lumen with squamous cell metaplasia (see **Accessory male sex organ, squamous cell metaplasia** for further information), with or without keratinization. The tumor is not invasive.

Reference

Creasy, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse male reproductive system. *Toxicol Pathol* 40(6 Suppl):40S–121S.

Links

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Accessory male sex organs, vegetative lesion, see the preferred term **Accessory male sex organs, mesenchymal proliferative lesion**.

Androblastoma, malignant, see the preferred term **Sertoli cell (SC) tumor, malignant**.

Arrhenoblastoma, malignant, see the preferred term **Sertoli cell (SC) tumor, malignant**.

Decidual-like reaction, see the preferred term **Accessory male sex organs, mesenchymal proliferative lesion**.

Embryonal carcinoma is a rare testicular tumor that arises from a mixture of pluripotent germ cells, sex-cord stromal cells, and cells of the visceral yolk sac. Neoplastic cells are generally large and undifferentiated and arranged in solid sheets; however, acinar, papillary, or tubular structures are observed. The stromal component is minimal, and the neoplasm often has areas of necrosis and hemorrhage.

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Reference

Creasy, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse male reproductive system. *Toxicol Pathol* 40(6 Suppl):40S–121S.

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https://www.ncbi.nlm.nih.gov/pubmed/22949412
http://www.goreni.org/

Epididymal histiocytic lymphoma, see the preferred term **Epididymal histiocytic sarcoma**.

Epididymal histiocytic sarcoma is a rare tumor restricted to the mouse and is the equivalent of the female mouse uterine histiocytic sarcoma. Epididymal histiocytic sarcomas are typically confined to the cauda epididymis and may be associated with secondary sperm granulomas. Local tissue invasion as well as distant metastases may occur, primarily to the peritoneum and liver. Macroscopically, tumors exhibit nodularity. Microscopically, cells form sheets, are pleomorphic, and vary from round to fusiform in shape. Multinucleated giant cells may be observed. Nuclei are also pleomorphic and may be cleaved. The mitotic index is typically high, and cells have an eosinophilic, frequently foamy cytoplasm and may contain periodic acid-Schiff (PAS)-positive deposits, red blood cells (erythrophagocytosis), and pigment.

Differential diagnoses: **Testis, efferent ducts and epididymis sperm granuloma**; **Leydig cell adenoma**.

Synonym(s): **Epididymal reticulum cell sarcoma**; **epididymal histiocytic lymphoma**; **epididymal histiogenic tumor**.

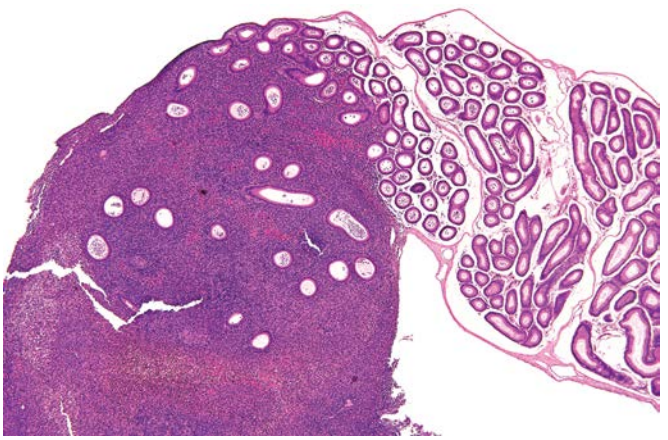


FIGURE 6 Epididymal histiocytic sarcoma, mouse, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

Reference

Creasy, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse male reproductive system. *Toxicol Pathol* 40(6 Suppl):40S–121S.

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https://www.ncbi.nlm.nih.gov/pubmed/22949412
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Epididymal histiogenic tumor, see the preferred term **Epididymal histiocytic sarcoma**.

Epididymal mesothelial hyperplasia is a proliferative lesion localized to the serosa of the epididymis in the rat. It may be incidental or xenobiotic induced. Histologically, the lesion is comprised of focal thickening or villous projections, sometimes protruding from a fibrovascular stalk. Projections are lined by cuboidal cells with little or no stratification. Mitotic activity and cellular atypia are not present, although fibrosis and inflammation may accompany the lesion. Mesothelial hyperplasia may be a precursor to mesothelioma.

Reference

Creasy, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse male reproductive system. *Toxicol Pathol* 40(6 Suppl):40S–121S.

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Epididymal reticulum cell sarcoma, see the preferred term **Epididymal histiocytic sarcoma**.

Germinoma, see the preferred term **Seminoma, benign** or **Seminoma, malignant**.

Gonadal stromal tumor, see the preferred term **Sertoli cell (SC) tumor, benign**.

Interstitial cell adenoma, see the preferred term **Leydig cell (LC) adenoma**.

Interstitial cell carcinoma, see the preferred term **Leydig cell (LC) carcinoma**.

Interstitial cell hyperplasia, see the preferred term **Leydig Cell (LC) hyperplasia**.

Interstitial cell tumor, benign, see the preferred term **Leydig cell (LC) adenoma**.

Interstitial cell tumor, benign, see the preferred term **Leydig cell (LC) adenoma in the epididymis**.

Interstitial cell tumor, malignant, see the preferred term **Leydig cell (LC) carcinoma**.

Leydig cell (LC) adenoma is a benign testicular tumor in rats and mice. Microscopically, it is composed of unencapsulated neoplastic Leydig cells that cause compression of the surrounding tissue. They can occur unilaterally or bilaterally. Tumor cells are polyhedral in shape with abundant cytoplasm and a centrally located, round nucleus. The cytoplasm is eosinophilic, vacuolated, or finely granular. The nucleus

has evenly distributed chromatin and a prominent nucleolus. The nuclear-to-cytoplasmic ratio is low, and mitotic figures are infrequent. Large tumors may contain cellular pleomorphism with a subset of less well-differentiated, spindle-shaped cells containing scant, basophilic cytoplasm. Tumors may contain cystic areas filled with proteinaceous material, dilated thin-walled blood vessels, hemorrhage, and necrosis. Stroma is scant. LC adenoma is observed spontaneously in the aging rodent but may also be induced by xenobiotics that increase luteinizing hormone (LH) levels in the rat, or by hyperestrogenic compounds in the mouse. Finasteride, a 5-alpha-reducase inhibitor, is an example of a xenobiotic that produces Leydig cell tumors in mice. The biological relevance in man is limited due to the low prevalence of Leydig cell tumors in man. A general rule of thumb used to differentiate Leydig cell adenomas from hyperplasia is a lesion larger than the lumen diameter of three seminiferous tubules. A variant of the testicular Leydig cell adenoma has been reported in the rat, termed the retiform pattern of Leydig cell adenoma. It is characterized by glandular or tubular structures lined by Alcian blue–positive ciliated cuboidal to columnar cells that may be filled with periodic acid-Schiff (PAS)-positive material.

Differential diagnoses: **Leydig cell hyperplasia**; **Leydig cell carcinoma**.

Synonym(s): **Leydig cell tumor, benign**; **interstitial cell tumor, benign**; **interstitial cell adenoma**.

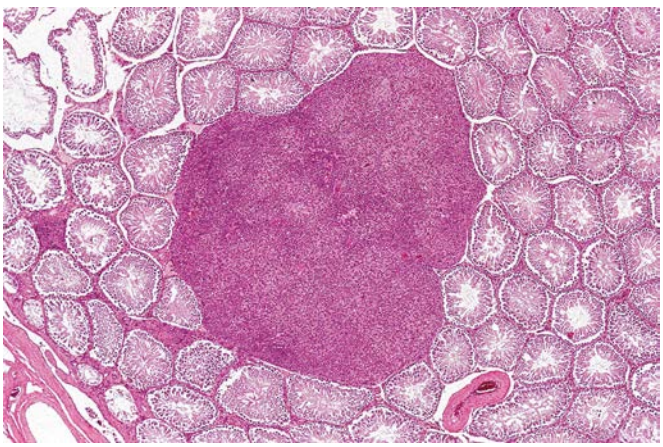


FIGURE 7 Leydig cell adenoma, testis, rat, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

References

Al-Agha, O.M., and Axiotis, C.A. 2007. An in-depth look at Leydig cell tumor of the testis. *Arch Pathol Lab Med* 131(2):311–317.

Creasy, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse male reproductive system. *Toxicol Pathol* 40(6 Suppl):40S–121S.

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Leydig cell (LC) adenoma in the epididymis is a rare tumor that has been observed in the B6C3F1 mouse. There are no reports of epididymal Leydig cell hyperplasia or carcinoma. Diagnosis should be confirmed with immunohistochemistry; Leydig cells stain positive with calretinin and inhibin. Microscopically, epididymal Leydig cell adenoma is described as a nodular or diffuse mass with surrounding compression, displacement, or replacement of adjacent epididymal tissue. The tumor cells have a polyhedral shape with abundant cytoplasm and a centrally located, round nucleus. The cytoplasm is eosinophilic and may be vacuolated. The nucleus is round with evenly distributed chromatin and a prominent nucleolus. The nuclear-to-cytoplasmic ratio is low. Mitotic figures are infrequent. Occasionally, there is a subset of small lipofuscin-containing neoplastic cells with hyperchromatic chromatin and scant cytoplasm.

Differential diagnoses: **Testis, efferent ducts and epididymis sperm granuloma**; **Epididymal histiocytic sarcoma**.

Synonym(s): **Leydig cell tumor, benign**; **interstitial cell tumor, benign**.

Reference

Creasy, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse male reproductive system. *Toxicol Pathol* 40(6 Suppl):40S–121S.

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Leydig cell (LC) carcinoma in the testis is an uncommon tumor in the rat and mouse. It typically progresses from a Leydig cell adenoma. It may be induced by xenobiotics that increase LH levels in the rat, or by hyperestrogenic compounds in the mouse. False positives can occur in man and the dog, where Leydig cells may reside in the testicular capsule without neoplastic transformation. The biological relevance in man is limited due to the low prevalence of Leydig cell tumors. In the rodent, microscopic evidence of Leydig cell carcinoma consists of capsular or surrounding tissue invasion, and/or distant metastasis. Microscopically, tumors share similar morphological characteristics with the LC adenoma, except for areas of increased cellular pleomorphism characterized by poorly differentiated basophilic cells or spindle cells with scant cytoplasm. The mitotic index remains low.

Differential diagnoses: **Leydig cell (LC) adenoma**; **Seminoma, malignant**; Granulosa cell tumor, benign.

Synonym(s): **Leydig cell tumor, malignant**; **interstitial cell tumor, malignant**; **interstitial cell carcinoma**.

References

Al-Agha, O.M., and Axiotis, C.A. 2007. An in-depth look at Leydig cell tumor of the testis. *Arch Pathol Lab Med* 131(2):311–317.

Creasy, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse male reproductive system. *Toxicol Pathol* 40(6 Suppl):40S–121S.

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https://www.ncbi.nlm.nih.gov/pubmed/17284120

Leydig cell (LC) hyperplasia is a focal, multifocal, or diffuse change characterized by proliferative LC aggregates or bridging strands between the seminiferous tubules. Size corresponding to a diameter of smaller than or equal to three seminiferous tubules is used to differentiate focal hyperplasia from adenoma. Diffuse LC hyperplasia most commonly occurs as a compensatory response to decreased spermatogenesis, or a physiological response to hormone imbalance, particularly increased levels of luteinizing hormone from the pituitary, and released stimulatory paracrine factors within the testis. Mice LC are larger and more numerous than rat LC (see **Leydig cell hypertrophy** for further information). LC hyperplasia in mice tends to occur diffusely in the subcapsular region, whereas in rats, LC hyperplasia is most commonly focal or multifocal. LC hyperplasia is most common in F344 rats and may be seen in young animals. LC hyperplasia in the rat can be readily induced by a wide range of chemically diverse compounds including dopamine agonists, antiandrogens, LHRH analogs, peroxisome proliferators, and histamine receptor antagonists. In contrast, xenobiotic induction of LC hyperplasia in mice is less common, and generally associated with estrogenic compounds or 5α-reductase inhibitors. LC hyperplasia may be observed as an incidental finding in ageing canine testes. It has also been associated with flutamide administration in beagle dogs. The number of LCs in the minipig normally exhibits great variability, which should be considered if LC hyperplasia is suspected.

Differential diagnoses: **Leydig cell (LC) adenoma**; **Leydig cell (LC) hypertrophy**.

Synonym(s): **Interstitial cell hyperplasia**.

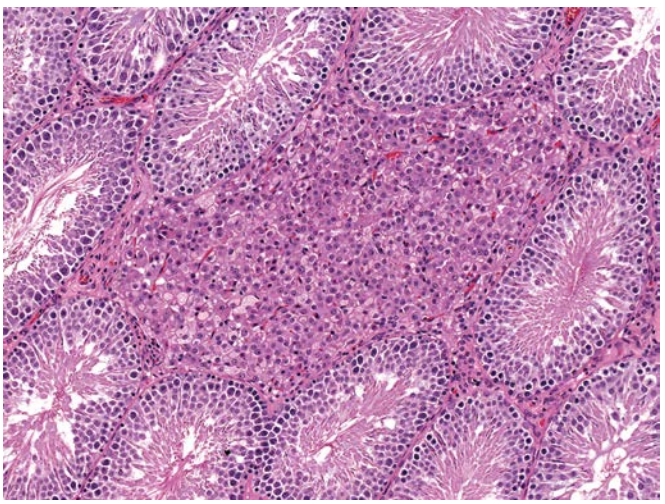


FIGURE 8 Leydig cell hyperplasia, testis, rat, H&E. (Reproduced with permission of Society of Toxicologic Pathology from Creasy, D. et al. 2012. Toxicol Pathol 40(6 Suppl):40S–121S.)

Reference

Creasy, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse male reproductive system. *Toxicol Pathol* 40(6 Suppl):40S–121S.

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Leydig cell (LC) hyperplasia, functional occurs as a diffuse increase in the number of testicular Leydig cells and is a physiological adaptive response to hormone imbalances. It can result from increased luteinizing hormone (LH) release from the pituitary gland, decreased spermatogenesis, release of stimulatory paracrine factors within the testis, or alterations in estrogen levels. This diagnosis should be made with caution as numbers of Leydig cells may appear to be increased relative to possible atrophy of the surrounding seminiferous tubules. Morphologic confirmation of functional Leydig cell hyperplasia may require unbiased quantitative analysis using prospective stereological methods.

Reference

Creasy, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse male reproductive system. *Toxicol Pathol* 40(6 Suppl):40S–121S.

Links

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Leydig cell tumor, benign, see the preferred term **Leydig cell (LC) adenoma**.

Leydig cell tumor, benign, see the preferred term **Leydig cell (LC) adenoma in the epididymis**.

Leydig cell tumor, malignant, see the preferred term **Leydig cell (LC) carcinoma**.

Neuroectodermal tumor originates from small round cells of neuroectodermal origin. They are composed of basophilic homogenous neoplastic cells arranged in Homer–Wright rosettes or pseudorosettes. Neoplastic cells variably express S100, neuron-specific enolase, synaptophysin, neurofilament-68 kDa, microtubule-associated protein 2, and vimentin. Neuroendocrine tumors often coexist with mature forms of germ cell tumors, such as teratomas, and can be concurrently present with classical seminomas in the testes.

Synonym(s): **Primitive neuroectodermal tumor**.

Reference

Saegusa, Y. et al. 2011. Spermatocytic seminoma with neuroectodermal differentiation and Sertoli cell tumor in a dog. *Vet Pathol* 48(5):1024–1028.

Link

http://vet.sagepub.com/content/48/5/1024.full

Preputial gland adenocarcinoma is a malignant neoplasm of acinar cells of the preputial gland, consisting of irregular nests of acinar cells with nuclear and cellular atypia and high mitotic activity. Neoplastic cells may infiltrate the gland's fibrous capsule and the adjacent subcutaneous tissue. Ducts within the neoplasm are sometimes cystic, containing keratin and debris, and are lined by squamous epithelium. Solid, cystic, papillary, papillary cystic, and mixed cell subtypes are described, but subtyping is not recommended in regulatory toxicity studies.

Differential diagnosis: **Preputial gland adenoma**.

Synonym(s): **Preputial gland cystadenocarcinoma**.

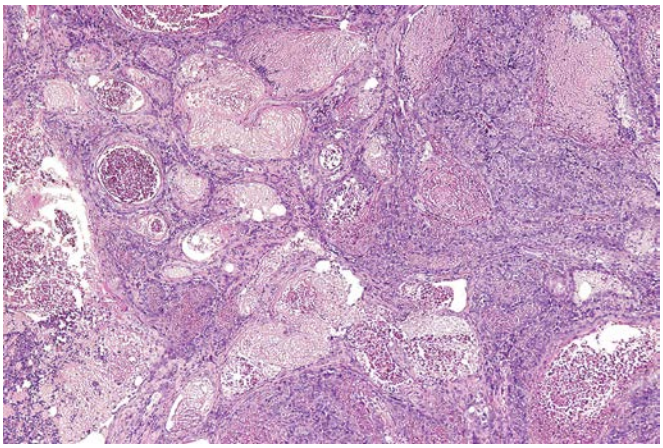


FIGURE 9 Preputial gland adenocarcinoma, metastatic, lung, F344/N rat, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

Reference

Rudmann, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse mammary, Zymbal's, preputial, and clitoral glands. *Toxicol Pathol* 40(6 Suppl):7S–39S.

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Preputial gland adenoma is a rare spontaneous neoplasm of acinar cells. Grossly, the tumor is firm, tan, and multilobulated, and is often bilateral on the lower abdominal wall near prepuce. Microscopically, the neoplasm is well circumscribed, often encapsulated, and has a solid growth pattern similar to normal glands, with compression of adjacent tissue but no invasion. Neoplastic cells may show sebaceous and/or squamous differentiation and form stratified epithelial nests of well-differentiated cells with few mitoses. These nests may have a central cystic area with debris. Cystic and papillary growth variants are observed in the rat but not in the mouse.

Differential diagnosis: **Preputial gland adenocarcinoma**.

Synonym(s): **Preputial gland cystadenoma**.

Reference

Rudmann, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse mammary, Zymbal's, preputial, and clitoral glands. *Toxicol Pathol* 40(6 Suppl):7S–39S.

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Preputial gland basal cell carcinoma, see the preferred term **Preputial gland basal cell tumor, malignant**.

Preputial gland basal cell tumor, benign is a rare neoplasm arising from basal cells lining the preputial gland ducts. Neoplastic cells are well differentiated and arranged in circumscribed nests. Cytoplasm is abundant, eosinophilic, and nuclei are oval with a low mitotic rate. Neoplastic nests are separated from adjacent, nonneoplastic parenchyma by bundles of collagenous connective tissue.

Differential diagnosis: **Preputial gland adenoma**.

Reference

Rudmann, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse mammary, Zymbal's, preputial, and clitoral glands. *Toxicol Pathol* 40(6 Suppl):7S–39S.

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Preputial gland basal cell tumor, malignant is a rare neoplasm arising from basal cells lining the preputial gland ducts. Neoplastic cells are arranged in circumscribed nests and are basophilic with elongated to oval nuclei and a high mitotic rate. Neoplastic nests are locally invasive and are separated from adjacent, nonneoplastic parenchyma by bundles of collagenous connective tissue.

Differential diagnoses: **Preputial gland adenocarcinoma**; **Preputial gland basal cell tumor, benign**; **Preputial gland squamous cell carcinoma**.

Synonym(s): **Preputial gland basal cell carcinoma**.

Reference

Rudmann, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse mammary, Zymbal's, preputial, and clitoral glands. *Toxicol Pathol* 40(6 Suppl):7S–39S.

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Preputial gland cystadenocarcinoma, see the preferred term **Preputial gland adenocarcinoma**.

Preputial gland cystadenoma, see the preferred term **Preputial gland adenoma**.

Preputial gland epidermoid carcinoma, see the preferred term **Preputial gland sex organs, squamous cell carcinoma**.

Preputial gland hyperplasia is a spontaneous, age-related lesion in the rat and mouse, and typically stems from reactive hyperplasia due to inflammation, rather than arising as a primary neoplastic precursor. However, iatrogenic testosterone

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administration has been known to result in primary hypertrophy and hyperplasia of acinar cells. Hyperplastic foci may be unilateral or bilateral and be associated with ductal dilation and chronic inflammation. Hyperplasia may be restricted to the acini or ducts. When acinar in origin, preputial gland hyperplasia is focal in distribution, and composed of cells resembling normal acinar epithelium. Cells contain eosinophilic, hyalinized cytoplasmic granules which are characteristic of the preputial gland, have a single, centrally located round nucleus with peripheral chromatin, and one or two nucleoli. Foci may be surrounded by dark, flat basal cells. When confined to the ducts, preputial gland hyperplasia resembles stratified squamous epithelium and is typically 3–7 flattened layers thick. Acanthosis and hyperkeratosis often occur secondary to accompanying inflammation.

Differential diagnosis: **Preputial gland adenoma**.

References

Haines, D.C. and Eustis, S.L. 1990. Specialized sebaceous glands. In: Boorman, G.A., Eustis, S.L., Elwell, M.R., Montgomery, C.A., MaKenzie, W.F. (eds.) *Pathology of the Fischer Rat: Reference and Atlas*. San Diego: Academic Press, pp. 279–293.

Rudmann, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse mammary, Zymbal's, preputial, and clitoral glands. *Toxicol Pathol* 40(6 Suppl):7S–39S.

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Preputial gland squamous cell carcinoma is a malignant tumor derived from squamous epithelial cells. Diagnostic criteria include presence of epidermoid cells that are arranged in cords, sheets, or irregular nests with or without keratinization, and with evidence of invasion and metastasis. In rodents, the squamous cell carcinoma is induced by numerous carcinogens and ionizing radiation. The tumor may have an adenosquamous morphology with tubular and glandular structures in addition to extensive squamous differentiation.

Synonym(s): **Preputial gland epidermoid carcinoma**.

Reference

Rudmann, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse mammary, Zymbal's, preputial, and clitoral glands. *Toxicol Pathol* 40(6 Suppl):7S–39S.

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Preputial gland squamous cell papilloma is an uncommon benign tumor in the rodent which arises from the ductal cells of the preputial gland. The neoplasm is characterized by a papillary growth pattern into the duct lumina of well-differentiated, keratinized, or nonkeratinized squamous epithelium overlying connective tissue cores. The tumor may have a rather complex arborizing structure, and the adjacent preputial gland is frequently hyperplastic.

References

Mitsumori, K. and Elwell, M.R. 1988. Proliferative lesions in the male reproductive system of F344 rats and B6C3F1 mice: Incidence and classification. *Environ Health Perspect* 77:11–21.

Rudmann, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse mammary, Zymbal's, preputial, and clitoral glands. *Toxicol Pathol* 40(6 Suppl):7S–39S.

Yoshida, H. 1983. Preputial tumors induced by intragastric intubation of 7,12-dimethylbenz[a]anthracene in gonadectomized female and male rats. *J Cancer Res Clin Oncol* 105:299–302.

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http://www.goreni.org/
https://www.ncbi.nlm.nih.gov/pubmed/3289903
https://www.ncbi.nlm.nih.gov/pubmed/6406514

Primitive neuroectodermal tumor (PNETs), see the preferred term **Neuroectodermal tumor**.

Prostatic adenocarcinoma, see the preferred term **Accessory male sex organs, adenocarcinoma**.

Prostatic adenoma, see the preferred term **Accessory male sex organs, adenoma**.

Prostatic carcinoma (with neuroepithelial differentiation), see the preferred term **Prostatic neuroendocrine tumor, malignant**.

Prostatic carcinosarcoma, see the preferred term **Accessory male sex organs, carcinosarcoma**.

Prostatic epithelial mesenchymal tumor, see the preferred term **Accessory male sex organs, carcinosarcoma**.

Prostatic intraepithelial neoplasia (PIN), see the preferred term **Accessory male sex organs, atypical hyperplasia**.

Prostatic neuroendocrine tumor, malignant is a neoplasm observed in the ventral lobe of the prostate or submucosal glands of urethra in genetically engineered mouse strains, especially TRAMP mice. They consist of accumulations of small basophilic cells within acinar epithelium arranged in packets, pseudorosettes, or sheets of cells separated by fine fibrous stroma. Neoplastic cells may be markedly pleomorphic with atypical mitoses and are often angiocentric and/or separated by zones of necrosis. Malignant neuroendocrine tumors stain positive for synaptophysin and neuron-specific enolase (NSE). Prostatic acini are often entrapped, and invasion into surrounding tissue and metastases to lung and other tissues may occur. The origin of neuroendocrine cells is still controversial but it has become increasingly clear that they are different from normal prostate neuroendocrine (NE) cells in their differential expression of proteins. They have also been reported in FVB/N mice containing the SV40 T-Ag. In TRAMP mice, neuroendocrine tumors are considered a subset of poorly differentiated carcinomas which undergo an epithelial to neuroendocrine

shift. Neuroendocrine cells are present in small numbers between acinar and ductal cells of the normal prostate, where they secrete a variety of growth factors.

Synonym(s): **Prostatic carcinoma (with neuroepithelial differentiation)**.

Reference

Creasy, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse male reproductive system. *Toxicol Pathol* 40(6 Suppl):40S–121S.

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https://www.ncbi.nlm.nih.gov/pubmed/22949412
http://www.goreni.org/

Prostatic poorly differentiated adenocarcinoma, see the preferred term **Accessory male sex organs, carcinosarcoma**.

Prostatic sarcomatoid carcinoma, see the preferred term **Accessory male sex organs, carcinosarcoma**.

Rete testis adenoma has been reported in rodents both as spontaneous age-related, and xenobiotic-induced lesions. Histologically, adenomas are composed of tubular and papillary structures lined by single or multiple layers of epithelial cells in the mediastinal testis, causing compression of the adjacent tissue. Neoplastic epithelium is flattened to cuboidal in rats, and cuboidal to tall columnar or pleomorphic with abundant eosinophilic cytoplasm in mice. Nuclei are round to oval and vesicular, with a single nucleolus and rare mitoses. Rete testis adenomas are negative for vimentin, but may produce mucins, and therefore be periodic acid-Schiff (PAS) and/or Alcian blue positive. Proliferative lesions of the rete testes are rare in aging rats but more common in mice, and have been reported to occur in both species following prenatal treatment with diethylstilbestrol and cadmium chloride. In CD-1 mice, adenomas often have tubular distension and spermatozoa-filled cystic structures. Rete testis adenomas may also occur in dogs and monkeys.

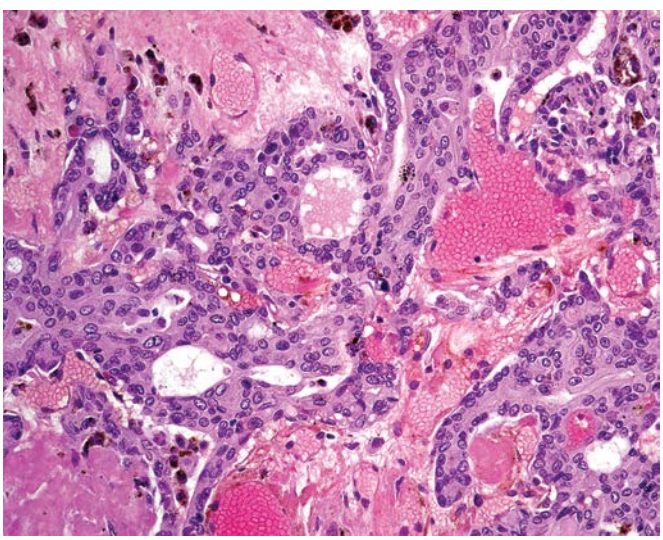


FIGURE 10 Rete testis adenoma, testis, mouse, H&E. (Reproduced with permission of Society of Toxicologic Pathology from Creasy, D. et al. 2012. Toxicol Pathol 40(6 Suppl):40S–121S.)

Differential diagnosis: **Rete testis carcinoma**.

Reference

Creasy, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse male reproductive system. *Toxicol Pathol* 40(6 Suppl):40S–121S.

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https://www.ncbi.nlm.nih.gov/pubmed/22949412
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Rete testis carcinoma has been reported in rodents both as spontaneous, age-related, and xenobiotic-induced lesions. Carcinomas are characterized by invasion, marked atypia, a high mitotic rate, and sometimes hemorrhage, mucin, necrosis, and/or a schirrous response. They are composed of poorly differentiated tubulopapillary growths with cuboidal pleomorphic cells in rats, and tall columnar cells in mice. Mitoses are common and often atypical. Rete testis carcinomas are negative for vimentin but may produce mucins, and therefore be periodic acid-Schiff (PAS) and/or Alcian blue positive. Proliferative lesions of the rete testes are rare in aging rats but more common in mice, and have been reported to occur in both species following prenatal treatment with diethylstilbestrol and cadmium chloride.

Differential diagnosis: **Rete testis adenoma**.

Reference

Creasy, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse male reproductive system. *Toxicol Pathol* 40(6 Suppl):40S–121S.

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http://www.goreni.org/

Rete testis hyperplasia may be spontaneous or xenobiotic-induced, occurs most commonly in the mouse (CD-1 strain especially), and rarely in the rat. Rete testis hyperplasia may be focal or multifocal and is composed of tubules lined by a single layer of flattened to cuboidal (rat), or tall columnar (mouse) epithelial cells with multiple layers of crowding. Intratubular papillary or rosette-like projections with scant stroma are common in mice. Mitotic figures are rare, and cystic structures filled with spermatozoa may be present. Associated sperm stasis and dilation of rete testis tubules may compress adjacent structures, but the architecture is preserved. The epithelium is negative for vimentin, but may produce mucins, and consequently can be periodic acid-Schiff (PAS) and/or Alcian blue positive. Proliferative lesions of the rete testis have been reported following prenatal treatment with diethylstilbestrol.

Differential diagnosis: **Rete testis adenoma**.

Reference

Creasy, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse male reproductive system. *Toxicol Pathol* 40(6 Suppl):40S–121S.

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http://www.goreni.org/

Seminal vesicle epithelial stromal tumor is a benign tumor that has been reported exclusively in one rodent strain, the TRAMP transgenic mouse. It is composed of proliferating stromal and epithelial cells. Cells are densely packed and have frequent mitotic figures. Stromal components are immunohistochemically positive for SV40-Tag protein and desmin and are lined by cuboidal to columnar epithelium. The epithelial component forms papillary, cystic, and tubuloglandular structures.

References

Creasy, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse male reproductive system. *Toxicol Pathol* 40(6 Suppl):40S–121S.

Tani, Y. et al. 2005. Epithelial-stromal tumor of the seminal vesicles in the transgenic adenocarcinoma mouse prostate model. *Vet Pathol* 42(3):306–314.

Links

https://www.ncbi.nlm.nih.gov/pubmed/22949412
http://www.goreni.org/

Seminoma, benign is the most common type of testicular tumor in man and they are relatively common in aged dogs, zebrafish (*Danio rerio*), and medaka (*Oryzias latipes*). They are rarely seen in rodents. Histologically, neoplastic cells are arranged in sheets and localized within the confines of one or a few tubular profiles. Cells are well differentiated, large, and often polyhedral with distinct cell boundaries, resembling spermatogonia, spermatocytes, and/or spermatids. Occasional multinucleate cells and frequent mitoses with or without atypia may be present, but there is no evidence of invasion. Seminomas stain positive for S-100 and vimentin.

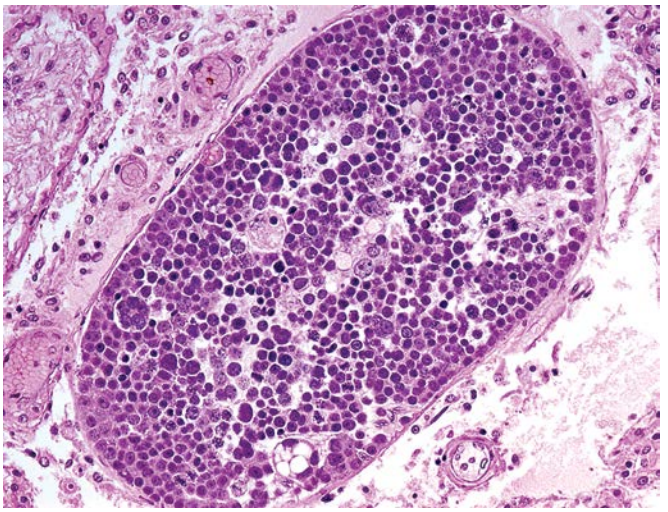


FIGURE 11 Seminoma, benign, testis, rat, H&E. (Reproduced with permission of Society of Toxicologic Pathology from Creasy, D. et al. 2012. Toxicol Pathol 40(6 Suppl):40S–121S.)

Differential diagnosis: **Seminoma, malignant**.

Synonym(s): **Germinoma**; **spermatocytoma**; **spermatocytic seminoma**.

References

Bush, J.M. et al. 2011. Testicular germ cell tumours in dogs are predominantly of spermatocytic seminoma type and are frequently associated with somatic cell tumours. *Int J Androl* 34(4 Pt 2):e288–e295.

Creasy, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse male reproductive system. *Toxicol Pathol* 40(6 Suppl):40S–121S.

Spitsbergen, J.M., Buhler, D.R., and Peterson, T.S. 2014. Neoplasia and neoplasm-associated lesions in laboratory colonies of zebrafish emphasizing key influences of diet and aquaculture system design. *ILAR J* 53(2):114–125.

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http://www.goreni.org/
https://www.ncbi.nlm.nih.gov/pubmed/21615421
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4154580/

Seminoma, malignant is the most common type of testicular tumor in man and are relatively common in aged dogs, zebrafish (*Danio rerio*), and medaka (*Oryzias latipes*). They are rarely seen in rodents. Histologically, neoplastic cells are arranged in sheets and localized within the confines of one or a few tubular profiles. Cells are well differentiated, large, and often polyhedral with distinct cell boundaries, resembling spermatogonia, spermatocytes, and/or spermatids. Malignant seminomas can be differentiated from benign seminomas by evidence of invasion through the tubular basement membrane, invasion of tumor cells throughout the interstitial tissue, and anisocytosis. Seminomas stain positive for S-100 and vimentin.

Differential diagnosis: **Seminoma, benign**.

Synonym(s): **Germinoma**; **spermatocytoma**; **spermatocytic seminoma**.

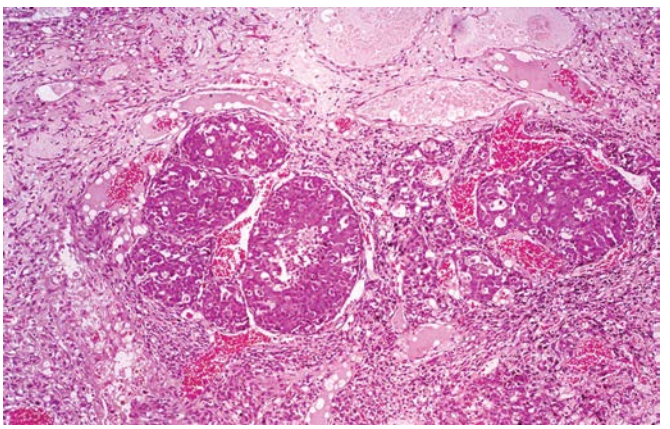


FIGURE 12 Seminoma, malignant, testis, rat, H&E. (Reproduced with permission of Society of Toxicologic Pathology from Creasy, D. et al. 2012. Toxicol Pathol 40(6 Suppl):40S–121S.)

References

Bush, J.M. et al. 2011. Testicular germ cell tumours in dogs are predominantly of spermatocytic seminoma type and are frequently associated with somatic cell tumours. *Int J Androl* 34(4 Pt 2):e288–e295.

Creasy, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse male reproductive system. *Toxicol Pathol* 40(6 Suppl):40S–121S.

Spitsbergen, J.M., Buhler, D.R., and Peterson, T.S. 2014. Neoplasia and neoplasm-associated lesions in laboratory colonies of zebrafish emphasizing key influences of diet and aquaculture system design. *ILAR J* 53(2):114–125.

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https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4154580/

Sertoli cell (SC) tumor, benign is a rare spontaneous tumor in the testes in rodents that derives from Sertoli cells, the multifunctional supporting cells within the testicular tubules. SC tumors are composed of interdigitating rows of tubules lined with elongated, palisading cells situated on a thin fibrovascular stromal basement membrane, without invasion or cellular pleomorphism. Bilateral SC tumors with malignant features have been reported in transgenic mice expressing the large T protein of polyoma virus in the seminiferous epithelium. Benign SC tumors are uncommon in man.

Differential diagnosis: **Sertoli cell tumor, malignant**.

Synonym(s): **Sertoli cell tubular adenoma**; **sustentacular cell tumor, benign**; **sex cord stromal tumor**; **gonadal stromal tumor**; **androblastoma, benign**; **arrhenoblastoma, benign**.

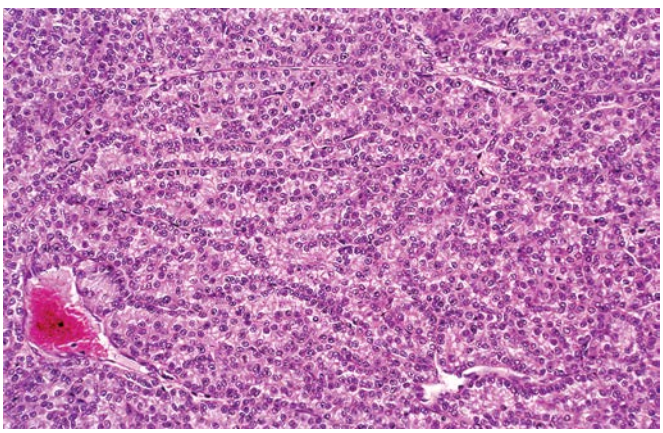


FIGURE 13 Sertoli cell tumor, benign, testis, rat. H&E. (Reproduced with permission of Society of Toxicologic Pathology from Creasy, D. et al. 2012. Toxicol Pathol 40(6 Suppl):40S–121S.)

References

Creasy, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse male reproductive system. *Toxicol Pathol* 40(6 Suppl):40S–121S.

Creasy, M.C. and Chapin, R.E., 2013. Male reproductive system. In: Haschek, W., Rousseaux, C., Wallig, M. (eds.) *Haschek and Rousseaux's Handbook of Toxicologic Pathology*, 3rd ed. Elsevier, pp. 2494–2598.

Greaves, P. 2012. Male Genital Tract. In: Greaves, P. (ed.) *Histopathology of Preclinical Toxicity Studies. Interpretation and Relevance in Drug Safety Development*, 4th ed. Academic Press, Elsevier, pp. 615–666.

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http://www.goreni.org/

Sertoli cell (SC) tumor, malignant is an extremely rare, spontaneous malignant tumor in the testes of rodents that derives from Sertoli cells, the multifunctional supporting cells within the testicular tubules. Diagnostic criteria are as for the benign tumor (see **Sertoli cell tumor, benign** for further information) but malignant forms are less differentiated, with local invasion of the adjacent testicular structures. Areas of necrosis may be present, and mitotic figures are common, especially in poorly differentiated areas. Sertoli cell tumors are occasionally observed in dogs, and like those in rodents, increase in incidence with age. In nonhuman primates, single cases of testicular tumors are reported, but malignant tumors consisting solely of Sertoli cells have not been reported. Bilateral malignant Sertoli cell tumors are reported in the testes of transgenic mice expressing the large T protein of polyoma virus in the seminiferous epithelium.

Differential diagnosis: **Sertoli cell tumor, benign**.

Synonym(s): **Sertoli cell tubular carcinoma**; **sustentacular cell tumor, malignant**; **Sex-cord stromal tumor, malignant**; **Androblastoma, malignant**; **Arrhenoblastoma, malignant**.

References

Creasy, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse male reproductive system. *Toxicol Pathol* 40(6 Suppl):40S–121S.

Creasy, M.C. and Chapin, R.E., 2013. Male reproductive system. In: Haschek, W., Rousseaux, C., Wallig, M. (eds.) *Haschek and Rousseaux's Handbook of Toxicologic Pathology*, 3rd ed. Elsevier, pp. 2494–2598.

Greaves, P. 2012. Male genital tract. In: Greaves, P. (ed.) *Histopathology of Preclinical Toxicity Studies. Interpretation and Relevance in Drug Safety Development*, 4th ed. Academic Press, Elsevier, pp. 615–666.

Paquis-Flucklinger, V.P., Rassoulzadegan, M., and Michiels, J.F. 1994. Experimental Sertoli cell tumours in mouse and their progression into mixed germ cell-sex cord proliferation. *Am J Path* 144:454–459.

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Sertoli cell tubular adenoma, see the preferred term **Sertoli cell (SC) tumor, benign**.

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Sertoli cell tubular carcinoma, see the preferred term **Sertoli cell (SC) tumor, malignant**.

Sertoli-Leydig cell mixed tumor, benign is rare and composed of two different cell types reminiscent of Sertoli and Leydig cells, possibly indicating a common embryonic origin. Neoplastic Sertoli cells (SC) form variably sized tubules arranged perpendicular to the basement membrane. Cells are pale and vacuolated, with elongated cytoplasm extending into a lumen. Nuclei are cleaved and have a single prominent nucleolus; cells may show eosinophilic cytoplasmic inclusions, and tubules may contain corpora amylacea. Neoplastic Leydig cells (LC) have eosinophilic or vacuolated cytoplasm and central, round nuclei with evenly distributed chromatin, and single prominent nucleolus, as observed in pure Leydig cell tumors.

Reference

Creasy, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse male reproductive system. *Toxicol Pathol* 40(6 Suppl):40S–121S.

Links

https://www.ncbi.nlm.nih.gov/pubmed/22949412
http://www.goreni.org/

Sex cord stromal tumor, see the preferred term **Sertoli cell (SC) tumor, benign**.

Sex-cord stromal tumor, malignant, see the preferred term **Sertoli cell (SC) tumor, malignant**.

Spermatocytic seminoma, see the preferred term **Seminoma, benign** or **Seminoma, malignant**.

Spermatocytoma, see the preferred term **Seminoma, benign** or **Seminoma, malignant**.

Sustentacular cell tumor, benign, see the preferred term **Sertoli cell (SC) tumor, benign**.

Sustentacular cell tumor, malignant, see the preferred term **Sertoli cell (SC) tumor, malignant**.

Testicular choriocarcinoma is a rare spontaneous tumor in rats and mice arising from pluripotent cells originating from a displaced visceral yolk sac. The neoplasm is composed of trophoblastic giant cells and smaller, darker-staining cytotrophoblasts. Trophoblastic giant cells are mononuclear, and often appear irregular and bizarre. These cells secrete luteotropic and mammotrophic hormones, and immunohistochemically stain positive for human chorionic gonadotropin and prolactin.

Differential diagnoses: Testicular seminoma, malignant; **Testicular yolk sac carcinoma**; **Embryonal carcinoma**.

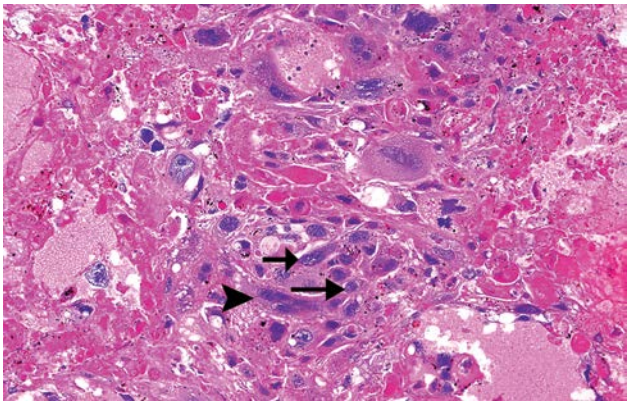


FIGURE 14 Choriocarcinoma, cytotrophoblasts (arrows) and syncytiotrophoblasts (arrow head), testis, mouse, H&E. (Reproduced with permission of Society of Toxicologic Pathology from Creasy, D. et al. 2012. Toxicol Pathol 40(6 Suppl):40S–121S.)

References

Creasy, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse male reproductive system. *Toxicol Pathol* 40(6 Suppl):40S–121S.

Jamadagni, S.B., Jamadagni, P., Lacy, S.H., Williams, B., Upadhyay, S., Gaidhani, S., and Hazra, J. 2013. Spontaneous nonmetastatic choriocarcinoma, yolk sac carcinoma, embryonal carcinoma, and teratoma in the testes of a Swiss albino mouse. *Toxicol Pathol* 41(3):532–536.

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https://www.ncbi.nlm.nih.gov/pubmed/22949412
http://www.goreni.org/
https://www.ncbi.nlm.nih.gov/pubmed/23104768

Testicular granulosa cell tumor, benign is a spontaneous tumor that occurs primarily in the mouse, and rarely in the rat. Benign testicular granulosa cell tumors have also been produced experimentally in castrated rats by transplanting splenic tissue into the testis. In addition, there is an unpublished case due to cadmium chloride administration. Morphologically, tumors are similar to the female counterpart, the ovarian granulosa cell tumor: tissue is replaced by cords and sheets of tumor cells, and blood-filled sinuses may be observed. Cells are small and

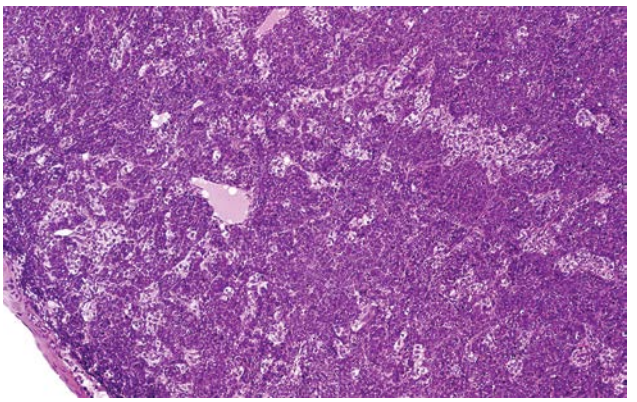


FIGURE 15 Granulosa cell tumor, testis, mouse, H&E. (Reproduced with permission of Society of Toxicologic Pathology from Creasy, D. et al. 2012. Toxicol Pathol 40(6 Suppl):40S–121S.)

basophilic with scant cytoplasm and have a single nucleus with stippled chromatin and a single nucleolus. Tumor cells vary from round to spindle-shaped. The mitotic index is low.

Differential diagnoses: **Seminoma, malignant**; **Sertoli cell tumor, benign**; **Leydig cell adenoma**.

Reference

Creasy, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse male reproductive system. *Toxicol Pathol* 40(6 Suppl):40S–121S.

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Testicular mesothelial hyperplasia is a proliferative lesion localized to the serosa of the tunica vaginalis of the testis in the rat. It may be incidental or xenobiotic induced. Histologically, the lesion is comprised of focal thickening or villous projections, sometimes protruding from a fibrovascular stalk. Projections are lined by cuboidal cells with little or no stratification. Mitotic activity and cellular atypia are not present, although fibrosis and inflammation may accompany the lesion. Mesothelium hyperplasia may be a precursor to mesothelioma.

Reference

Creasy, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse male reproductive system. *Toxicol Pathol* 40(6 Suppl):40S–121S.

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https://www.ncbi.nlm.nih.gov/pubmed/22949412
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Testicular mesothelioma, malignant is a malignant neoplasm that preferentially develops on the tunica vaginalis of the rat testis. Mesothelioma is particularly common in the Fischer 344 strain and has not been described in the mouse. Histologically, mesotheliomas consist of papillary projections or fronds of neoplastic cells arising from the region of the rete/pampiniform plexus. These tumors invade along the mesothelial surface with frequent extension into the epididymis and the peritoneal cavity. Mesotheliomas are causally associated with Leydig cell (LC) tumors that lead to an autocrine growth factor–induced mesothelial mitogenesis and decreased prolactin activity. Their incidence has been increased by exposure to xenobiotics including acrylamide and potassium bromate. Xenobiotic induction of mesotheliomas of the tunica vaginalis in rats (along with LC tumors) is considered of limited relevance to man, based on the different hormonal and tumor profile of the two species.

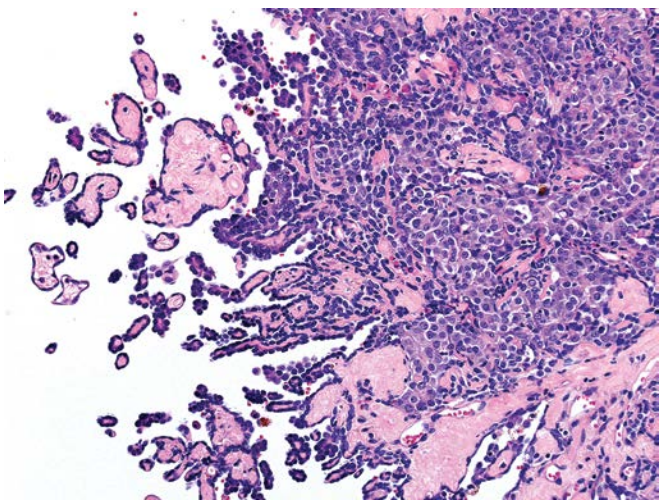


FIGURE 16 Mesothelioma, testis, rat, H&E. (Reproduced with permission of Society of Toxicologic Pathology from Creasy, D. et al. 2012. Toxicol Pathol 40(6 Suppl):40S–121S.)

Reference

Creasy, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse male reproductive system. *Toxicol Pathol* 40(6 Suppl):40S–121S.

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Testicular teratoma, benign is a rare, spontaneous tumor in the testis of many species (including human) which arises from pluripotent germ cells. Essential for the diagnosis is the identification of the three embryonal germ cell layers. The tissue components are well differentiated and often contain cysts lined by epithelium (cuboidal, enteric, or respiratory) and surrounded by smooth muscle cells. Teratomas may also contain pancreatic, gastric, thyroid, neuronal, cartilage, bone, and/or skeletal muscle elements. In certain strains of mice (129 and P53 −/− transgenic) the incidence of teratomas is significantly increased. Although this tumor type can theoretically be present in all tissues, they are most frequently seen in the genital system, and development starts as early as day 12 (4–8). Teratomas can be found as a combination of tumors: teratoma and embryonal carcinoma).

Differential diagnosis: **Testicular teratoma, malignant**.

References

Creasy, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse male reproductive system. *Toxicol Pathol* 40(6 Suppl):40S–121S.

Damjanov, I. 1993. The pathology of human teratomas. In: Damjanov, I., Knowles, B.B., Solter, D. (eds.) *The Human Teratomas, Experimental and Clinical Biology*. Clifton NJ: Humana Press, pp. 23–66.

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http://www.goreni.org/

Testicular teratoma, malignant is a rare, spontaneous tumor in the testis of many species (including human) which arises from pluripotent germ cells. Essential for the diagnosis is the identification of the three embryonal germ cell layers. The neoplasm is characterized by poorly differentiated nervous, epithelial, and mesenchymal tissues with local invasion and/

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or metastasis. Within the tumor, necrosis and hemorrhages are usually present. Teratomas may also contain pancreatic, gastric, thyroid, neuronal, cartilage, bone, and/or skeletal muscle elements. In certain strains of mice (129 and P53 −/− transgenic) the incidence of teratomas is significantly increased. Although this tumor type can theoretically be present in all tissues, they are most frequently seen in the genital system, and development starts as early as day 12 (4–8). Teratomas can be found as a combination of tumors: teratoma and embryonal carcinoma.

Differential diagnosis: **Testicular teratoma, benign**.

References

Creasy, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse male reproductive system. *Toxicol Pathol* 40(6 Suppl):40S–121S.

Damjanov, I. 1993. The pathology of human teratomas. In: Damjanov, I., Knowles, B.B., Solter, D. (eds.) *The Human Teratomas, Experimental and Clinical Biology*. Clifton NJ: Humana Press, pp. 23–66.

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Testicular yolk sac carcinoma is a rare, spontaneous malignant tumor arising from the extraembryonic portion of the egg cylinder or visceral yolk sac. The tumor has been described in rats, mice, and children. Tumor cells are derived from the parietal and visceral layer. Cells from the parietal layer are polygonal or cuboidal with abundant periodic acid-Schiff (PAS)-positive, eosinophilic material. They form clusters, sheets, rosettes, cords, or papillary structures. Tumor cells from the visceral layer are columnar or polygonal and contain giant nuclei with clumped chromatin. They form papillary structures around capillaries or cell clusters, but do not contain PAS-positive droplets. The tumor is aggressive and grows mainly along the peritoneal surfaces. In both rodents and human, serum alpha-fetoprotein may be useful as a diagnostic marker.

References

Creasy, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse male reproductive system. *Toxicol Pathol* 40(6 Suppl):40S–121S.

Wei, Y. et al. 2014. Testicular yolk sac tumors in children: A review of 61 patients over 19 years. *World J Surg Oncol* 12:400.

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RESPIRATORY SYSTEM

Bronchial adenoma, see the preferred term **Laryngeal, tracheal, bronchial, and bronchiolar papilloma**.

Bronchiolar goblet cell hyperplasia is characterized by varying degrees of increases in the numbers of goblet cells in the airway epithelium. In severe cases, the epithelium appears to be entirely composed of large, mucus-filled cells having a characteristic goblet shape. There is usually an associated inflammatory infiltrate in the airway wall. The combined term hyperplasia/metaplasia may also be used when a combination of both processes appears to be present.

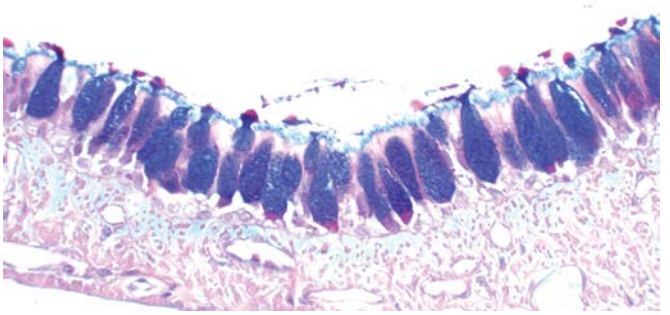


FIGURE 1 Goblet cell hyperplasia, lung, dog, PAS/AB.

Reference

Renne, R. et al. 2009. Proliferative and nonproliferative lesions of the rat and mouse respiratory tract. *Toxicol Pathol* 37(7 Suppl):5S–73S.

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Bronchiolar goblet cell metaplasia is characterized by varying degrees of increases in the numbers of goblet cells in the airway epithelium. In severe cases, the epithelium appears to be entirely composed of large, mucus-filled cells having a characteristic goblet shape. In the terminal bronchioles, where goblet cells are normally absent, they are believed to be derived from club cells (i.e., bronchiolar exocrine cells) which have transdifferentiated to an altered secretory phenotype; hence the term metaplasia is applied. There is usually an associated inflammatory infiltrate in the airway wall. The combined term hyperplasia/ metaplasia may also be used when a combination of both processes is present.

Reference

Renne, R. et al. 2009. Proliferative and nonproliferative lesions of the rat and mouse respiratory tract. *Toxicol Pathol* 37(7 Suppl):5S–73S.

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Bronchiolization, see the preferred term **Bronchioloalveolar hyperplasia**.

Bronchioloalveolar adenoma is a benign neoplasm that forms discrete nodules within the pulmonary parenchyma

with some compression of the adjacent alveoli. The tumor expands by growing along adjacent alveolar walls, and in some neoplasms the original alveolar architecture may still be discerned in some areas. However, infilling of the alveolar spaces by projections and multilayering may result in a more solid appearance leading to tumors with predominantly alveolar, solid, or papillary features, or admixes within a single neoplasm. Papillary growths into open, adjacent bronchiolar lumina are a relatively common feature, which must be distinguished from true invasive growth. The cells are cuboidal or columnar, sometimes vacuolated, and manifest a low mitotic rate with little atypia or pleomorphism. In the past there was debate as to the cellular origin of these neoplasms, with both club cells (i.e., bronchiolar exocrine cells) and type II pneumocytes being proposed; however, with the advent of immunohistochemistry using antibodies against SP-A and SP-C, the type II pneumocyte has been determined as the most frequent component cell.

Differential diagnoses: **Bronchioloalveolar hyperplasia**; **Bronchioloalveolar carcinoma**.

Synonym(s): **Type II cell adenoma**.

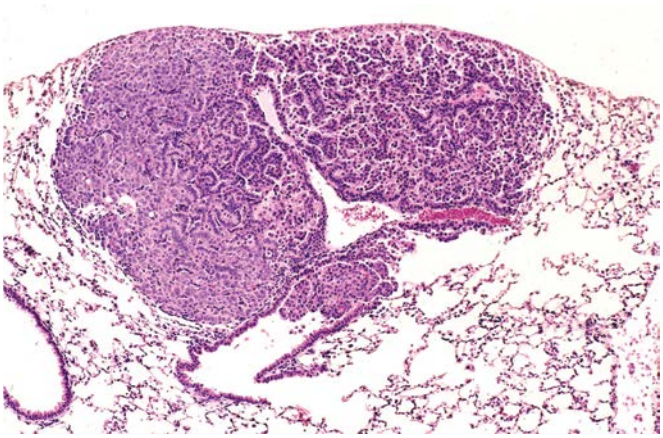


FIGURE 2 Bronchioloalveolar adenoma, lung rat, H&E.

Reference

Renne, R. et al. 2009. Proliferative and nonproliferative lesions of the rat and mouse respiratory tract. *Toxicol Pathol* 37(7 Suppl):5S–73S.

Links

https://www.ncbi.nlm.nih.gov/pubmed/20032296
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Bronchioloalveolar carcinoma is the malignant counterpart of the bronchioloalveolar adenoma, and is generally larger, with a higher mitotic rate, nuclear pleomorphism, and varied growth patterns with local invasion. In mice these neoplasms may invade the pleura, at which point they often assume a mesenchymal phenotype, as do their distant metastases. Another useful criterion on which to diagnose malignancy is the presence of peripheral "buds," apparently isolated from the main body of the tumor, in the surrounding alveoli. Affecting mice in particular, apparent multiple bronchioloalveolar carcinomas may be found within an animal, often in different lobes; these present a diagnostic conundrum in that it is impossible to determine whether they represent a single malignant tumor with intrapulmonary metastases, or distinct individual neoplasms. The tumor may show foci of squamous metaplasia, though these will not be a major feature.

Differential diagnoses: **Bronchioloalveolar adenoma**; **Pulmonary acinar carcinoma**; **Pulmonary adenosquamous carcinoma**; **Pulmonary squamous cell carcinoma**.

Synonym(s): **Pulmonary adenocarcinoma**.

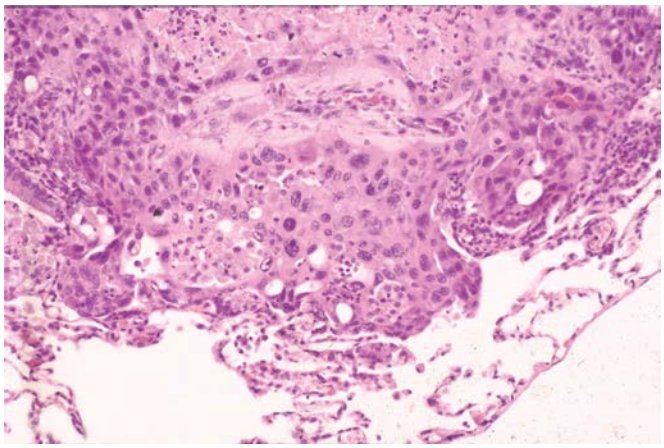


FIGURE 3 Bronchioloalveolar carcinoma, lung, rat, H&E.

Reference

Renne, R. et al. 2009. Proliferative and nonproliferative lesions of the rat and mouse respiratory tract. *Toxicol Pathol* 37(7 Suppl):5S–73S.

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Bronchioloalveolar hyperplasia is characterized by the replacement of alveolar epithelium by the peripheral extension of the bronchiolar epithelium into the alveolar ducts and adjacent alveoli. The bronchioloalveolar structure remains discernible and forms a framework for the lesion. This extension is usually composed of bronchiolar "club cells," but may also involve cells showing ciliated, goblet, or squamous differentiation. In the squamous form, the superficial cells often contain keratohyalin granules, and the cells may keratinize. Occasionally, only one side of an individual alveolar wall section may be affected, the other being lined by normal type I and type II cells. As the well-differentiated cell types involved are not normally present in these locations, these lesions may be regarded as forms of metaplasia. As nascent club cells are often devoid of their characteristic apical bleb shape, they may be difficult to distinguish from local type II cell hyperplasia. The use of immunohistochemical markers such as CC16 for club cells or SP-A or SP-C for type II cells may be used to distinguish the two cell types.

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Differential diagnoses: **Bronchioloalveolar adenoma**; **Bronchioloalveolar carcinoma**; **Pulmonary acinar carcinoma**.

Synonym(s): **Bronchiolization**.

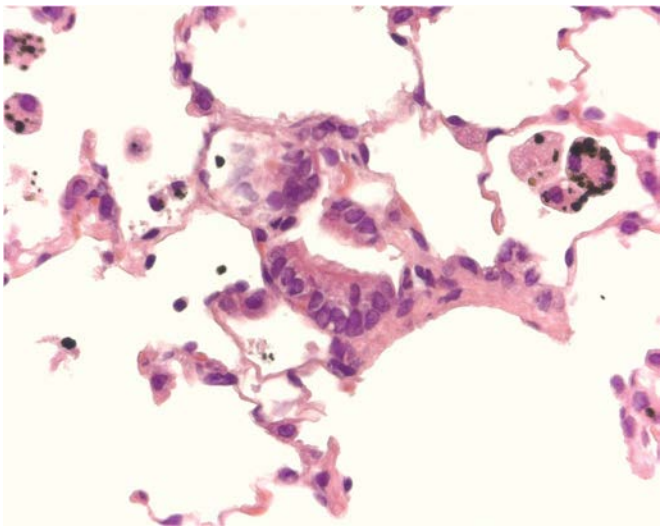


FIGURE 4 Bronchioloalveolar hyperplasia, lung, rat, H&E.

Reference

Renne, R. et al. 2009. Proliferative and nonproliferative lesions of the rat and mouse respiratory tract. *Toxicol Pathol* 37(7 Suppl):5S–73S.

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Epidermoid carcinoma, see the preferred term **Pulmonary squamous cell carcinoma**.

Laryngeal, tracheal, bronchial, and bronchiolar adenocarcinoma is the result of malignant transformation of the surface or submucosal glandular epithelium of the larynx or airways or may arise within a pre-existing adenoma. Tumors may be solid, pseudoglandular, and early masses may have a papillary appearance. Tumor cells can range from well differentiated with goblet cells present to anaplastic with few differentiating features, a high degree of pleomorphism, and frequent abnormal mitoses. Evidence for malignancy includes cellular or nuclear atypia, frequent or abnormal mitoses, penetration of the basement membrane, and invasion and metastasis (frequently to the lung). There may be regions of squamous differentiation, but these are not major features.

Differential diagnoses: **Laryngeal, tracheal, bronchial, and bronchiolar papilloma**; **Laryngeal, trachea, bronchi and bronchioles epithelial hyperplasia with atypia**; **Laryngeal, tracheal, bronchial, and bronchiolar squamous cell carcinoma**.

Reference

Renne, R. et al. 2009. Proliferative and nonproliferative lesions of the rat and mouse respiratory tract. *Toxicol Pathol* 37(7 Suppl):5S–73S.

Links

https://www.ncbi.nlm.nih.gov/pubmed/20032296
http://www.goreni.org/

Laryngeal, tracheal, bronchial, and bronchiolar benign neuroendocrine cell tumor represents neoplastic proliferation of the dispersed neuroendocrine cell population within laryngeal or airway epithelium. Benign neuroendocrine cell tumor is composed of basophilic cells with stippled chromatin and eosinophilic, faintly granular cytoplasm and forms a nodule that projects into the laryngeal or airway lumen. Mitotic figures are rare. In larger masses, scant fibrovascular stroma may divide the tumor parenchyma into lobules. Definitive identification can be made with immunohistochemistry for calcitonin gene-related peptide or protein gene product 9.5.

Differential diagnoses: **Laryngeal, tracheal, bronchial, and bronchiolar neuroendocrine cell hyperplasia**; **Laryngeal, tracheal, bronchial, and bronchiolar malignant neuroendocrine cell tumor**; **Laryngeal, tracheal, bronchial, and bronchiolar papilloma**.

Reference

Renne, R. et al. 2009. Proliferative and nonproliferative lesions of the rat and mouse respiratory tract. *Toxicol Pathol* 37(7 Suppl):5S–73S.

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https://www.ncbi.nlm.nih.gov/pubmed/20032296
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Laryngeal, tracheal, bronchial, and bronchiolar epithelial hyperplasia is an increase in the thickness of the affected epithelium due to cellular proliferation. This may be seen in squamous and respiratory epithelium, usually in response to an irritant. Particularly in the larynx, squamous epithelial hyperplasia can lead to overgrowth and blockage of the ducts of the submucosal glands, leading to ectasia of these structures. Respiratory epithelial hyperplasia may form protrusions into the airway or laryngeal lumen that are differentiated from papilloma by the lack of

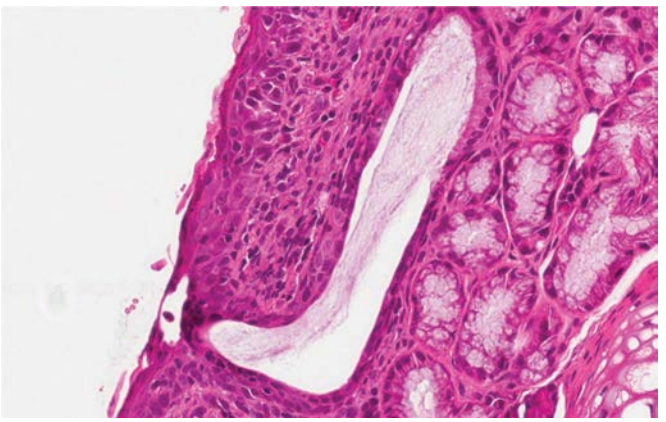


FIGURE 5 Laryngeal squamous epithelial hyperplasia with submucosal duct ectasia, larynx, rat, H&E.

a branching growth pattern, and central connective tissue stalk. Epithelial hyperplasia is frequently seen in response to exposure to an irritant, and as such may be seen in association with degeneration, metaplasia, and inflammation. Goblet cell hyperplasia is also a common response to airway irritation.

Differential diagnoses: Larygneal, tracheal, bronchial, and bronchiolar epithelial metaplasia; **Laryngeal, tracheal, bronchial, and bronchiolar papilloma**; **Laryngeal, tracheal, bronchial, and bronchiolar adenocarcinoma**.

Reference

Renne, R. et al. 2009. Proliferative and nonproliferative lesions of the rat and mouse respiratory tract. *Toxicol Pathol* 37(7 Suppl):5S–73S.

Links

https://www.ncbi.nlm.nih.gov/pubmed/20032296
http://www.goreni.org/

Laryngeal, tracheal, bronchial, and bronchiolar malignant neuroendocrine cell tumor represents neoplastic proliferation of the dispersed neuroendocrine cell population within laryngeal or airway epithelium. Malignant neuroendocrine tumors are extremely rare and are composed of basophilic cells with stippled chromatin and eosinophilic, faintly granular cytoplasm that forms a nodule which projects into the laryngeal or airway lumen. In larger masses, scant fibrovascular stroma may divide the tumor parenchyma into lobules. Mitotic figures are rare, and malignancy is determined by the presence of local tissue invasion and metastasis. Definitive identification can be made with immunohistochemistry for calcitonin gene-related peptide or protein gene product 9.5.

Differential diagnoses: **Laryngeal, tracheal, bronchial, and bronchiolar neuroendocrine cell hyperplasia**; **Laryngeal, tracheal, bronchial, and bronchiolar benign neuroendocrine cell tumor**; **Laryngeal, tracheal, bronchial, and bronchiolar papilloma**.

Reference

Renne, R. et al. 2009. Proliferative and nonproliferative lesions of the rat and mouse respiratory tract. *Toxicol Pathol* 37(7 Suppl):5S–73S.

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Laryngeal, tracheal, bronchial, and bronchiolar neuroendocrine cell hyperplasia is a rare finding characterized by the presence of clusters (>40 cells) of basophilic cells with stippled chromatin and eosinophilic, faintly granular cytoplasm projecting into the laryngeal or airway lumen. Smaller clusters of neuroendocrine cells, termed neuroepithelial bodies, are a normal anatomical feature in bronchi and bronchioles, and must be differentiated from neuroendocrine cell hyperplasia. Positive identification can be made with immunohistochemistry for calcitonin gene-related peptide or protein gene product 9.5.

Differential diagnoses: **Laryngeal, tracheal, bronchial, and bronchiolar benign neuroendocrine cell tumor**; **Laryngeal, tracheal, bronchial, and bronchiolar malignant neuroendocrine cell tumor**.

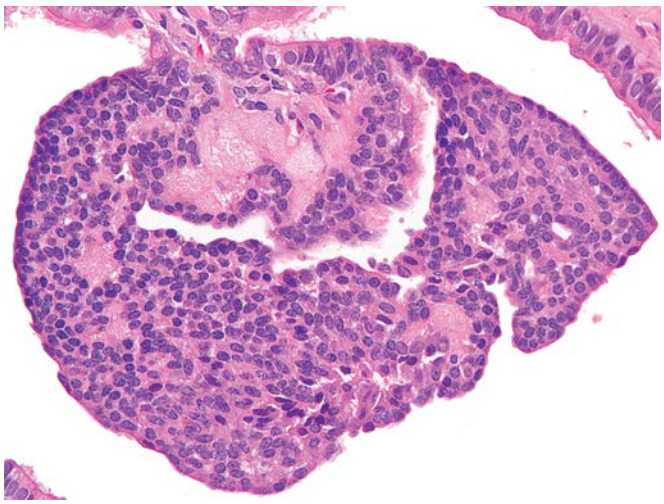


FIGURE 6 Neuroendocrine cell hyperplasia, bronchus, rat, H&E. (Reproduced with permission of the Society of Toxicologic Pathology from Renne, R. et al. 2009 *Toxicol Pathol* 37(7 Suppl):5S–73S.)

Reference

Renne, R. et al. 2009. Proliferative and nonproliferative lesions of the rat and mouse respiratory tract. *Toxicol Pathol* 37(7 Suppl):5S–73S.

Links

https://www.ncbi.nlm.nih.gov/pubmed/20032296
http://www.goreni.org/

Laryngeal, tracheal, bronchial, and bronchiolar papilloma is usually an exophytic growth of well-differentiated respiratory or squamous epithelium on a stalk of vascularized connective tissue with an intact basement membrane which frequently expands or distorts the airway in which it is located. A papilloma originating in the terminal bronchioles may expand into the alveolar parenchyma and become difficult to differentiate from a bronchioloalveolar adenoma.

Differential diagnoses: **Laryngeal, tracheal, bronchial, and bronchiolar inflammatory polyp**; **Laryngeal, tracheal, bronchial, and bronchiolar epithelial hyperplasia with atypia**; **Laryngeal, tracheal, bronchial, and bronchiolar adenocarcinoma**; **Laryngeal, tracheal, bronchial, and bronchiolar squamous cell carcinoma**; **Laryngeal, tracheal, bronchial, and bronchiolar benign neuroendocrine cell tumor**; **Laryngeal, tracheal, bronchial, and bronchiolar malignant neuroendocrine cell tumor**.

Synonym(s): **Bronchial adenoma**.

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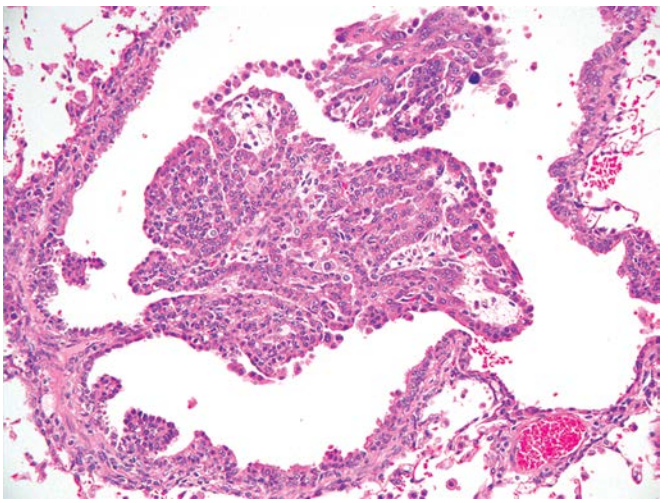


FIGURE 7 Papilloma, bronchus, mouse, H&E. (Reproduced with permission of the Society of Toxicologic Pathology from Renne, R. et al. 2009. *Toxicol Pathol* 37(7 Suppl):5S–73S.)

Reference

Renne, R. et al. 2009. Proliferative and nonproliferative lesions of the rat and mouse respiratory tract. *Toxicol Pathol* 37(7 Suppl):5S–73S.

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Laryngeal, tracheal, bronchial, and bronchiolar squamous cell carcinoma represents a malignant transformation of squamous epithelium present in the larynx, or of metaplastic squamous epithelium in other locations in the larynx and airways. A well-differentiated tumor may be readily identified by the typical appearance of branching cords of cells with prominent intercellular bridges and keratinization; however, a poorly differentiated nonkeratinizing squamous cell carcinoma may be confused with adenocarcinoma, and such tumors may only reliably be differentiated with the use of additional techniques such as immunohistochemical detection of keratins or ultrastructural identification of tonofilaments.

Differential diagnoses: **Laryngeal, tracheal, bronchial, and bronchiolar adenocarcinoma**; **Laryngeal, tracheal, bronchial, and bronchiolar papilloma**.

Reference

Renne, R. et al. 2009. Proliferative and nonproliferative lesions of the rat and mouse respiratory tract. *Toxicol Pathol* 37(7 Suppl):5S–73S.

Links

https://www.ncbi.nlm.nih.gov/pubmed/20032296
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Larynx, trachea, bronchi, and bronchioles epithelial hyperplasia with atypia represents a hyperplastic epithelium containing cells of abnormal phenotype with features such as increased variation in cellular or nuclear size and shape. Another characteristic feature can be the appearance of bi- or multinucleate cells.

Differential diagnoses: **Laryngeal, tracheal, bronchial, and bronchiolar adenocarcinoma**; **Laryngeal, tracheal, bronchial, and bronchiolar papilloma**; **Laryngeal, tracheal, bronchial, and bronchiolar squamous cell carcinoma**.

Reference

Renne, R. et al. 2009. Proliferative and nonproliferative lesions of the rat and mouse respiratory tract. *Toxicol Pathol* 37(7 Suppl):5S–73S.

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Larynx, trachea, bronchi, and bronchioles squamous metaplasia is the replacement of the respiratory epithelium normally present at these locations with a squamous epithelium that may be keratinized or nonkeratinized. Squamous metaplasia in the larynx is a common response to irritants, and the most sensitive region for this change in the rodent larynx is the base of the epiglottis. Squamous metaplasia can be reversible, and extensive squamous metaplasia of respiratory epithelium in the airways will have a negative effect on mucociliary clearance.

Reference

Renne, R. et al. 2009. Proliferative and nonproliferative lesions of the rat and mouse respiratory tract. *Toxicol Pathol* 37(7 Suppl):5S–73S.

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Mucoepidermoid carcinoma, see the preferred term **Pulmonary adenosquamous carcinoma**.

Nasal cavity adenocarcinoma is the result of malignant transformation of the epithelium lining the nasal cavity (transitional, respiratory or secretory), the submucosal gland epithelium, or it may arise within a pre-existing adenoma. Adenocarcinoma may also be located in the nasopharynx, the paranasal sinus, larynx, and airways. Tumors may be solid, pseudoglandular, or have a papillary appearance. Tumor cell phenotype may resemble the originating epithelium, such as the presence of many goblet cells, or may be anaplastic with few differentiating features, a high degree of pleomorphism, and frequent abnormal mitoses. Evidence for malignancy includes cellular or nuclear atypia, frequent or abnormal mitoses, penetration of the basement membrane, invasion, and

metastasis (frequently to the lung). There may be regions of squamous differentiation, but these are not a major feature.

Differential diagnoses: **Nasal cavity adenoma**; **Nasal cavity adenosquamous carcinoma**; **Nasal cavity neuroepithelial carcinoma**.

Reference

Renne, R. et al. 2009. Proliferative and nonproliferative lesions of the rat and mouse respiratory tract. *Toxicol Pathol* 37(7 Suppl):5S–73S.

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Nasal cavity adenoma is the result of neoplastic transformation of the transitional, respiratory, or secretory epithelial lining of the nasal cavity, and may be exophytic or endophytic. Adenoma may also arise in the nasopharynx or paranasal sinus. Given the regional distribution of epithelial types in the nasal cavity, there is a corresponding distribution of adenoma types. Cells are usually nonciliated cuboidal to columnar, and there may be many goblet cells arranged in sheets or forming acinar or pseudoacinar structures. Glandular structures may contain periodic acid-Schiff (PAS)-positive secretory material and be associated inflammatory cells. Eosinophilic globules within the cytoplasm of adenomas may be a prominent feature, and while there may be regions of squamous differentiation, these are not prominent.

Differential diagnoses: **Nasal cavity squamous cell papilloma**; **Nasal cavity adenocarcinoma**.

Reference

Renne, R. et al. 2009. Proliferative and nonproliferative lesions of the rat and mouse respiratory tract. *Toxicol Pathol* 37(7 Suppl):5S–73S.

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http://www.goreni.org/

Nasal cavity adenosquamous carcinoma contains malignant glandular and squamous epithelial components, and can arise from respiratory epithelium, submucosal gland duct epithelium, or from olfactory epithelium. Keratin pearl formation may be visible within the squamous regions. This neoplasm can also arise from the epithelial lining of the nasopharynx and paranasal sinus. Tumors are frequently poorly differentiated, and evidence for malignancy includes cellular or nuclear atypia, frequent or abnormal mitoses, penetration of the basement membrane, invasion, and metastasis.

Differential diagnoses: **Nasal cavity squamous cell papilloma**; **Nasal cavity adenocarcinoma (with regions of squamous metaplasia)**; **Nasal cavity squamous cell carcinoma**.

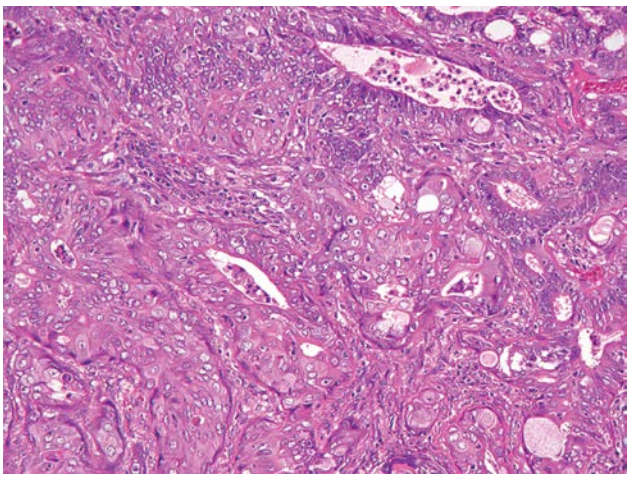


FIGURE 8 Adenosquamous carcinoma, nasal cavity, rat, H&E. (Reproduced with permission of the Society of Toxicologic Pathology from Renne, R. et al. 2009. *Toxicol Pathol* 37(7 Suppl):5S–73S.)

Reference

Renne, R. et al. 2009. Proliferative and nonproliferative lesions of the rat and mouse respiratory tract. *Toxicol Pathol* 37(7 Suppl):5S–73S.

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Nasal cavity basal cell hyperplasia appears as a focal thickening of the basal cell layer and may involve any of the nasal cavity epithelia. Affected basal cells are closely packed and are typically more basophilic than the overlying epithelium. The change is often seen as part of the spectrum of response to epithelial irritation, may be associated with inflammation and degeneration of the overlying epithelium, and may be a prelude to metaplasia. The overlying epithelium is particularly fragile and may be sloughed or lost during processing. Basal cell hyperplasia of nasal cavity olfactory epithelium was noted in rats following exposure to a PDE-IV inhibitor.

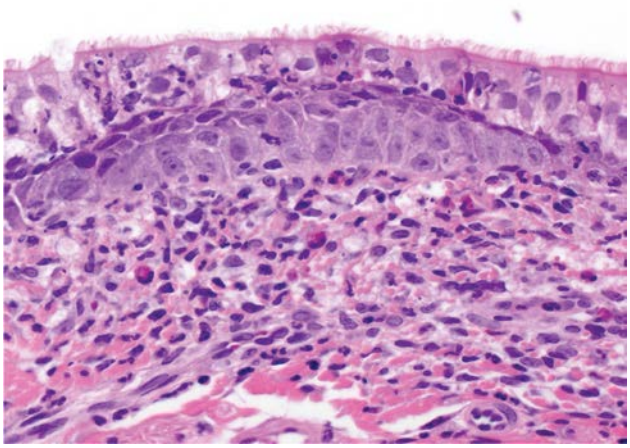


FIGURE 9 Basal cell hyperplasia, nasal cavity, rat, H&E.

A2

Reference

Lewis, D. and McKevitt, T. 2013. Respiratory system. In: Sahota, P., Popp, J., Hardisty, J., Gopinath, C. (eds.) *Toxicologic Pathology: Nonclinical Safety Assessment*. Boca Raton, FL: CRC Press, pp. 367–419.

Link

https://www.crcpress.com/Toxicologic-Pathology-Nonclinical-Safety-Assessment/Sahota-Popp-Hardisty-Gopinath/p/book/9781138199545

Nasal cavity epithelial hyperplasia represents a proliferation of the affected epithelium with an increase in the number of cell layers wherein mild pleomorphism and occasional mitotic figures may be seen. Hyperplasia is often part of the response to a nasal cavity irritant, and as such may be seen in association with degeneration, metaplasia, and inflammation. Squamous cell hyperplasia can occur in the nasal vestibule and ventral meatus; however, as the thickness of the epithelium can vary slightly, low-grade changes must be carefully differentiated from epithelium at the same level in control animals. Respiratory epithelial hyperplasia may include a decrease in the number of ciliated cells, and mucous cell hyperplasia within respiratory epithelium may be recorded separately, or as a standalone finding if it is the predominant change. A large increase in numbers of mucous cells within the transitional epithelium may be recorded as hyperplasia/metaplasia, as there are few cells of this type present in control animals; thus metaplasia is likely to play a role in the change. General hyperplasia of transitional epithelium is differentiated simply by an increase in the number of cell layers beyond that seen in controls. Olfactory epithelial hyperplasia similarly can involve any or all of the sensory, sustentacular, or basal cell populations.

Differential diagnoses: **Nasal cavity epithelial hyperplasia with atypia**; **Nasal cavity adenoma**; **Nasal cavity adenocarcinoma**.

Reference

Renne, R. et al. 2009. Proliferative and nonproliferative lesions of the rat and mouse respiratory tract. *Toxicol Pathol* 37(7 Suppl):5S–73S.

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Nasal cavity epithelial hyperplasia with atypia represents a hyperplastic epithelium containing cells of abnormal phenotype with features such as increased variation in size and shape of the cells and their nuclei, and an increased proportion of cells with an undifferentiated "basal cell" phenotype. Another characteristic feature can be the appearance of bi- or multinucleate cells.

Differential diagnosis: **Nasal cavity adenocarcinoma**.

Reference

Renne, R. et al. 2009. Proliferative and nonproliferative lesions of the rat and mouse respiratory tract. *Toxicol Pathol* 37(7 Suppl):5S–73S.

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Nasal cavity epithelial metaplasia occurs in two forms: from a transitional, respiratory, or olfactory epithelium to a squamous phenotype, or metaplasia of olfactory epithelium to a respiratory phenotype. The former is a common sequel to chronic irritation and may be seen in association with nasal cavity inflammation, or adjacent to regions of epithelial degeneration, necrosis, and regeneration. Respiratory metaplasia of olfactory epithelium is most commonly seen in the dorsal medial meatus, may be associated with local areas of olfactory epithelial atrophy or degeneration, and can be seen spontaneously as an age-related change in rats or mice. Given that the natural boundary between the respiratory and olfactory epithelia may vary slightly, and that a consistent appearance relies on very precise sectioning with regard to anatomic landmarks, this change should be interpreted with caution. Both forms of metaplasia may include the epithelium of subjacent glandular ducts. Nasal cavity epithelial metaplasia is not regarded as a preneoplastic change; although in some cases squamous metaplasia may progress to papilloma or squamous cell carcinoma, in other circumstances it can be reversible.

Differential diagnosis: **Nasal cavity epithelial regeneration**.

Reference

Renne, R. et al. 2009. Proliferative and nonproliferative lesions of the rat and mouse respiratory tract. *Toxicol Pathol* 37(7 Suppl):5S–73S.

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Nasal cavity neuroepithelial carcinoma arises from cells of the olfactory epithelium (basal, sustentacular, or sensory cells), is composed of round to columnar cells with basally located nuclei, and characteristically forms rosettes (cells arranged around an open central lumen resembling a true acinus) or pseudorosette structures (i.e., a circular arrangement of cells with a poorly defined central space often filled with amorphous material). Neoplastic cells are often divided into lobules by fibrovascular septa, and invasion of the ethmoid bone and brain is common. If rosette or pseudorosette structures are not apparent, and in the absence of ultrastructural confirmation of olfactory epithelial origin, a diagnosis of adenocarcinoma is recommended.

Differential diagnosis: **Nasal cavity adenocarcinoma**.

Synonym(s): **Olfactory neuroblastoma**; **olfactory neuroepithelioma**.

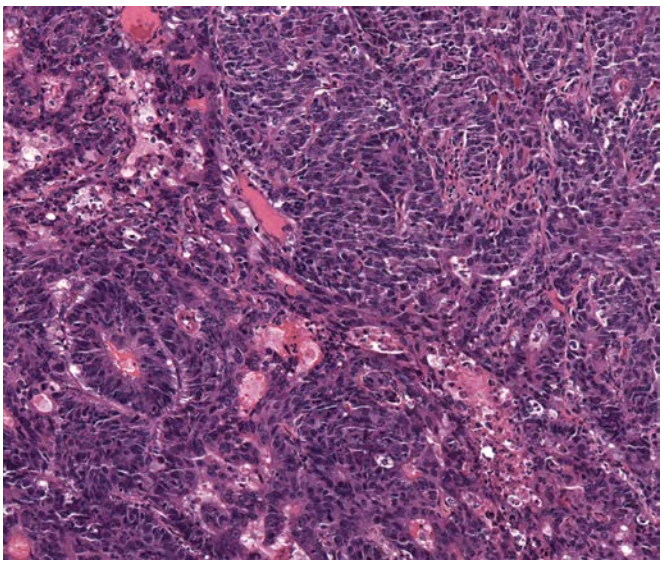


FIGURE 10 Neuroepithelial cell carcinoma, nasal cavity, rat, H&E. (Reproduced with permission of the Society of Toxicologic Pathology from Renne, R. et al. 2009. *Toxicol Pathol* 37(7 Suppl):5S–73S.)

Reference

Renne, R. et al. 2009. Proliferative and nonproliferative lesions of the rat and mouse respiratory tract. *Toxicol Pathol* 37(7 Suppl):5S–73S.

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Nasal cavity squamous cell carcinoma is most commonly located in the nasal vestibule and is associated with the preexisting squamous epithelium in that location, though it can arise from metaplastic squamous epithelium in other locations within the nasal cavity and airways. A well-differentiated tumor may be readily identified by the typical appearance of branching cords of cells with prominent intercellular bridges and keratinization; however, a poorly differentiated nonkeratinizing squamous cell carcinoma may be confused with adenocarcinoma. Such tumors may only be reliably differentiated with the use of additional techniques such as immunohistochemical detection of keratins or ultrastructural identification of tonofilaments.

Differential diagnoses: **Nasal cavity adenocarcinoma**; **Nasal cavity squamous cell papilloma**.

Reference

Renne, R. et al. 2009. Proliferative and nonproliferative lesions of the rat and mouse respiratory tract. *Toxicol Pathol* 37(7 Suppl):5S–73S.

Links

https://www.ncbi.nlm.nih.gov/pubmed/20032296
http://www.goreni.org/

Nasal cavity squamous cell papilloma is usually an exophytic growth of well-differentiated, regularly arranged squamous epithelium on a stalk of vascularized connective tissue with an intact basement membrane. The papilloma may originate from the squamous epithelium of the nasal vestibule, or from metaplastic squamous epithelium in other locations within the nasal cavity. Rarely, the papilloma may grow beneath the mucosal surface. This is described as an endophytic, or inverted, papilloma.

Differential diagnoses: **Nasal cavity epithelial hyperplasia**; **Nasal cavity squamous cell carcinoma**.

Reference

Renne, R. et al. 2009. Proliferative and nonproliferative lesions of the rat and mouse respiratory tract. *Toxicol Pathol* 37(7 Suppl):5S–73S.

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Nasal yolk sac tumor (YST) is a rare, primitive germ cell neoplasm, i.e., found in rodents wherein the histological features reflect the structure of the embryonic yolk sac. It is thought to arise from the parietal cells. The rodent yolk sac is an extraembryonic structure which, unlike in human, is composed of trophoblasts and endodermal parietal cells that secrete a thick (Reichert's) basement membrane. Extragonadal germ cell tumors in humans are usually found along the midline, including the nasal passages. Nasal YSTs in rats are indistinguishable from those seen in the reproductive tracts, and are composed of nests, ribbons, or single cells embedded in an amorphous, eosinophilic, strongly periodic acid-Schiff (PAS)- and laminin-positive hyaline matrix. Metastases may be seen in the cervical lymph nodes. Ultrastructurally, the matrix is composed of concentric alternating high and low electron–dense layers. Thus the matrix is consistent with exuberant basement membrane synthesis.

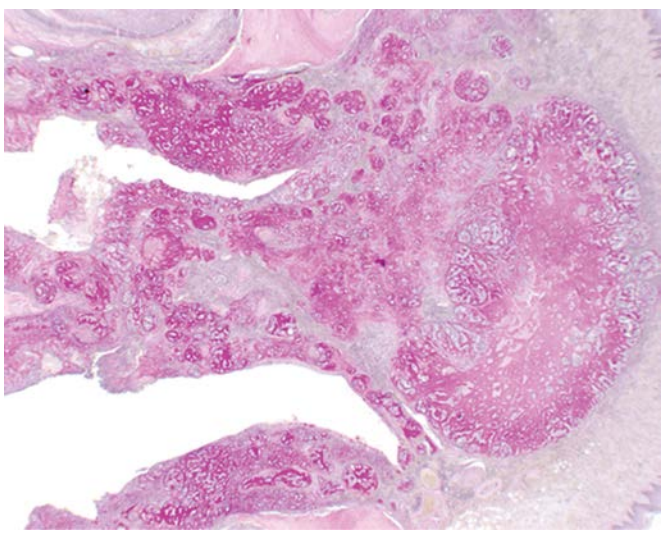


FIGURE 11 Yolk sac tumor, nasal cavity rat, H&E.

Reference

Renne, R. et al. 2009. Proliferative and nonproliferative lesions of the rat and mouse respiratory tract. *Toxicol Pathol* 37(7 Suppl):5S–73S.

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Links

https://www.ncbi.nlm.nih.gov/pubmed/20032296
http://www.goreni.org/

Olfactory neuroblastoma, see the preferred term **Nasal cavity neuroepithelial carcinoma**.

Olfactory neuroepithelioma, see the preferred term **Nasal cavity neuroepithelial carcinoma**.

Pneumocyte type II cell hyperplasia is characterized by the presence of a continuous single layer of cuboidal epithelial cells lining the existing alveolar walls, thus maintaining the original alveolar architecture. It has two distinct etiologies: (1) as part of a repair process, which leads to re-epithelialization of the alveolar walls following injury, and (2) as a response to direct stimulation, such as occurs following administration of keratinocyte growth factor. Initially the proliferating cells appear basophilic, but as they mature the cytoplasm may become vacuolated due to the onset of surfactant synthesis and its storage in lamellar bodies. The hyperplasia may be associated with aggregations of foamy macrophages, suggesting increased release of surfactant and its phagocytosis. In the case of alveolar repair, the nascent type II cells can transdifferentiate into type I cells to bring about repair of the alveolar wall; however, in cases of severe injury they may transdifferentiate into myofibroblasts and initiate fibrosis.

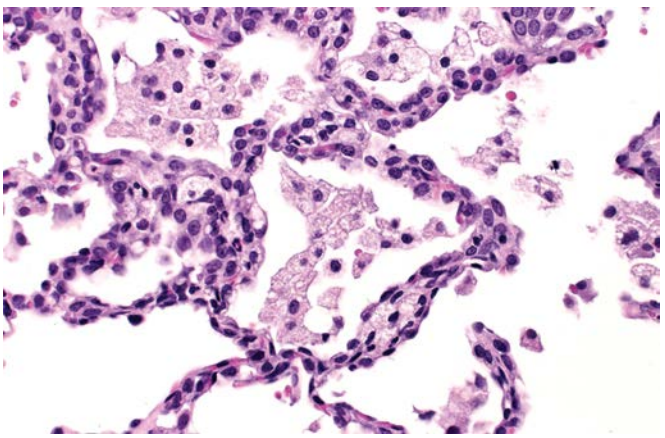


FIGURE 12 Pneumocyte type II cell hyperplasia, lung, rat, H&E.

Reference

Lewis, D. and McKevitt, T. 2013. Respiratory system. In: Sahota, P., Popp, J., Hardisty, J., Gopinath, C. (eds.) *Toxicologic Pathology: Nonclinical Safety Assessment*. Boca Raton, FL: CRC Press, pp. 367–419.

Link

https://www.crcpress.com/Toxicologic-Pathology-Nonclinical-Safety-Assessment/Sahota-Popp-Hardisty-Gopinath/p/book/9781138199545

Pulmonary acinar carcinoma in mice is believed to originate from club cells (i.e., bronchiolar exocrine cells) from the bronchiolar walls, or from within the alveoli following metaplasia from type II pneumocytes. The tumor has a predominantly acinar pattern, and there is a characteristic maintenance of the preexisting alveolar wall structure. The cells are cuboidal, columnar, or pleomorphic, and may contain eosinophilic cytoplasmic globules. A large portion or the entire tumor may show differentiation to a cell type (e.g., mucinous adenocarcinoma). There are clear features of malignancy, including penetration of the basement membrane and tissue destruction.

Differential diagnosis: **Bronchioloalveolar carcinoma**.

Reference

Mohr, U. (ed.) 2001. *International Classification of Rodent Tumors-The Mouse. Respiratory system and Mesothelium*, 1st ed. Berlin: Springer-Verlag, pp. 126–127.

Pulmonary adenocarcinoma, see the preferred term **Bronchioloalveolar carcinoma**.

Pulmonary adenosquamous carcinoma is characterized by the presence of bronchioloalveolar carcinomatous and malignant squamous phenotypes within the same mass, and is believed to arise from a clonal shift to a malignant squamous phenotype from an initial carcinoma. Some examples of this tumor type contain abundant mucus-secreting cells, giving rise to the historic synonym "mucoepidermoid carcinoma." The key feature is the presence of malignancy in both cell populations. There may be keratinization of the squamous cell component of the tumor. These tumors tend to be highly invasive.

Differential diagnoses: **Bronchioloalveolar carcinoma**; **Pulmonary squamous cell carcinoma**.

Synonym(s): **Mucoepidermoid carcinoma**.

Reference

Renne, R. et al. 2009. Proliferative and nonproliferative lesions of the rat and mouse respiratory tract. *Toxicol Pathol* 37(7 Suppl):5S–73S.

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https://www.ncbi.nlm.nih.gov/pubmed/20032296
http://www.goreni.org/

Pulmonary choristoma is a rare, congenital, tumor-like proliferation characterized by the presence of normal mature cells or tissues growing at a location different from their proper location (i.e., ectopically). They are thus distinct from hamartomas, which are malformations of cells or tissues normally found at a site. A choristoma in the lung is composed of randomly orientated, small bundles of eosinophilic, phosphotungstic acid-hematoxylin (PTAH)-positive skeletal muscle fibers. The lesions are located within the pulmonary parenchyma, are poorly circumscribed, and do not cause compression. Their pathogenesis is uncertain, but they may represent intrapulmonary sequestration of an embryonal foregut malformation following premature caudal migration during early embryonic life, proliferation of ectopic pluripotential cells, or proliferation and myoblastic differentiation of pulmonary mesenchymal cells. Choristoma should not be confused with the normal presence of cardiac muscle around the major

branches of pulmonary veins in rodents and the normally thick walls of the oblique zone of the pulmonary arteries, particularly in rats.

Differential diagnoses: **Rhabdomyoma**; **Rhabdomyosarcoma**.

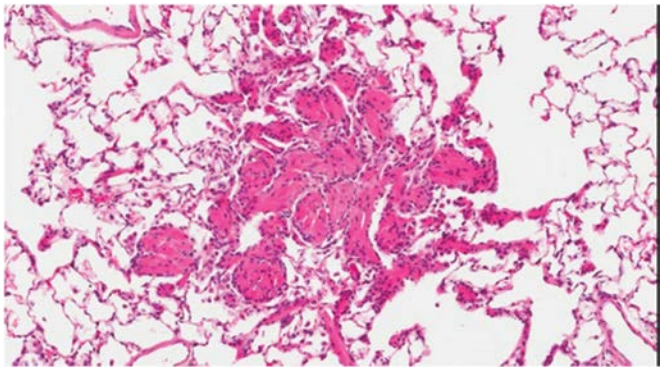


FIGURE 13 Pulmonary choristoma, lung, rat, H&E.

Reference

Wijnands, M. and van Esch, E. 2012. Skeletal muscle choristoma in the lung of a female Sprague-Dawley rat: A case report. *Exp Toxicol Pathol* 64:239–241.

Link

https://www.ncbi.nlm.nih.gov/pubmed/20926269

Pulmonary club cell regeneration and hyperplasia is characterized by nascent cells that are basophilic, lack the characteristic apical bleb of mature club cells, and have the ability to renew or to differentiate into ciliated or goblet cells. The club cell is the progenitor cell in the terminal and respiratory bronchioles and as such, is largely responsible for epithelial repair following damage. In the case of continuous insult, they become hyperplastic, increasing the epithelial height, and may subsequently undergo squamous metaplasia.

Reference

Lewis, D. and McKevitt, T. 2013. Respiratory system. In: Sahota, P., Popp, J., Hardisty, J., Gopinath, C. (eds.) *Toxicologic Pathology: Nonclinical Safety Assessment*. Boca Raton, FL: CRC Press, pp. 367–419.

Link

https://www.crcpress.com/Toxicologic-Pathology-Nonclinical-Safety-Assessment/Sahota-Popp-Hardisty-Gopinath/p/book/9781138199545

Pulmonary cystic keratinizing epithelioma is more complex than the simple pulmonary keratinizing cyst, often being multilocular, presumably due to sequential extension into the adjacent alveoli, but does not show true invasive growth. The squamous epithelium is variable in height, organization, and differentiation, and there is usually abundant keratinization. A nonkeratinizing variant (nonkeratinizing epithelioma) may also be seen in the rat.

Differential diagnoses: **Pulmonary squamous metaplasia**; **Pulmonary keratinizing cyst**; **Pulmonary squamous cell carcinoma**.

Synonym(s): **Pulmonary squamous cyst**; **pulmonary squamous epithelioma**.

Reference

Renne, R. et al. 2009. Proliferative and nonproliferative lesions of the rat and mouse respiratory tract. *Toxicol Pathol* 37(7 Suppl):5S–73S.

Links

https://www.ncbi.nlm.nih.gov/pubmed/20032296
http://www.goreni.org/

Pulmonary keratinizing cyst is a rat-specific lesion comprised of a simple, well-differentiated, keratin-filled, unilocular cyst. The lesions are often relatively large, making their origin from alveolar or terminal bronchiolar epithelia difficult to determine. They are lined by a well-differentiated squamous epithelium. Mitoses are rare, and there is no evidence of invasive growth.

Differential diagnoses: **Pulmonary squamous metaplasia**; **Pulmonary cystic keratinizing epithelioma**; **Pulmonary squamous cell carcinoma**.

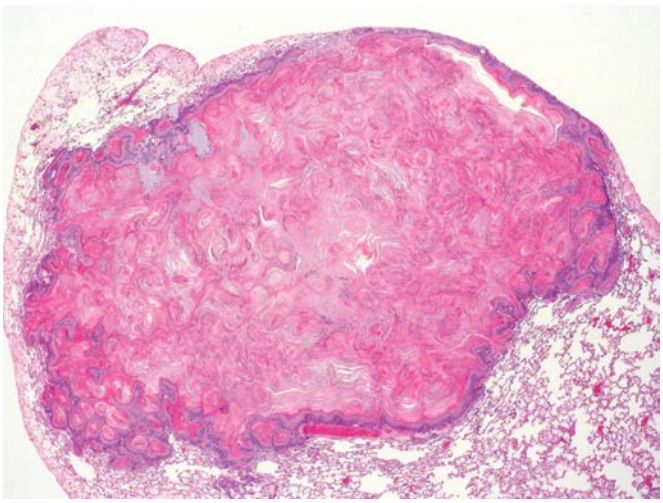


FIGURE 14 Pulmonary keratinizing cyst, lung, rat, H&E.

Reference

Renne, R. et al. 2009. Proliferative and nonproliferative lesions of the rat and mouse respiratory tract. *Toxicol Pathol* 37(7 Suppl):5S–73S.

Links

https://www.ncbi.nlm.nih.gov/pubmed/20032296
http://www.goreni.org/

Pulmonary mesothelial hyperplasia is characterized by an increase in the thickness of the usual single layer of superficial pleural mesothelial cells, and may include short, papillary outgrowths. It is usually associated with an inflammatory reaction, and sometimes fibrosis. The usually elongate, flattened

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mesothelial cells assume a cuboidal, columnar, or bulbous shape in the hyperplastic state. The lesion may be secondary to underlying pulmonary inflammation or neoplasia, and in some cases may be aggravated by mechanical abrasion against the parietal pleura due to protrusion into the pleural space, and inflexibility of an underlying pulmonary lesion.

Reference

Renne, R. et al. 2009. Proliferative and nonproliferative lesions of the rat and mouse respiratory tract. *Toxicol Pathol* 37(7 Suppl):5S–73S.

Links

https://www.ncbi.nlm.nih.gov/pubmed/20032296
http://www.goreni.org/

Pulmonary osseous metaplasia is characterized by the appearance of foci of eosinophilic, poorly mineralized, osseous material in the alveoli. The material usually only occupies a few adjacent alveoli and does not provoke an inflammatory reaction. The etiology is mostly uncertain, but in some cases the foci clearly develop from microliths.

Reference

Renne, R. et al. 2009. Proliferative and nonproliferative lesions of the rat and mouse respiratory tract. *Toxicol Pathol* 37(7 Suppl):5S–73S.

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https://www.ncbi.nlm.nih.gov/pubmed/20032296
http://www.goreni.org/

Pulmonary squamous cell carcinoma is a rare malignant tumor that can occur in all laboratory species and is believed to arise from either the alveolar or terminal bronchiolar epithelia. It is characterized by an irregular growth pattern, variable keratinization, and the usual hallmarks of malignancy that include cellular atypia, pleomorphism, increased mitoses, and areas of necrosis. Local invasion may be difficult to detect due to the "open" nature of the pulmonary parenchyma, but invasion of the pleura, airway, and vascular walls may be seen. A particular feature of this tumor is the presence of "giant cells," and cellular debris within areas of necrosis. A neutrophilic inflammatory response is also common.

Differential diagnoses: **Pulmonary squamous metaplasia**; **Pulmonary adenosquamous carcinoma**; **Bronchioloalveolar carcinoma**; **Pulmonary cystic keratinizing epithelioma**; **Pulmonary keratinizing cyst**.

Synonym(s): **Epidermoid carcinoma**.

Reference

Renne, R. et al. 2009. Proliferative and nonproliferative lesions of the rat and mouse respiratory tract. *Toxicol Pathol* 37(7 Suppl):5S–73S.

Links

https://www.ncbi.nlm.nih.gov/pubmed/20032296
http://www.goreni.org/

Pulmonary squamous cyst, see the preferred term **Pulmonary cystic keratinizing epithelioma**.

Pulmonary squamous epithelioma, see the preferred term **Pulmonary cystic keratinizing epithelioma**.

Pulmonary squamous metaplasia is a replacement of alveolar epithelium by squamous cells with or without keratinization and is considered to arise from club cells or type II pneumocytes. This change can be a result of chronic inflammation and can be induced in rats fed a vitamin A–deficient diet.

Differential diagnoses: **Pulmonary squamous cell carcinoma**; **Pulmonary adenosquamous carcinoma**; **Bronchioloalveolar carcinoma**; **Pulmonary cystic keratinizing epithelioma**; **Pulmonary keratinizing cyst**.

Reference

Renne, R. et al. 2009. Proliferative and nonproliferative lesions of the rat and mouse respiratory tract. *Toxicol Pathol* 37(7 Suppl):5S–73S.

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http://www.goreni.org/

Type II cell adenoma, see the preferred term **Bronchioloalveolar adenoma**.

SKIN

Acanthoma, infundibular, keratinizing, see the preferred term **Keratoacanthoma**.

Acanthosis, see the preferred term **Epidermal hyperplasia**.

Adenoid cystic carcinoma, primary, see the preferred term **Eccrine gland carcinoma**.

Adnexal hyperkeratosis is the result of increased keratinocyte turnover within the hair follicle infundibulum or sebaceous gland duct. The follicular infundibulum is dilated and filled with excessive keratin that resembles epidermal differentiation. The hair follicle canal may be cystic. Ducts of adnexal glands may also become keratin plugged. Keratin plugging can result in retained hairs or secretions. A specific example of systemic toxicity resulting in follicular hyperkeratosis is chloracne, induced following systemic exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), commonly referred to as dioxin, and other related environmental contaminants. Chloracne is characterized by acneiform lesions or comedones that tend to form on the face/head and trunk but generally not on the extremities. Histopathologically, comedones consist of cystically dilated and hyperkeratotic hair follicles without substantive inflammation.

References

Diegel, K.L., Danilenko, D.M., and Wojcinski, Z.W. 2013. In: Haschek-Hock, W.M., Rousseaux, C.G., and Wallig, M.A. (eds.) *Integument in Handbook of Toxicologic Pathology*, 3rd ed. Elsevier Press.

Mecklenburg, L. et al. 2013. Proliferative and non-proliferative lesions of the rat and mouse integument. INHAND initiative invited review. *J Toxicol Pathol* 26(Suppl 1):27S–57S.

Link

https://www.ncbi.nlm.nih.gov/pubmed/25035577

Adnexal hyperplasia of the cutaneous adnexa mostly affects sebaceous glands. Sebaceous glands are enlarged and show an increased number of sebaceous cells (refer to **Skin** in Appendix 3 for further information) in individual acini with few immature cells, and many mature glandular cells arranged around prominent central ducts. Sebaceous cell hyperplasia can be found in cases of chronic inflammatory irritation of the skin. It can also occur in tandem with squamous cell hyperplasia. An increase in the overall size of hair follicles with otherwise normal architecture associated with an increased number of hair follicle keratinocytes has been described in some genetically engineered mice and can be associated with an increase in the diameter of the follicular dermal papilla.

Differential diagnosis: **Sebaceous cell adenoma**.

Synonym(s): **Sebaceous hyperplasia**.

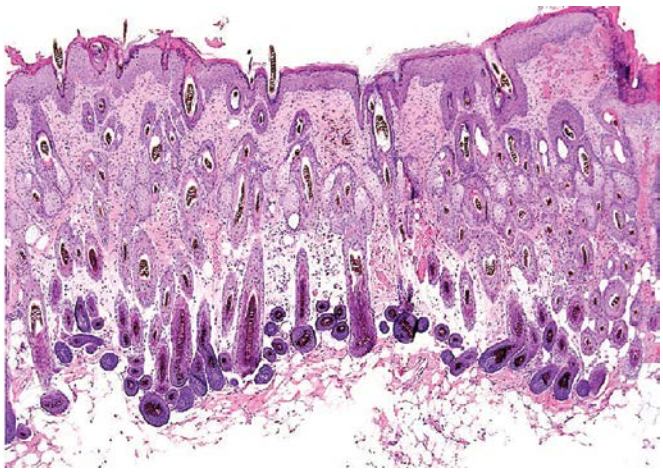


FIGURE 1 Adnexal hyperplasia in a mouse, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

References

Diegel, K.L., Danilenko, D.M., and Wojcinski, Z.W. 2013. In: Haschek-Hock, W.M., Rousseaux, C.G., and Wallig, M.A. (eds.) *Integument in Handbook of Toxicologic Pathology*, 3rd ed. Elsevier Press.

Mecklenburg, L. et al. 2013. Proliferative and non-proliferative lesions of the rat and mouse integument. INHAND initiative invited review. *J Toxicol Pathol* 26(Suppl 1):27S–57S.

Basal cell carcinoma is a malignant neoplasm derived from stem cells within hair follicles and/or the interfollicular epidermis. These tumors are poorly circumscribed with some association with the epidermis and/or the adnexa, and extensive local invasion into the dermis and/or subcutis. They are composed of lobules and cords of closely packed cells that are supported by variable amounts of fibrovascular stroma. Tumor cells generally resemble normal epidermal basal cells without intercellular bridges, and palisade at the periphery of lobules. Central necrosis in tumor lobules may be present; these necrotic areas are referred to as pseudocysts. In pigmented animals, melanin pigmentation is commonly found. Desmoplasia (i.e., growth of dense fibrous tissue) in the surrounding stroma is common, and extensive local invasion may be present. The primary differential diagnosis for basal cell carcinoma is sebaceous gland carcinoma, which is distinguished from basal cell carcinoma by its distinct glandular/lobular pattern with obvious sebaceous glandular differentiation. Squamous cell carcinoma is another differential diagnosis and is distinguished from basal cell carcinoma by demonstrating distinct squamous differentiation with the presence of intercellular bridges. The development of both benign and malignant basal cell tumors has been convincingly linked to upregulated hedgehog (Hh) signaling through several lines of evidence including genetic mutation analyses, mouse models, and clinical success in the treatment of basal cell carcinomas using Hh-signaling inhibitors. In addition, many if not all basal cell tumors are believed to derive from hair follicle stem cells, as both basal cell tumors and follicular stem cells

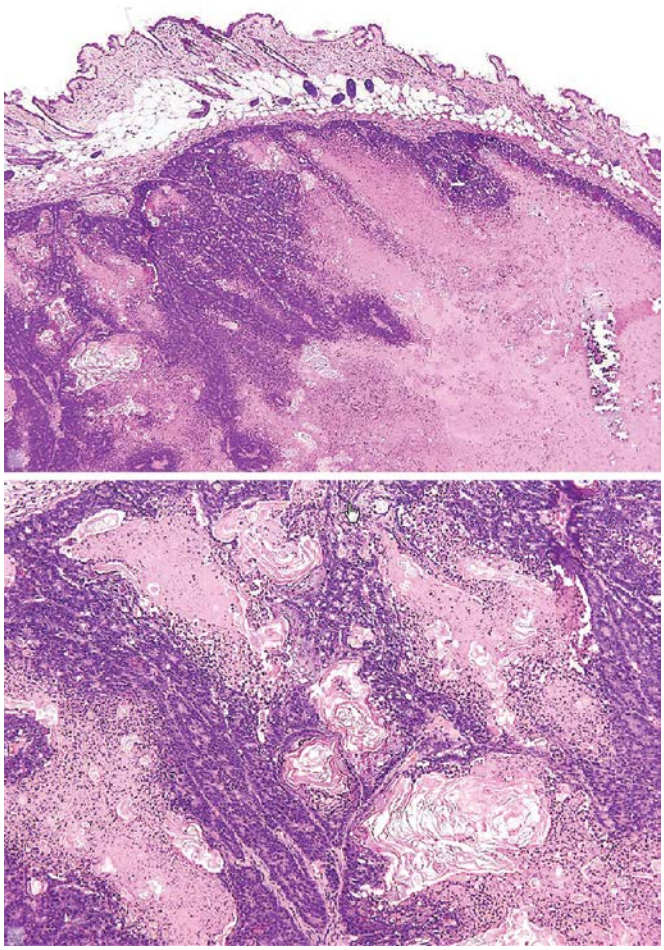


FIGURE 2 Basal cell carcinoma in a mouse at low (top) and high (bottom) power magnifications, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

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express keratin 15, and Hh signaling has been shown to be critical for normal hair follicle developmental morphogenesis. In humans, the vast majority of basal cell tumors have identifiable mutations in at least one allele of patched 1 (*PTCH1*), a tumor suppressor gene that encodes an Hh signaling receptor. In addition, some basal cell tumors have activating mutations in smoothened (SMO), a positive regular of Hh signaling. Hh signaling occurs when Hh ligands bind to *PTCH1*, specifically through SMO, and relieve inhibition of the Hh pathway. This leads to activation of the Gli family of transcription factors and eventually to cellular proliferation. A basal cell tumor from a *PTCH1* heterozygous null C57BL/6 mouse.

Differential diagnoses: **Sebaceous cell carcinoma**; **Squamous cell carcinoma**.

Synonym(s): **Basal cell tumor, malignant**; **basosquamous cell carcinoma**.

References

Diegel, K.L., Danilenko, D.M., and Wojcinski, Z.W. 2013. In: Haschek-Hock, W.M., Rousseaux, C.G., and Wallig, M.A. (eds.) *Integument in Handbook of Toxicologic Pathology*, 3rd ed. Elsevier Press.

Mecklenburg, L. et al. 2013. Proliferative and non-proliferative lesions of the rat and mouse integument. INHAND initiative invited review. *J Toxicol Pathol* 26(Suppl 1):27S–57S.

Basal cell hyperplasia is an increase in the number of epidermal basal keratinocytes and occurs in conjunction with epidermal hyperplasia. Hyperplasia of the epidermal basal cell zone can be identified as an increase in thickness of the more basophilic-staining basal keratinocyte layer on hematoxylin and eosin (H&E) or by an increase in thickness of the cytokeratin 5- or 14-staining layer by immunohistochemical (IHC) staining. Basal cell hyperplasia alone is not considered to be a separate diagnostic entity and is also not considered to be a precursor of basal cell neoplasms (benign or malignant), as basal cell tumors are derived from follicular stem cells.

References

Diegel, K.L., Danilenko, D.M., and Wojcinski, Z.W. 2013. In: Haschek-Hock, W.M., Rousseaux, C.G., and Wallig, M.A. (eds.) *Integument in Handbook of Toxicologic Pathology*, 3rd ed. Elsevier Press.

Mecklenburg, L. et al. 2013. Proliferative and non-proliferative lesions of the rat and mouse integument. INHAND initiative invited review. *J Toxicol Pathol* 26(Suppl 1):27S–57S.

Basal cell tumor is a benign neoplasm derived from stem cells within hair follicles and/or the interfollicular epidermis and is classified into three distinct types: basosquamous type, trichoblastoma type, and granular type. All basal cell tumors are fairly well circumscribed and multilobulated with some association with the epidermis. The neoplasm is composed of uniform lobules, islands, or cords of closely packed cells that are supported by a variable degree of fibrovascular stroma. Neoplastic basal cells may also be arranged in cords or fine ribbons that may become cystic. There is no invasion of the basement membrane, and no compression or desmoplasia (i.e., growth of dense fibrous tissue) of the surrounding dermal mesenchyme. Tumor cells generally resemble normal epidermal basal cells without intercellular bridges, and palisade at the periphery of lobules. Foci of squamous cell differentiation may occur, and sebaceous cells may also be present. In the basosquamous type of basal cell tumor, foci of keratinization are present. In the trichoblastoma type, small foci of sebaceous cells and/or trichogenesis are present. In the granular type, there are basal cells containing periodic acid-Schiff (PAS)-positive granules. Primary differential diagnoses are hair follicle tumors, which show trichogenic differentiation, sebaceous cell adenomas, which demonstrate distinct sebaceous differentiation, and basal cell carcinomas, that demonstrate greater cellular and nuclear heterogeneity, greater numbers of mitotic figures, and an increased tendency to invade.

Differential diagnoses: **Hair follicle tumor**; **Sebaceous cell adenoma**; **Basal cell carcinoma**.



FIGURE 3 An early benign cutaneous basal cell tumor arising from the epidermal surface of a patched 1 (*PTCH1*) heterozygous null C57BL/6 mouse, H&E. (Figure used by permission from Diegel, K.L. et al. 2013. In: Haschek-Hock, W.M. et al. (eds.) *Integument in Handbook of Toxicologic Pathology*, 3rd ed. Elsevier Press.)

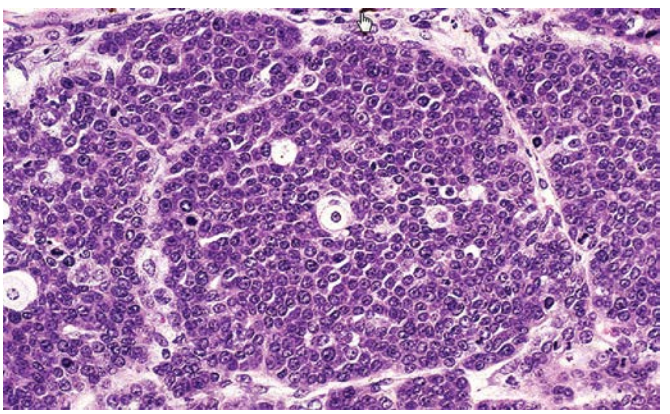


FIGURE 4 Another example of a benign basal cell tumor in a mouse, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

References

Diegel, K.L., Danilenko, D.M., and Wojcinski, Z.W. 2013. In: Haschek-Hock, W.M., Rousseaux, C.G., and Wallig, M.A. (eds.) *Integument in Handbook of Toxicologic Pathology*, 3rd ed. Elsevier Press.

Mecklenburg, L. et al. 2013. Proliferative and non-proliferative lesions of the rat and mouse integument. INHAND initiative invited review. *J Toxicol Pathol* 26(Suppl 1):27S–57S.

Basal cell tumor, malignant, see the preferred term **Basal cell carcinoma**.

Basosquamous cell carcinoma, see the preferred term **Basal cell carcinoma**.

Canine cutaneous histiocytoma (CCH) is a very common benign cutaneous proliferative tumor in dogs, particularly young dogs less than 3 years of age. CCH most commonly presents grossly as a solitary, raised, nodular mass, most frequently on the head, and especially on the ears. Older masses are often ulcerated, and with time, spontaneously regress in the vast majority of cases. Histologically, they are well circumscribed but not encapsulated, and consist of diffuse sheets of large mononuclear cells that abut an often hyperplastic and ulcerated epidermal surface and replace the cutaneous adnexa. The large mononuclear cells contain abundant pale eosinophilic cytoplasm, i.e., sometimes granular and/or finely vacuolated. Nuclei are pleomorphic and often folded. Mitotic figures are usually quite common except in regressing tumors. Cells frequently abut the overlying, often hyperplastic, epidermis and completely replace adnexal structures. Lymphocytic infiltrates are frequently seen within the CCH cells, and these infiltrates increase along with areas of necrosis as the tumor regresses. CCH is considered to be a benign proliferation of Langerhans cell, as cells in all CCHs express CD1a, CD11c, and E-cadherin, all markers of Langerhans cells in the dog.

Differential diagnoses: **Lymphoma (cutaneous, or epitheliotrophic, canine)**; **Mycosis fungoides**.

Reference

Moore, P.F. 2014. A review of histiocytic diseases of the dogs and cats. *Vet Pathol* 51:167–184.

Link

https://www.ncbi.nlm.nih.gov/pubmed/24395976

Carcinoma, primary adenoid cystic, see the preferred term **Eccrine gland carcinoma**.

Cutaneous lymphoma (canine), see the preferred term **Lymphoma, epitheliotrophic (canine)**

Eccrine gland carcinoma is a malignant neoplasm arising from areas where eccrine glands are present (see **Adnexa** for further information), and usually in the paw area. These tumors are not common but have been reported in transgenic mice. These epithelial neoplasms may or may not have the cytologic features of malignancy (e.g., cellular atypia, mitotic figures) and may be cystic. Benign tumors of the cutaneous apocrine/sweat glands are relatively common in dogs (adenomas), with the malignant variant less common (adenocarcinoma). In humans, a cell-specific marker (p16INK4a) may be helpful in diagnosing sweat gland origin of cutaneous tumors.

Differential diagnoses: **Sebaceous cell carcinoma**; **Squamous cell carcinoma**; **Basal cell carcinoma**.

Synonym(s): **Sweat gland tumor**; **primary adenoid cystic carcinoma (rat)**; **hidradenoma (human)**.

References

Diegel, K.L., Danilenko, D.M., and Wojcinski, Z.W. 2013. In: Haschek-Hock, W.M., Rousseaux, C.G., and Wallig, M.A. (eds.) *Integument in Handbook of Toxicologic Pathology*, 3rd ed. Elsevier Press.

Mecklenburg, L. et al. 2013. Proliferative and non-proliferative lesions of the rat and mouse integument. INHAND initiative invited review. *J Toxicol Pathol* 26(Suppl 1):27S–57S.

Moore, P.F. 2014. A review of histiocytic diseases of the dogs and cats. *Vet Pathol* 51:167–184.

Epidermal cyst, see the preferred term **Squamous cyst**.

Epidermal hyperplasia is an increase in the thickness of the epidermis resulting from increased numbers of layers of non-keratinized cells, usually the stratum spinosum and the stratum granulosum. An increase in thickness of the keratinized layer is called hyperkeratosis and is commonly seen concurrently with epidermal hyperplasia. Importantly, as a stand-alone term, the normal differentiation from stratum basale to stratum granulosum and cornification is maintained; keratinocytes with atypia should not be present, and the basement membrane continuity is not breached in hyperplastic epidermis. Diagnostically, if there is cellular atypia this should be noted as a modifier. Hyperplastic epidermis frequently forms finger-like projections called rete ridges (or rete pegs) down into the dermis. Epidermal hyperplasia is usually an adaptive response to injury and is part of the wound healing response. The stratum basale (location of epidermal stem cells; also called stratum germinativum) is induced to proliferate, and then cells of the stratum basale rapidly differentiate into cells of the superior strata, resulting in increased thickness of these layers. Epidermal hyperplasia limited to the stratum basale is infrequent and occurs in association with some skin tumors (e.g., papillomas, keratoacanthomas). It has also been observed in mice carrying a spontaneous mutation of the *Patched-1* gene, the receptor for sonic hedgehog (Hh), where the stratum basale shows severe hyperplasia while the suprabasilar layers are normal. Basal cell tumors are thought to originate from follicles and not from cells of the basal layer of the epidermis, although recent studies have shown that the long-term resident epidermal interfollicular stem cells in the stratum basale have an important role in basal cell tumor carcinogenesis. In toxicologic pathology, epidermal hyperplasia is usually observed in response to epidermal cell irritation/death from various insults including, but not limited to, ultraviolet light exposure, chemical exposure (e.g., diisopropylcarbodiimide, retinoids, sodium lauryl sulfate) and physical abrasion (wounding), or after disruption of the cornified layer

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or protective innate or adaptive immune mechanisms. Direct induction of proliferation has been reported after exposure to tetradecanoyl phorbol acetate or sodium xylene sulfonate or with treatment with growth factors or hormones (e.g., epidermal growth factor, growth hormone).

Differential diagnoses: **Papilloma**; **Squamous cell carcinoma**.

Synonym(s): **Acanthosis**; **squamous hyperplasia**.

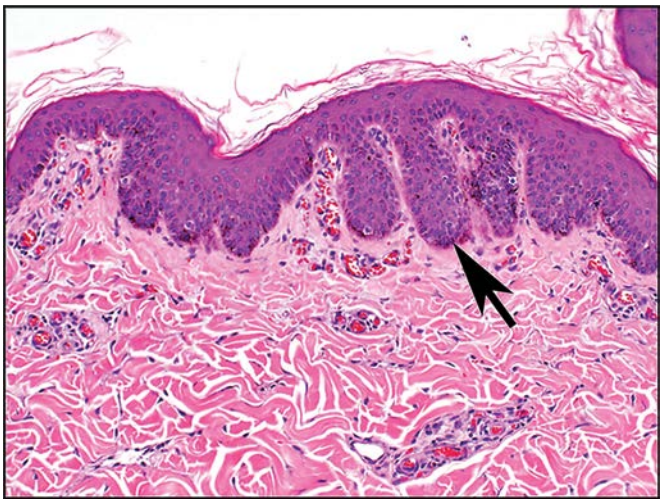


FIGURE 5 Epidermal hyperplasia in skin from a minipig, H&E. Note elongated rete pegs (arrow).

References

Diegel, K.L., Danilenko, D.M., and Wojcinski, Z.W. 2013. In: Haschek-Hock, W.M., Rousseaux, C.G., and Wallig, M.A. (eds.) *Integument in Handbook of Toxicologic Pathology*, 3rd ed. Elsevier Press.

Mecklenburg, L. et al. 2013. Proliferative and non-proliferative lesions of the rat and mouse integument. INHAND initiative invited review. *J Toxicol Pathol* 26(Suppl 1):27S–57S.

Fibrosarcoma, pleiomorphic, see the preferred term **Histiocytoma, malignant fibrous**.

Fibrosarcoma, undifferentiated, see the preferred term **Histiocytoma, malignant fibrous**.

Hair follicle hyperplasia, see the preferred term **Adnexal hyperplasia**.

Hair follicle tumor, benign is a well-demarcated, multilobular, benign neoplasm derived from hair follicle epithelium. Each lobule exhibits some degree of hair follicle differentiation with one or multiple cysts. Mitoses are rare, and there is no invasion into the surrounding tissues. The type and degree of hair follicle differentiation determines the type of hair follicle tumor. Trichofolliculoma type has a large central cyst lined by squamous epithelium with numerous radiating, fairly well-differentiated hair follicles with some degree of hair shaft formation and may include sebocytes. The central cyst contains keratin and hair shafts. Trichoepithelioma type has numerous basilar type cells that may either abruptly become keratinized or irregularly differentiate into inner or outer root sheaths, or hair matrix cells. The center of the lobules contains a keratinized cyst. The basal membrane at the periphery of the lobules is often invaginated, resembling a dermal papilla. Trichilemmoma type has small islands of epithelial cells surrounded by a prominent basal membrane and arranged in a circular pattern. The peripheral cells in these islands are basaloid, while the central cells have highly eosinophilic keratin. Suprabasilar cells are often vacuolated due to glycogen accumulation.

Differential diagnoses: **Squamous cyst**; **Adnexal hyperkeratosis**; **Squamous cell carcinoma**; **Basal cell tumor**; **Basal cell carcinoma**; **Keratoacanthoma**; **Papilloma (endophytic)**.

Synonym(s): **Pilomatricoma**; **trichoepithelioma**; **trichofolliculoma**; **trichilemmoma**.

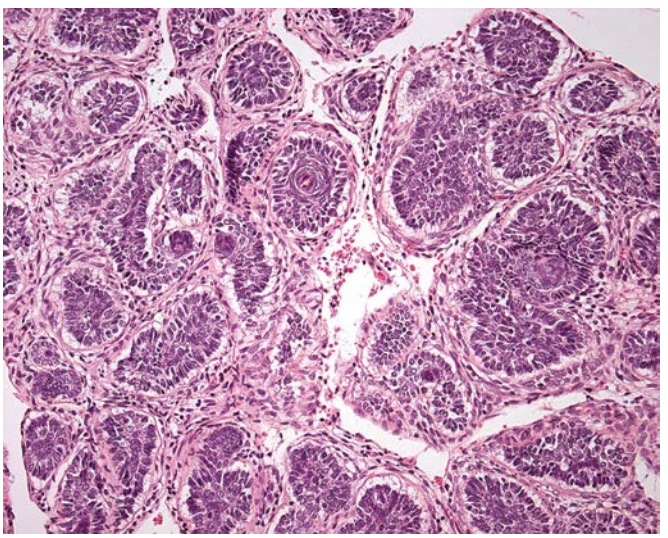


FIGURE 6 Benign hair follicle tumor (trichilemmoma) in the skin of a rat, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

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Hair follicle tumor, malignant has not been described in rodents. In dogs, malignant pilomatricomas have been described in a few isolated diagnostic cases, but not in toxicologic studies. Malignant hair follicle tumors in dogs are locally aggressive and often invade and/or metastasis to bone. Histologically, these tumors are poorly differentiated but have some features such that hair follicle differentiation can be recognized, and manifest nuclear and cytologic atypia, with numerous mitotic figures and invasion beyond the basement membrane.

Differential diagnoses: **Squamous cell carcinoma**; **Basal cell carcinoma**; **Hair follicle tumor, benign**.

Synonym(s): **Pilomatrix carcinoma**.

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Hidradenoma, see the preferred term **Eccrine gland carcinoma**.

Histiocytoma, malignant fibrous is a malignant neoplasm comprised of cells of unknown origin. The two most widely accepted hypotheses are that this tumor either arises from undifferentiated early (stem) mesenchymal cells or represents a collection of undifferentiated sarcomas that have morphological similarities. Two neoplastic cell types in variable numbers are usually observed, a fusiform (fibro- or myofibroblast-like) cell population and polygonal, histiocyte-like cells. The tumor cells are organized in storiform or cartwheel patterns. Neoplastic multinucleated giant cells, a myxoid background, florid angiogenesis and/or variable numbers of inflammatory cells can also be observed in these tumors. The subcutis is a frequent site of occurrence of this tumor in rodents and the dog. In rodents, this tumor can be induced at this site by various implanted materials such as polymers (e.g., 3 polyvinyl chlorides, 1 polyhydroxyethyl methacrylate, 1 dimethyl polysiloxane), zirconia, nickel alloys, dinitropyrene, and has been associated with the subcutaneous injection site of a pegylated protein. In cats, this tumor has been observed at sites of vaccine injection. The *Ras, p53*, and *FoxM1* pathways are all considered important in the neoplastic pathogenesis and metastatic potential of malignant fibrous histiocytoma.

Differential diagnosis: **Sarcoma, NOS**.

Synonym(s): **Fibrosarcoma, pleiomorphic**; **sarcoma, undifferentiated pleiomorphic**.

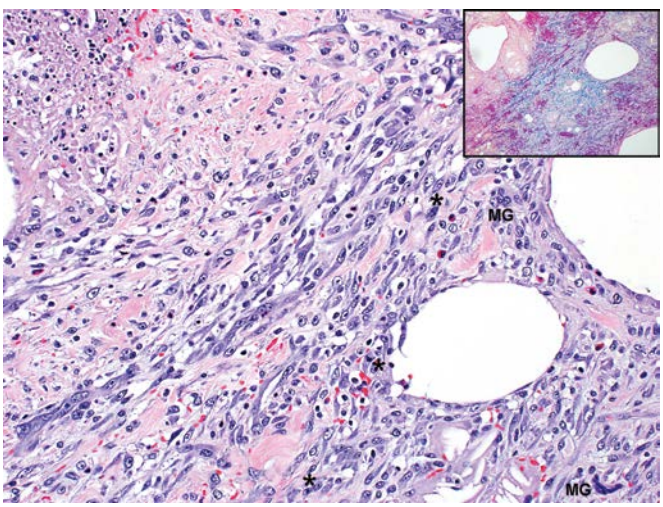


FIGURE 7 Elongated (fusiform) pleomorphic cells, often multinucleated, with histiocytoid, and multinucleated giant cells (MG). Several mitotic figures (*) are visible. From site of iron dextran injection behind ear of a Gottingen minipig, H&E. Insert: Iron positivity (blue) in areas of mass (iron stain).

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Horn cyst, see the preferred term **Squamous cyst**.

Keratin cyst, see the preferred term **Squamous cyst**.

Keratoacanthoma is a benign neoplasm of hair follicles. Its characteristic presentation is a cystic, shaftless, dilated follicular structure invaginating into the dermis/hypodermis with a thickened epithelial wall, and an opening pore to the epidermis. Less frequently, the dilated follicular structure can be completely embedded within the dermis/subcutis. The central dilated part of the follicle is filled with lamellar keratin. The thickened follicular epithelial wall is comprised of increased layers of stratified squamous epithelial

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cells continuous with cords and nests of stratified squamous epithelium frequently centered on keratin lamellae. The squamous epithelial cells frequently contain keratohyalin granules. Keratoacanthomas can be associated with administration of immunosuppressive compounds (e.g., dimethylbenzanthracene, leflunomide), with *N*-methyl-*N*-nitrosourea, TGF-beta neutralization, with tar exposure, with skin trauma and sunburns, or with the presence of viruses (e.g., papillomavirus). It seems a relatively frequent tumor in old male Sprague Dawley rats.

Differential diagnoses: **Epidermal hyperplasia, cystic and noncystic**; **Squamous cell papilloma**; **Trichofolliculoma**; **trichoepithelioma**.

Synonym(s): **Acanthoma, infundibular keratinizing**.

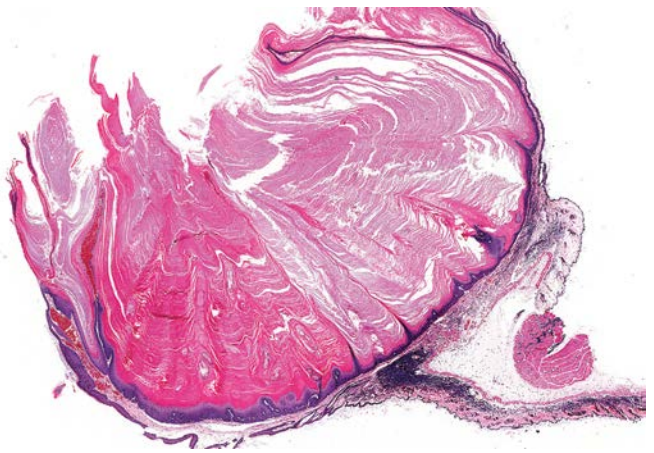


FIGURE 8 Keratoacanthoma in a mouse, H&E. Note the opening pore into the epidermis, keratin plugging (K) and cupping into the dermis and subcutis.

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Lymphoma, cutaneous, see the preferred term **Lymphoma, epitheliotrophic (canine)**.

Lymphoma, epitheliotrophic (canine) is a spontaneous neoplasm of skin and mucous membranes that occurs in old dogs (mean age 11 years). The neoplastic lymphocytic infiltrate demonstrates very prominent epitheliotropism, particularly for adnexal structures, especially hair follicles and apocrine sweat glands. Neoplastic lymphocytes are all of T-cell origin, exhibiting CD3 expression, and the vast majority express CD8.

Differential diagnosis: **Canine cutaneous histiocytoma**.

Reference

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Mast cell hyperplasia is the proliferation of mature mast cells in locations where they normally reside and occurs frequently with allergic diseases or following parasitic infections. Injection of stem cell factor (SCF) or IL-9 in mice can lead to mast cell hyperplasia. Mast cell hyperplasia has also been associated with fibrotic chronic inflammatory reactions due to radiation injury in the lung or with bile trapping in the liver.

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Mast cell tumor is a neoplasm composed of mast cells and a relatively frequent skin tumor in dogs. The behavior often

depends on the grade of tumor, which is dependent on histologic or cytologic examination of the neoplastic tissue. This neoplasm is observed far less frequently in other laboratory animal species such as rodents and the nonhuman primate. In the dog, most of these tumors are well differentiated (low grade) with cell features resembling mature, nonneoplastic mast cells including a round shape, central to paracentral nucleus, and light blue cytoplastic granules following staining with metachromatic stains. More aggressive (high grade) tumors are characterized by cellular pleiomorphism including the presence of giant cells and less well-defined or unidentifiable cytoplastic granules. Mature nonneoplastic eosinophils are frequently observed within mast cell tumors. Paraneoplastic syndromes associated with mast cell tumors include local edema and erythema, systemic anaphylactic reactions, and gastrointestinal ulcerations. Occurrence in organs other than the skin (liver, spleen, GI tract) usually carries a more serious prognosis. The cytoplasmic granules of neoplastic mast cells stain purple or blue with metachromatic stains such as Giemsa or toluidine blue, respectively. Neoplastic mast cell in undifferentiated tumors can be recognized by immunohistochemical staining with c-KIT or mast cell tryptase. In mice, this tumor has been induced by *N*-methyl-*N*'-nitro-*N*-nitrosoguanidine (MNNG) initiation followed by 12-*O*-tetradecanoylphorbol-13-acetate (TPA) promotion or by irradiation.

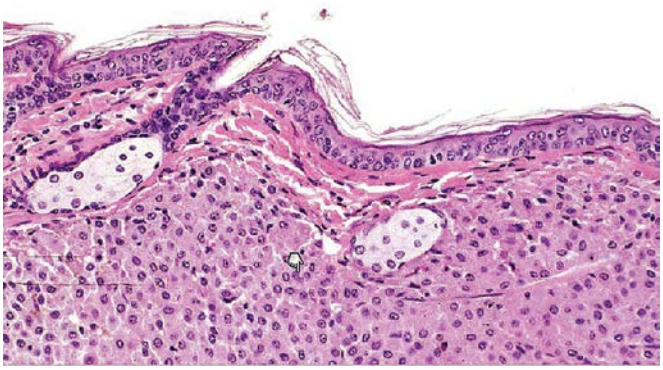


FIGURE 9 Mast cell tumor in a mouse, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

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Mastocytoma, see the preferred term **Mast cell tumor**.

Meibomian gland adenoma is a benign neoplasm of the specialized sebaceous glands of the eyelids/lashes. Characteristics are those of **sebaceous cell adenoma**. These tumors are common in older dogs.

References

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Moore, P.F. 2014. A review of histiocytic diseases of the dogs and cats. *Vet Pathol* 51:167–184.

Meibomian gland carcinoma is a rare, malignant or invasive neoplasm of the specialized sebaceous glands of the eyelids/lashes. Characteristics are those of **sebaceous cell carcinoma**.

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Melanocytoma, see the preferred term **Melanoma/melanocytic tumor**.

Melanoma/melanocytic tumor is a benign or malignant neoplasm arising from melanocytes. Melanocytes are localized mainly within the basal keratinocytes in the epidermis or follicular epithelium and less frequently in the dermis. The neoplastic cells in melanomas are usually arranged in sheets, nests, and/or whorls with fusiform, polygonal, and/or epithelioid cells in various proportions. Neoplastic cells usually contain cytoplasmic melanin. Most, if not all, melanocytomas are pigmented, and nonpigmented malignant tumors

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are called amelanotic melanomas. In dog, most skin melanomas are benign, while benign melanomas of the skin are rare in rats and mice. The main pathways involved in melanoma development are the *braf/erk/mek* and the *pten/pi3k/akt*. Other important genes include *c-Kit*, *cyclins/cyclin-dependent kinases*, *gnaq/gna11*, *mitf*, *Nras*, and *p53/Bcl*. Melanomas can be identified using the Fontana-Masson stain to detect melanins, or by the DOPA reaction that detects tyrosinase, a key enzyme in melanin synthesis. Immunohistochemistry (S-100, Melan-A, HMB-45, tyrosinase, MiTF antigens) or transmission electron microscopy (to identify melanosomes) can be utilized in the confirmation/identification of melanomas. Recently, a mouse two-step model of melanocytic nevi/melanoma formation has been established using dimethylbenz(a) anthracene (DMBA) as an initiator followed by chronic application of 12-*O*-tetradecanoyl-phorbol-13-acetate as a promoting agent.

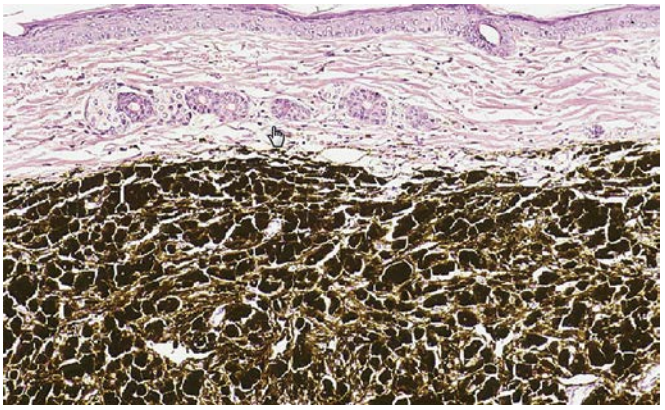


FIGURE 10 Benign melanocytic tumor in a mouse, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

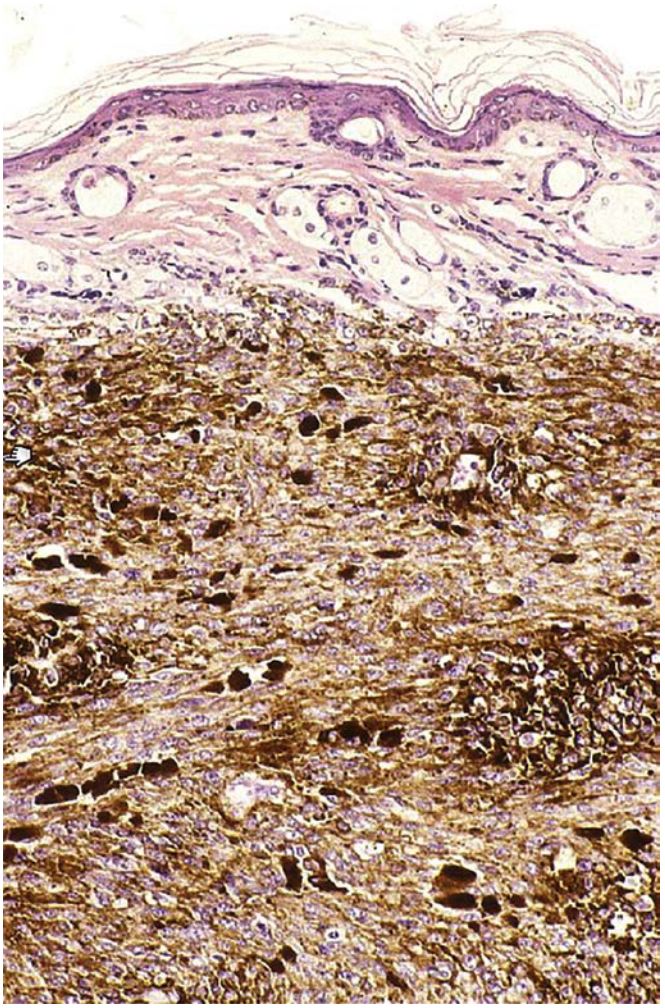


FIGURE 11 Malignant melanoma in the dermis of a mouse, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

Differential diagnoses: **Basal cell carcinoma**; Nerve sheath tumor.

Synonym(s): **Melanocytoma**.

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Mycosis fungoides, see the preferred term **Lymphoma, epitheliotrophic (canine)**.

Papilloma, see the preferred term **Squamous cell papilloma**.

Pilomatricoma, see the preferred term **Hair follicle tumor, benign**.

Pilomatrix carcinoma, see the preferred term **Hair follicle tumor, malignant**.

Primary adenoid cystic carcinoma, see the preferred term **Eccrine gland carcinoma**.

Sebaceous cell adenoma is a benign neoplasm of the sebaceous glands. These tumors are either exophytic (protruding) or endophytic (growing into the dermis) and well demarcated. Cells comprising the tumor are arranged in lobules and can vary in morphology (basaloid/precursor cells, well-differentiated sebocytes/gland cells, or squamous/duct-forming cells), but are well differentiated. Mitotic figures may be present, cystic areas are common, and the stroma is usually scant and fibrovascular. These tumors are rare in mice and rats, uncommon in nonhuman primates, but common in dogs, particularly older dogs.

Differential diagnoses: **Sebaceous cell hyperplasia**; **Sebaceous gland carcinoma**; **Basal cell tumor**.

Synonym(s): **Sebaceous gland adenoma**.

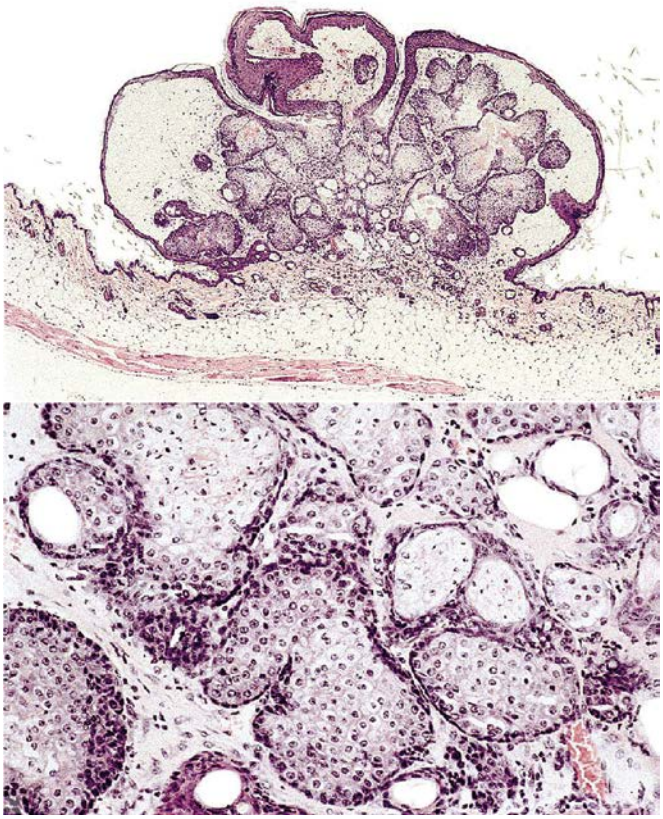


FIGURE 12 Sebaceous cell adenoma in a mouse at low (top) and high (bottom) magnifications, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

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Sebaceous cell carcinoma is a malignant neoplasm of sebaceous cells. Derived from immature sebocytes, these tumors are invasive, unlike their benign counterpart. Cells are poorly differentiated/basaloid and often vary in size and morphology (pleomorphic). Mitotic figures are frequent. There may be cystic foci, squamous cell differentiation, and necrosis. Lipid vacuolation of the cell cytoplasm typical of mature sebocytes may be present, but in smaller numbers of cells compared to the benign counterpart. These tumors can metastasize but are generally considered of low malignancy grade. Sebaceous cell carcinomas are rare in laboratory animal species.

Differential diagnoses: **Sebaceous cell adenoma**; **Basal cell carcinoma**.

Synonym(s): **Sebaceous gland carcinoma**.

References

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Moore, P.F. 2014. A review of histiocytic diseases of the dogs and cats. *Vet Pathol* 51:167–184.

Sebaceous cell hyperplasia is a nonneoplastic proliferation of mature sebocytes/sebaceous cells. When these cells are increased in number without any substantive change in cellular detail or glandular architecture, it is considered a benign hyperplastic change. The cytoplasm of the cells may be expanded, as is overall size of the lobule/gland. This change can result in response to certain hormonal stimuli or, more typically, is associated with irritation and inflammation. Sebaceous gland hyperplasia is a common feature of adnexal dysplasia.

Differential diagnosis: **Sebaceous cell adenoma**.

References

Diegel, K.L., Danilenko, D.M., and Wojcinski, Z.W. 2013. In: Haschek-Hock, W.M., Rousseaux, C.G., and Wallig, M.A. (eds.) *Integument in Handbook of Toxicologic Pathology*, 3rd ed. Elsevier Press.

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Moore, P.F. 2014. A review of histiocytic diseases of the dogs and cats. *Vet Pathol* 51:167–184.

A2

Squamous cell carcinoma is an invasive, malignant neoplasm of the skin originating within the epidermis, breaching the epidermal basement membrane, extending into the dermis or underlying tissue. It is comprised of neoplastic epidermal keratinocytes with variable atypical features such as nuclear pleomorphism, anisocytosis, and increased mitoses. These tumors are not uncommon in laboratory animal species and may arise from areas in which the skin is exposed to chronic irritation or inflammation. Arsenic toxicity is known to induce these tumors. They are also occasionally seen as a background finding in the spectrum of spontaneous squamous cell proliferative lesions in the skin and nonglandular stomach of transgenic mouse strains used in carcinogenicity assessment. Squamous cell carcinomas can present as nonkeratinizing (without differentiation into cornified cells) or keratinizing (differentiation into fully keratinized cell layers), with the latter being considered a feature of more well-differentiated tumors.

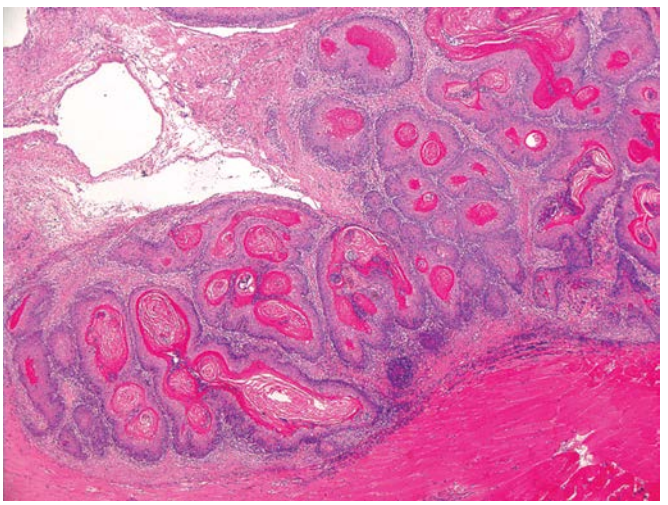


FIGURE 13 Squamous cell carcinoma in skin of a rat, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

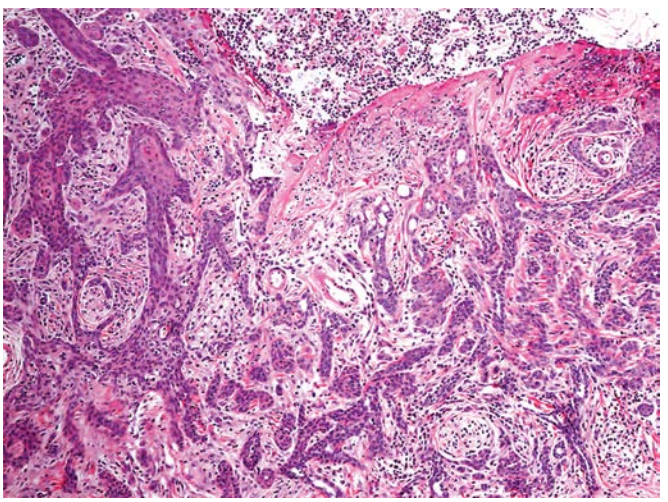


FIGURE 14 Squamous cell carcinoma in skin of a mouse, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

Differential diagnoses: **Squamous cell papilloma**; **Keratoacanthoma**; **Basal cell carcinoma**; **Mammary gland adenosquamous carcinoma**.

References

Diegel, K.L., Danilenko, D.M., and Wojcinski, Z.W. 2013. In: Haschek-Hock, W.M., Rousseaux, C.G., and Wallig, M.A. (eds.) *Integument in Handbook of Toxicologic Pathology*, 3rd ed. Elsevier Press.

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Moore, P.F. 2014. A review of histiocytic diseases of the dogs and cats. *Vet Pathol* 51:167–184.

Link

https://www.ncbi.nlm.nih.gov/pubmed/24395976

Squamous cell hyperplasia, see the preferred term **Epidermal hyperplasia**.

Squamous cell papilloma is the benign counterpart of malignant squamous cell carcinoma, as they also arise from epidermal keratinocytes. These masses may feature atypical cells and frequent mitotic figures. Typically, they are associated with extensive keratinization, but this is not always present. They may grow outward from the skin surface (exophytic) or extend inward (endophytic) but remain localized without breach of the basement membrane of the epidermis. They are more common than squamous cell carcinomas in transgenic mice used for carcinogenicity assessment and can also arise from cutaneous or mucocutaneous viral infections in a number of laboratory animal species (e.g., viral papillomas in mice, dogs, rabbits, and macaques). Development of disseminated papillomas is called papillomatosis.

Differential diagnoses: **Epidermal hyperplasia**; **Keratoacanthoma**; **Squamous cell carcinoma**.

Synonym(s): **Papilloma**.



FIGURE 15 Squamous cell papilloma in a mouse, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

References

Diegel, K.L., Danilenko, D.M., and Wojcinski, Z.W. 2013. In: Haschek-Hock, W.M., Rousseaux, C.G., and Wallig, M.A. (eds.) *Integument in Handbook of Toxicologic Pathology*, 3rd ed. Elsevier Press.

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Moore, P.F. 2014. A review of histiocytic diseases of the dogs and cats. *Vet Pathol* 51:167–184.

Squamous cyst occurs within the upper dermis and is composed of a wall of keratinizing epithelium, containing many concentric layers of keratin. Squamous cysts can occur in isolation or within squamous cell carcinomas. They may arise following injury to a hair follicle, but the cause is often unknown. Squamous cysts occur commonly in mice, especially the B6C3F1 strain, and hairless strains such as SKH1. In the SKH1 mouse (hr/hr mouse), the hairless condition is a result of hair follicles growing parallel with the surface of the epidermis instead of penetrating through the dermis to emerge through the epidermis. The abnormal hair follicles develop granulomas around them as well as many squamous cysts.

Differential diagnoses: **Epidermal hyperplasia**; **Squamous cell papilloma**; **Keratoacanthoma**.

Synonym(s): **Epidermal cyst**; **horn cyst**; **keratin cyst**.

References

Diegel, K.L., Danilenko, D.M., and Wojcinski, Z.W. 2013. In: Haschek-Hock, W.M., Rousseaux, C.G., and Wallig, M.A. (eds.) *Integument in Handbook of Toxicologic Pathology*, 3rd ed. Elsevier Press.
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Moore, P.F. 2014. A review of histiocytic diseases of the dogs and cats. *Vet Pathol* 51:167–184.

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https://www.ncbi.nlm.nih.gov/pubmed/24395976

Squamous hyperplasia, see the preferred term **Epidermal hyperplasia**.

Sweat gland tumor is a synonym for eccrine gland carcinoma in most species. In rodents, it is synonymous with primary adenoid cystic carcinoma. See the preferred term **Eccrine gland carcinoma**.

Tricholemmoma, see the preferred term **Hair follicle tumor, benign**.

Trichoepithelioma, see the preferred term **Hair follicle tumor, benign**.

Trichofolliculoma, see the preferred term **Hair follicle tumor, benign**.

SPECIAL SENSES: EYE

Choroidal neovascularization is the growth of new blood vessels that originate from the choroid through a break in Bruch's membrane into the retinal pigmented epithelial (RPE) layer or subretinal space. Subretinal fluid accumulation and subretinal, retinal, and vitreal hemorrhages can occur, and retinal detachment, scarring, or fibrosis may follow. Subretinal choroidal neovascularization is common in humans and is characteristic of age-related "wet" macular degeneration. Choroidal neovascularization is rare as a spontaneous occurrence in laboratory animals. It may be associated with a congenital abnormality of the retina, injury, or inflammation of the retina or other components of the uveal tract. Choroidal neovascularization may be induced by a laser in most rodent and non-rodent laboratory animal species, including monkeys and pigs. Other inducers are subretinal injection of vascular endothelial growth factor (VEGF) gene therapy, or oxidized lipids in rodents, or in certain transgenic mice.

Synonym(s): **Choroidal vascular hyperplasia**; **choroidal vascular proliferation**; **subretinal vascular proliferation**.

References

Grossniklaus, H.E., Kang, S.J., and Berglin, L. 2010. Animal models of choroidal and retinal neovascularization. *Prog Retin Eye Res* 29(6):500–519.
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https://www.ncbi.nlm.nih.gov/pubmed/28738417

Choroidal vascular hyperplasia, see the preferred term **Choroidal neovascularization**.

Choroidal vascular proliferation, see the preferred term **Choroidal neovascularization**.

Corneal endothelial hyperplasia is an abnormal increase in endothelial cells along the inner surface of the cornea, usually to fill in a defect or loss of endothelial cells, but migration of these cells may extend over the adjacent trabecular meshwork and iris. Migrating cells are often spindle-shaped, and there may be apparent thickening of Descemet's membrane and corneal endothelial hypertrophy. Corneal endothelial cells have regenerative capacity in rodents and rabbits and some regenerative capacity in dogs. In other species, cell migration and corneal endothelial hypertrophy rather than hyperplasia repairs endothelial defects.

Reference

INHAND Special Senses. Draft August 2017. 1–277.

A2

Corneal stromal neovascularization is the vascularization of a normally avascular corneal stroma. It may be associated with corneal stromal edema and inflammation. It is a common and beneficial acute response to corneal injury and is often associated with inflammatory mediators, but with persistence may lead to corneal scarring. Many rodent and rabbit models of induced corneal stromal neovascularization exist as a feature of corneal repair secondary to corneal injury or toxicity induced by a wide variety of chemicals, mechanical, drug, or microbial agents, or non-injury models of genetic or nutritional deficiencies. Some topical or systemic drugs can induce neovascularization in rodents, rabbits, dogs, or monkeys, such as EP4-prostaglandin E2 agonists, hypolipidemic agents, antineoplastic agents, immunosuppressive drugs, and antibody drug conjugates, or by mechanical corneal endothelial injury caused by intracameral drug delivery systems. Spontaneous corneal neovascularization is rare in laboratory animals, although this finding observed in keratoconjunctivitis in dogs is a useful model for dry eye disease.

Synonym(s): **Corneal vascular hyperplasia**.

References

Aguirre, S.A., Huang, W., Prasanna, G., and Jessen, B. 2009. Corneal neovascularization and ocular irritancy responses in dogs following topical ocular administration of an EP4-Prostaglandin E2 agonist. *Toxicol Pathol* 37:911–920.

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https://www.ncbi.nlm.nih.gov/pubmed/?term=cornea+neovascularization+AND+dogs+AND+models.
https://www.ncbi.nlm.nih.gov/pubmed/?term=cornea+neovascularization+AND+beagle
https://www.ncbi.nlm.nih.gov/pubmed/28973427

Corneal vascular hyperplasia, see the preferred term **Corneal neovascularization**.

Harderian gland acinar hyperplasia consists of well-demarcated, noncompressive, and tinctorially distinct foci of alveoli that contain increased numbers of cells that are sometimes hypertrophied with variable cytoplasmic staining, contain enlarged nuclei, and are pseudostratified, often with papillary projections. The alveolar architecture is generally normal, or with little distortion. A more diffuse hyperplasia occurs in regenerative responses secondary to degeneration or inflammation, and may include hypertrophy, anisokaryosis, cellular debris, and pigment accumulation. Nuclear pleomorphism and lack of compression of the adjacent tissue distinguish hyperplasia from adenoma in chronic toxicity studies. Hyperplasia may be a senile change, induced by trauma or inflammation, and chemically induced by benzene, benzidines, 3,3-dimethoxybenzidine and ginseng. As this gland is unique to laboratory animals, the presence of Harderian gland changes in carcinogenicity assessment is of questionable relevance to humans.

Differential diagnosis: **Harderian gland adenoma**.

References

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Albert, D.M., Frayer, W.C., Black, H.E., Massicotte, S.J., Sang, D.N., and Soque, J. 1986. The Harderian gland: Its tumors and its relevance to humans. *Trans the Am Ophthalmol Soc* 84:321–341.

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Links

https://www.toxpath.org/docs/SSNDC/EyeProliferativeRat.pdf
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1298742/pdf/

Harderian gland adenocarcinoma is similar to Harderian gland adenoma but consists of an expansive, distorted, and invasive mass of variably differentiated cuboidal or

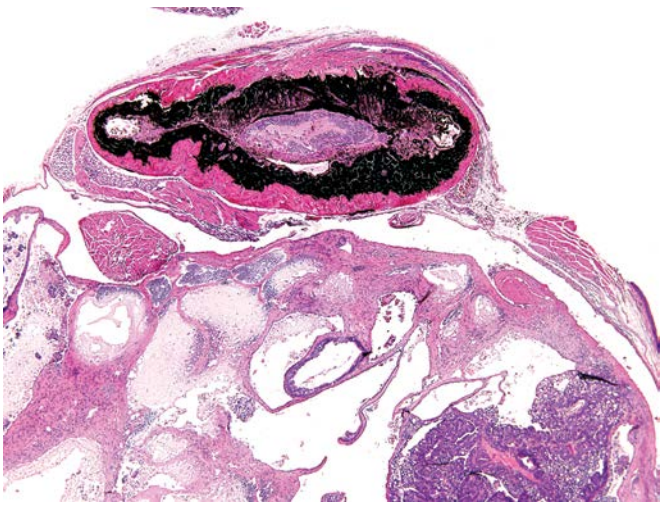


FIGURE 1 Harderian gland adenocarcinoma (squamous cell subtype) with invasion that has destroyed the eye (phthisis bulbi), B6C3F1 mouse, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

columnar acinar cells with anisokaryosis and little to no normal secretions or glandular architecture. Cellular pleomorphism, atypia, and mitoses are typical, and anaplastic neoplasms may consist of solid sheets of cells. Fibrosis and necrosis may also be present, and expansion of the tumor mass around the eye may cause exophthalmos. Harderian gland adenocarcinomas may be locally invasive or metastasize, and have been reported following administration of urethane and 2-acetylamino-flourorene in rats. Tumors of Harderian gland are much more frequent in mice than rats. In mice, spontaneous, radiation- and chemically induced adenomas occur more frequently than adenocarcinoma, and adenomas appear to frequently precede formation of adenocarcinomas.

Differential diagnosis: **Harderian gland adenoma**.

References

Ackerman, L.J., Yoshitomi, K., Fix, A.S., and Render, J.A. 1998. Proliferative lesions of the eye in rats. In: *Guides for Toxicologic Pathology*. Washington, DC: STP/ARP/AFIP.

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Harderian gland adenoma in rodents is typified by a well-demarcated, expansive mass of enlarged acinar cells, often with enlarged nuclei, and acini that may be cystic or pseudostratified with papillary growth into acinar lumina. Glandular architecture is usually abnormal with compression of the adjacent tissues which help to separate adenomas from hyperplasia (normal architecture) and adenocarcinoma (local invasion, atypia, and metastases). Adenomas are common as spontaneous, radiation- and chemically induced tumors preceding formation of adenocarcinomas in some strains of mice, have been reported with administration of urethane and 2-acetylamino-fluorene in rats, and are rarely reported in rabbits.

Differential diagnoses: Harderian gland hyperplasia; **Harderian gland adenocarcinoma**.

References

Ackerman, L.J., Yoshitomi, K., Fix, A.S., and Render, J.A. 1998. Proliferative lesions of the eye in rats. In: *Guides for Toxicologic Pathology*. Washington, DC: STP/ARP/AFIP.

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https://www.toxpath.org/docs/SSNDC/EyeProliferativeRat.pdf

Harderian gland tumors, see the preferred terms **Harderian gland adenoma** and **Harderian gland adenocarcinoma**.

Intraocular malignant melanoma, see the preferred term **Uveal melanoma**.

Intraocular schwannoma is a rare, malignant tumor of Schwann cells of intraocular ciliary nerves in rats and mice and other laboratory animals. The lesion is located in the iris and involves the ciliary body (uvea), invades the cornea, and fills the anterior chamber. This neoplasm is composed of plump, spindle-shaped cells with abundant eosinophilic cytoplasm arranged in parallel rows, containing atypical nuclei, and palisading around blood vessels. These tumors can be very difficult to differentiate from uveal leiomyomas and uveal melanomas on hematoxylin and eosin (H&E)-stained sections. Definitive diagnosis requires positive immunohistochemical staining for S-100, negative desmin staining, and/or visualization of desmosomes ultrastructurally.

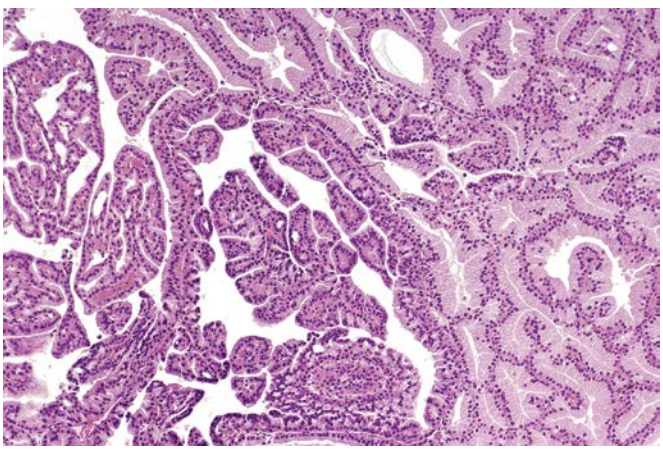


FIGURE 2 Harderian gland adenoma, B6C3F1 mouse, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

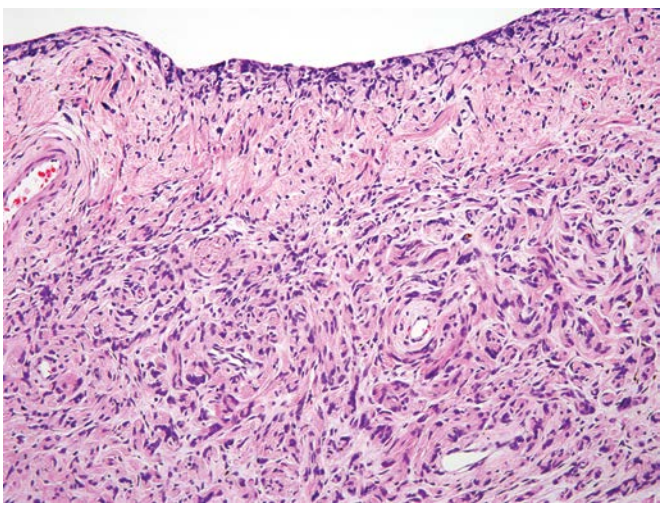


FIGURE 3 Intraocular schwannoma, malignant, uvea, H&E. (Image courtesy of L. Teixeira, University of Wisconsin.)

A2

Differential diagnoses: **Uveal leiomyoma**; **Uveal melanoma**.

Synonym(s): **Neurilemmoma, malignant**; **neurinoma, malignant**.

References

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Link

https://www.ncbi.nlm.nih.gov/pubmed/1771736

Lacrimal gland acinar hyperplasia consists of well-demarcated, noncompressive, and tinctorially distinct foci of glandular alveoli that contain increased numbers of cells with relatively normal cytoplasmic secretory (serous) vacuoles. Diffuse hyperplasia occurs in regenerative responses secondary to degeneration or inflammation, and may include hypertrophy, anisokaryosis, and cellular debris. Hyperplasia is mostly reported in rats treated with xenobiotics but may also occur in aged rodents and hamsters. Decreased lacrimal secretions also contribute to keratoconjunctivitis sicca (dry eye). Nuclear pleomorphism and lack of compression of adjacent tissue distinguish hyperplasia from adenoma in chronic toxicity studies.

Differential diagnosis: **Lacrimal gland adenoma** (see term description under 'L').

References

Ackerman, L.J., Yoshitomi, K., Fix, A.S., and Render, J.A. 1998. Proliferative lesions of the eye in rats. In: *Guides for Toxicologic Pathology*. Washington, DC: STP/ARP/AFIP.

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Link

https://www.toxpath.org/docs/SSNDC/EyeProliferativeRat.pdf

Lacrimal gland adenocarcinoma in laboratory animals consists of an expansive, distorted, and invasive mass of acini lined by moderately to poorly differentiated cuboidal cells with cellular pleomorphism, atypia, and mitotic figures. Neoplastic structures generally lack lobules and may form solid sheets of epithelial cells. Spontaneous, radiation- and chemically induced adenocarcinomas are reported in mice, but are rare in rats, and extremely rare in other laboratory animals.

Differential diagnosis: **Lacrimal gland adenoma**.

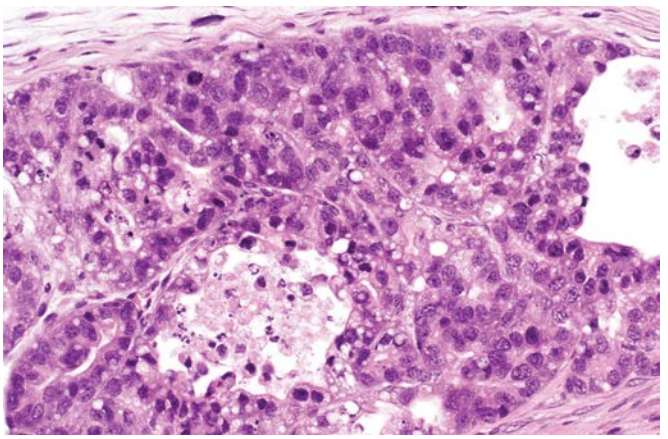


FIGURE 4 Lacrimal gland adenocarcinoma, B6C3F1 mouse, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

References

Ackerman, L.J., Yoshitomi, K., Fix, A.S., and Render, J.A. 1998. Proliferative lesions of the eye in rats. In: *Guides for Toxicologic Pathology*. Washington, DC: STP/ARP/AFIP.

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https://www.toxpath.org/docs/SSNDC/EyeProliferativeRat.pdf

Lacrimal gland adenoma in laboratory animals consists of a lobular and expansive mass of tubules and acini lined by well-differentiated cuboidal cells with round nuclei, relatively normal cytoplasmic secretory (serous) vacuoles, and few mitotic figures. The acini are often irregular and distorted, and slightly compress adjacent tissues. Adenocarcinomas are differentiated from adenomas by loss of acini, local invasion, distant metastases, cellular atypia, and increased mitoses. Ductal tumors have not been reported. Spontaneous, radiation- and chemically induced adenomas are reported in rodents but are extremely rare in other laboratory animals.

Differential diagnoses: **Lacrimal gland hyperplasia**; **Lacrimal gland adenocarcinoma**.

References

Ackerman, L.J., Yoshitomi, K., Fix, A.S., and Render, J.A. 1998. Proliferative lesions of the eye in rats. In: *Guides for Toxicologic Pathology*. Washington, DC: STP/ARP/AFIP.

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Link

https://www.toxpath.org/docs/SSNDC/EyeProliferativeRat.pdf

Lens epithelial hyperplasia is proliferation of a single layer of the anterior lenticular epithelium to form focal or multifocal

nodules under the lens capsule that may extend to the posterior lens capsule. Injury to the lens may result in lens epithelial hyperplasia or transformation to fibroblasts. Proliferation of lens epithelial cells to form a localized aggregate is a feature of subcapsular cataracts, and the response may include metaplasia to a mesenchymal phenotype more characteristic of a myofibroblast, secretion of collagen, and loss of lens epithelial cells, leaving behind cell-free collagen matrix and mineralization. Causative factors include needle or laser trauma, phacoemulsification, x-rays, and exposure to cigarette smoke.

Differential diagnosis: **Lens epithelium fibroplasia** (see term description under 'L').

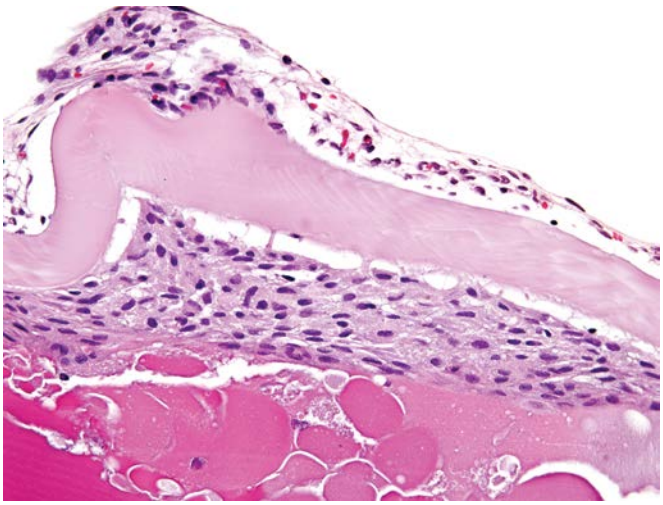


FIGURE 5 Lens epithelial hyperplasia with lens capsule hypertrophy, posterior iris adhesion, and degeneration lens fibers (cataract), F344 rat, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

References

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Links

https://www.ncbi.nlm.nih.gov/pubmed/10532446
https://www.ncbi.nlm.nih.gov/pubmed/478783

Nasolacrimal duct epithelial hyperplasia consists of mural or polypoid proliferation of the duct epithelium. The involved epithelium may vary from partially or nonkeratinized stratified squamous epithelium to pseudostratified cuboidal or columnar epithelium, or transitional epithelium. Hyperplasia may occur as an aging lesion in mice, in response to inhaled chemicals, or as a reactive response secondary to inflammation.

Reference

INHAND Special Senses. Draft August 2017. 1–277.

Nasolacrimal duct squamous cell carcinoma in rodents forms a mass of variably keratinized squamous epithelial cells with cellular and nuclear pleomorphism, atypia, and invasion through the basement membrane. The site of origin of a squamous cell carcinoma in the nasal cavity is often difficult to determine, but tumors may arise in the nasolacrimal duct and spread to adjacent tissues or may be local spread of squamous cell carcinomas from other locations in the nasal cavity to the nasolacrimal duct. Carcinomas are rarely reported except in chemical inhalation studies, as the nasolacrimal duct is not routinely examined in toxicology studies.

Differential diagnoses: Nasolacrimal duct squamous cell hyperplasia; **Nasolacrimal duct squamous cell papilloma**.

Reference

INHAND Special Senses. Draft August 2017. 1–277.

Nasolacrimal duct squamous cell papilloma in rodents consists of fronds of normal-appearing squamous cells, with variable keratinization, covering a fibrovascular stalk. The squamous cells, which may be nonkeratinized stratified, pseudostratified cuboidal, or columnar, maintain a regular architecture. Polypoid hyperplasia of squamous cells lacks the cellular stalk, and carcinomas include cellular atypia and invasion with destruction of the basement membrane. Papillomas are rarely reported except in response to inhaled chemicals.

Differential diagnoses: Nasolacrimal duct squamous cell hyperplasia; **Nasolacrimal gland squamous cell carcinoma**.

Reference

INHAND Special Senses. Draft August 2017. 1–277.

Neurilemmoma, malignant, see the preferred term **Intraocular schwannoma**.

Neurinoma, malignant, see the preferred term **Intraocular schwannoma**.

Ocular amelanotic melanoma, see the preferred term **Uveal melanoma**.

Ocular dermoid is a rare, nonneoplastic and proliferative congenital mass (choristoma) of normal but ectopic ectodermal and mesodermal tissue in the cornea and conjunctiva of dogs, rabbits, guinea pigs, and rodents. These lesions may contain keratinized epithelium, hair, blood vessels, fibrous tissue fat, nerves, glands, smooth muscle, and cartilage. The mass is often found in the lateral limbal region but may extend onto the cornea, sclera, conjunctiva, eyelid, or nictitating membrane. Long, coarse hairs extending from the surface of the mass frequently cause corneal and periocular irritation. Such masses need to be differentiated from invasive tumors of extraocular tissues.

Differential diagnosis: **Epidermal cyst**.

A2

References

INHAND Special Senses. Draft August 2017. 1–277.

Styer, C.M., Ferrier, W.T., Labelle, P., Griffey, S.M., and Kendall, L.V. 2015. Limbic dermoid in a New Zealand White rabbit (*Oryctolagus cuniculus*). *J Amer Assoc Lab An Sci* 44(6):46–48.

Wappler, O., Allgoewer, I., and Schaeffer, E.H. 2002. Conjunctival dermoid in two guinea pigs: A case report. *Vet Ophthal* 5(3):245–248.

Ocular melanosis, see the preferred term **Uveal melanocyte hyperplasia**.

Ocular neurilemmoma, malignant, see the preferred term **Intraocular schwannoma**.

Ocular neurinoma, malignant, see the preferred term **Intraocular schwannoma**.

Ocular squamous cell carcinoma of the cornea or conjunctiva is a rare neoplasm in rodents and other laboratory animals. The neoplasm is composed of cords and nests of neoplastic squamous cells. Acanthotic squamous epithelium from a squamous cell carcinoma has deep rete pegs, early keratin pearl formation, prominent intercellular bridges, anisocytosis, anisokaryosis, occasional dyskeratosis, or some combination thereof. Corneal stroma may be markedly thickened by chronic active inflammation with fibrosis. These tumors have been induced by ultraviolet B radiation in XPA-deficient mice.

Differential diagnosis: **Ocular squamous cell papilloma**.

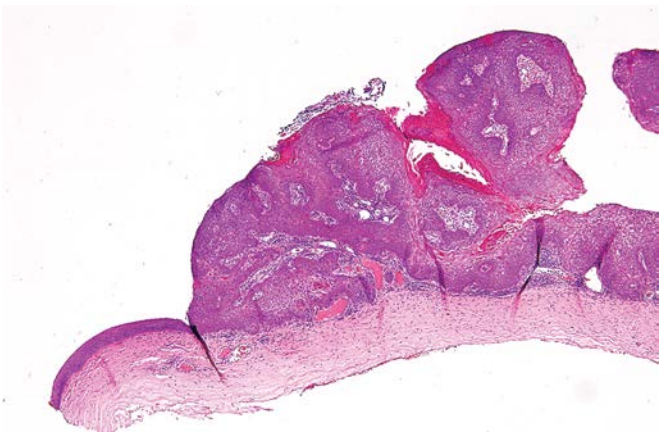


FIGURE 6 Ocular squamous carcinoma, invasion of cornea, dog, H&E. (Image courtesy of L. Teixeira, University of Wisconsin.)

References

De Vries, A., Gorgels, T.G., Berg, R.J., Jansen, G.H., and Van Steeg, H. 1998. Ultraviolet-B induced hyperplasia and squamous cell carcinomas in the cornea of XPA-deficient mice. *Exp Eye Res* 67(1):53–59.

INHAND Special Senses. Draft August 2017. 1–277.

Schafer, K. and Render, J. 2013. Toxicologic pathology of the eye: Alterations of the lens and posterior segment. In: Weir, A. and Collins, M. (eds.) *Assessing Ocular Toxicology in Laboratory Animals*. Springer Science+Business Media, pp. 219–257.

Link

https://www.ncbi.nlm.nih.gov/pubmed/2019354

Ocular squamous cell hyperplasia may arise from the cells of the corneal epithelium and epithelial cells of the bulbar and palpebral conjunctiva, and epithelium of the lacrimal duct in rodents and non-rodents. Diagnostic features include an increased number of cell layers of squamous epithelium with a rete peg–like growth pattern. They are often associated with epithelial hyperkeratosis and underlying stromal inflammation. Spontaneous corneal and/or conjunctival epithelial hyperplasia is a rare lesion in laboratory animals. Squamous cell hyperplasia may be caused by topically applied irritants, systemically administered toxins, reduced tear production, bacterial, viral, or fungal infections, nutritional deficiencies, heritable defects, and exophthalmos due to space-occupying masses. Often, squamous cell hyperplasia is associated with stromal inflammation, neovascularization, and/or fibrosis. Corneal hyperplasia may occur in chronic rodent studies, can be observed as a focal, diffuse, or nodular thickening of the corneal epithelial layer, and is not considered preneoplastic unless it includes squamous cell hyperplasia. Squamous cell hyperplasia and acute keratitis can be induced in female HRA/Skh mice treated with 8-methoxypsoralen combined with UVA radiation, and in XPA-deficient mice with UVB radiation. Corneal hyperplasia has been observed following epidermal growth factor administered systemically in cynomolgus monkeys resulting in diffuse, uniform thickening mostly of squamous cells of the corneal epithelium.

Differential diagnoses: **Squamous cell papilloma**; **Squamous cell carcinoma**.

Synonym(s): **Corneal keratinization**; **conjunctival keratinization**.

References

De Vries, A., Gorgels, T.G., Berg, R.J., Jansen, G.H., and Van Steeg, H. 1998. Ultraviolet-B induced hyperplasia and squamous cell carcinomas in the cornea of XPA-deficient mice. *Exp Eye Res* 67(1):53–59.

Dunnick, J.K., Forbes, P.D., Eustis, S.L., Hardisty, J.F., and Goodman, D.G. 1991. Tumors of the skin in the HRA/Skh mouse after treatment with 8-methoxypsoralen and UVA radiation. *Fundam Appl Toxicol* 16(1):92–102.

Geiss, V. and Yoshitomo, K. 1999. Eyes. In: Maronpot, R.R., Boorman, G.A., and Gaul, B.W. (eds.) *Pathology of the Mouse*. St Louis: Cache River Press, pp. 471–490.

INHAND Special Senses. Draft August 2017. 1–277.

Reindel, J., Gough, A., Pilcher, G., Bobrowski, W., Sobocinski, G., and De La Iglesia, F. 2001. Systemic proliferative changes and clinical signs in cynomolgus monkeys administered a recombinant derivative of human epidermal growth factor. *Toxicol Pathol* 29(2):159–73.

Schafer, K. and Render, J. 2013. Toxicologic pathology of the eye: Alterations of the lens and posterior segment. In: Weir, A. and Collins, M. (eds.) *Assessing Ocular Toxicology in Laboratory Animals*. Springer Science+Business Media, pp. 219–257.

Links

https://www.ncbi.nlm.nih.gov/pubmed/9702178
https://www.ncbi.nlm.nih.gov/pubmed/2019354
http://journals.sagepub.com/doi/pdf/10.1080/019262301317052431

Ocular squamous cell papilloma of the cornea or conjunctiva is a rare neoplasm in rodents and other laboratory species. Squamous cell papilloma is characterized by exophytic growth with development of multiple branched, arborizing fronds composed of a lining of variably keratinized squamous epithelium, and a variably developed vascular connective tissue core. A basal stalk and rounded, blunt papillary arms are present without invasion of the underlying tissue. No cellular dysplasia is observed, and no or only slight mitotic activity is present. Squamous cell papilloma is not known as a spontaneous finding in laboratory animal studies but papillomas may occur in inhalation carcinogenicity studies in rats. A variant of this neoplasm, an inverted mucoepidermoid papilloma with a downward growth pattern of the palpebral conjunctiva, has been observed in a F344/N rat.

Differential diagnosis: **Ocular squamous cell carcinoma**.

References

INHAND Special Senses. Draft August 2017. 1–277.

Schafer, K. and Render, J. 2013. Toxicologic pathology of the eye: Alterations of the lens and posterior segment. In: Weir, A. and Collins, M. (eds.) *Assessing Ocular Toxicology in Laboratory Animals*. Springer Science+Business Media, pp. 219–257.

Yoshitomi, K. and Boorman, G. 1994. Inverted mucoepidermoid papilloma and mucus cell adenocarcinoma of the palpebral conjunctiva in two F344 rats. *Vet Pathol* 31:254–258.

Link

https://www.ncbi.nlm.nih.gov/pubmed/8203092

Ocular trabecular meshwork cell activation, see the preferred term **Ocular trabecular meshwork proliferation**.

Ocular trabecular meshwork cell migration, see the preferred term **Ocular trabecular meshwork proliferation**.

Ocular trabecular meshwork proliferation is a nonspecific increase in the number or layers of mononuclear trabecular cells in the meshwork and in the filtration angle of the eye. Activated trabecular meshwork cells can be phagocytic, and synthesize growth factors, collagen, and neurotransmitters. Cellular proliferation changes aqueous humor outflow dynamics, and the reduced filtration contributes to glaucoma and accompanying panocular pathology. Injury, experimental laser photocoagulation, intraocular injections, and chemical or irritating agents induce trabecular meshwork cells to proliferate and migrate.

Differential diagnoses: **Iris inflammatory cell infiltrate**; **Ciliary body inflammatory cell infiltrate**.

Synonym(s): **Ocular trabecular meshwork cell migration**; **ocular trabecular meshwork cell activation**.

Reference

INHAND Special Senses. Draft August 2017. 1–277.

Retinal pigment epithelium (RPE) hyperplasia is a focal increase in the number of retinal pigment epithelial cells, often associated with trauma, inflammation, and retinal degeneration and detachment. Hyperplastic RPE may also be enlarged and contain **RPE vacuolation** or **RPE increased or decreased pigmentation**.

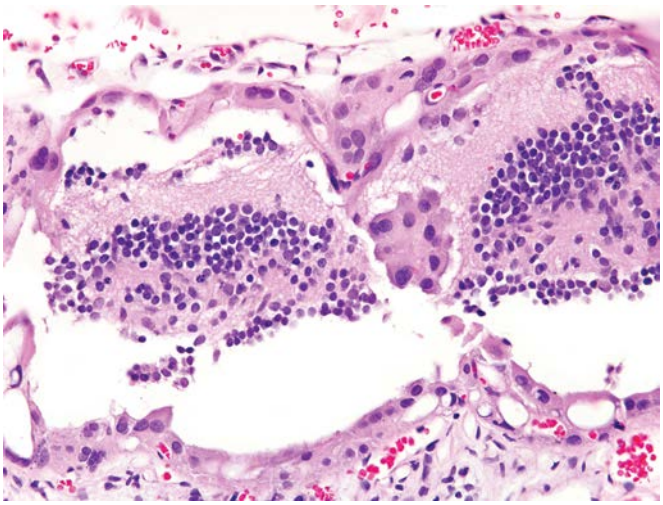


FIGURE 7 Retinal pigment epithelium (RPE) hyperplasia with retinal atrophy and retinal detachment, F344 rat, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

Reference

INHAND Special Senses. Draft August 2017. 1–277.

Retinoblastoma is a malignant embryonic tumor originating from primitive neuroectodermal cells of the retina. It does not occur naturally in laboratory animals but is the most common malignant ocular tumor in children. Mutant alleles of both copies of the RB genes impair apoptosis (frequently associated with loss of functional wild-type p53 protein) induce retinoblastoma, which can appear as a heritable bilateral form or as a unilateral nonheritable form. Retinoblastoma is characterized by trabeculae or sheets of small basophilic cells with scant cytoplasm, which may form rosettes or rows of vertical cells similar to photoreceptors. Necrosis, mineralization, and retinal detachment may be present, with invasion into multiple ocular structures and distant metastases. Retinoblastomas occur in genetically engineered mice with inactivation of the *Rb1* gene and related proteins, with orthotopic human xenografts, and retinoblastoma-like lesions occur after intraocular injection of rats with human adenovirus type 12 and nickel compounds.

Reference

Dyer, M.A., Rodriguez-Galindo, C., and Wilson, M.W. 2005. Use of preclinical models to improve treatment of retinoblastoma. *PLOS Med* 2(10), e332. http://doi.org/10.1371/journal.pmed.0020332

Link

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1261510

Subretinal vascular proliferation, see the preferred term **Choroidal neovascularization**.

A2

Uveal leiomyoma is a rare, benign, intraocular tumor of smooth muscle originating from the smooth muscle myofibers of the iris or ciliary muscles in the uvea. The spindle-shaped cells with granular cytoplasm and an elongated nucleus may palisade around blood vessels and form interlacing bundles or whorls. These neoplasms can be very difficult to differentiate from uveal melanomas and uveal schwannomas on hematoxylin and eosin (H&E)-stained sections. A definitive diagnosis requires demonstration of myofibrils by phosphotungstic/acid hematoxylin stain (PTAH), positive immunohistochemical staining for desmin, or ultrastructurally by visualization of cytoplasmic myofibrils, focal cytoplasmic densities, or surface-connected vesicles.

Differential diagnoses: **Uveal melanoma**; **Intraocular schwannoma**.

Reference

INHAND Special Senses. Draft August 2017. 1–277.

Uveal melanocyte hyperplasia in the rat and dog consists of aggregates of polygonal to poorly defined uveal melanocytes filled with usually large globules of pigment in the absence of other cellular or inflammatory changes. Cellular atypia is absent, and adjacent structures are architecturally normal and not displaced. The origin and significance this cellular change or its roles as a spontaneous or potential preneoplastic change is unknown. Iris increased pigmentation, a nonproliferative finding, may be a more appropriate term. This finding should also be differentiated from uveal melanoma arising as a tumor extension from the ciliary body and iris.

Differential diagnoses: **Uveal melanoma**; **Iris increased pigmentation**.

Synonym(s): **Ocular melanosis**.

References

INHAND Special Senses. Draft August 2017. 1–277.

Ackerman, L.J., Yoshitomi, K., Fix, A.S., and Render, J.A. 1998. Proliferative lesions of the eye in rats. In: *Guides for Toxicologic Pathology*. Washington, DC: STP/ARP/AFIP.

Uveal melanoma arises in the pigment cells (melanocytes) that reside within the iris, ciliary body, and choroid (collectively the uvea). Microscopically, tumors are often formed by spindle, epithelioid, or mixed cell populations. Bundles or whorls of perivascular-oriented spindle cells have indistinct borders with scant cytoplasm, and fusiform nuclei with indistinct nucleoli. Epithelioid cells have an ill-defined cell border, pale cytoplasm, and large oval nuclei, with or without nucleoli. Large epithelioid cells with bizarre nuclei, melanin granules, necrosis, and mitotic figures may be variably present. Local extension may occur, but metastases are less frequently reported in all species. Spontaneous ocular melanomas in dogs (mostly benign and rarely malignant) are commonly observed in the anterior uvea, and less frequently in the choroid, but spontaneous melanomas are extremely rare in nonhuman primates, have not been reported in some laboratory species (albino and pigmented), and benign melanomas have not been reported in rodents. Malignant melanomas, including amelanotic variants, have been induced in laboratory animals by several chemicals (e.g., nitrosourea compounds), viruses, irradiation, and by intraocular injection of tumor cells (with and without immunosuppression), xenograft implants, and in transgenic mice and zebrafish. In B6C3F1/CrlBR mice, malignant melanoma usually originates in a lymphoid organ with metastases to the choroid. In the rat, melanomas can be very difficult to differentiate from uveal leiomyoma or schwannoma by light microscopy. A definitive diagnosis requires positive immunohistochemical staining for S-100 and vimentin, negative staining for desmin, cytokeratin, and glial fibrillary acid protein, and particularly for differentiation from schwannomas, visualization of stage II melanosomes by transmission electron microscopy is diagnostic.

Differential diagnoses: **Uveal leiomyoma**; **Intraocular schwannoma**; **Iris increased pigmentation**.

Synonym(s): **Ocular amelanotic melanoma**; **intraocular malignant melanoma**.



FIGURE 8 Uveal melanoma, dog, H&E. (Image courtesy of L. Teixeira, University of Wisconsin.)

References

INHAND Special Senses. Draft August 2017. 1–277.

Stei, M.M., Loeffler, K.U., Holz, F.G., and Herwig, M.C. 2016. Animal models of uveal melanoma: Methods, applicability, and limitations. *BioMed Res Int* 2016:4521807. http://doi.org/10.1155/2016/4521807

Link

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4913058/

SPECIAL SENSES: EAR

Zymbal's gland adenocarcinoma, see the preferred term **Zymbal's gland carcinoma**.

Zymbal's gland carcinoma in rodents is a malignant tumor originating in sebaceous cells (sebaceous cell subtype) or

duct epithelium (squamous cell subtype) or as a mixture of both subtypes in the Zymbal's (auditory) gland located near the opening of the outer ear canal. Sebaceous cell carcinomas are often ulcerated with large irregular acini, sometimes with papillary projections, and acini may be cystic and contain sebum, cellular debris, and leukocytes, and in a stromal bed of proliferating fibroblasts. Neoplastic acini contain basal cells with hyperchromatic nuclei; the upper layers are composed of pleomorphic cells containing 1–2 oval or round nuclei and a granulated or vacuolated cytoplasm, with frequent mitoses. The squamous cell subtype of ductal epithelium consists of cells of variable differentiation to squamous cells, with or without keratinization, variation in cell size, loss of intercellular bridges, atypical mitotic figures, and frequent invasion into the adjacent tissues including skin, ear, and cranium. Hyperplasia may precede Zymbal's gland neoplasia. Carcinomas may be spontaneous in rats and less frequently in mice, and they may be induced by cupferron, chloroprene, 1,3-butadiene, benzene, benzidines, aminostilbenes, 2-amino-3-methylimidazo[4,5f] quinolone, and a variety of other chemicals that may stimulate the cytochrome P-450 metabolizing enzymes in these glands. As this gland is unique to rodents, the presence of Zymbal's gland carcinomas in carcinogenicity studies is of questionable relevance to humans.

Differential diagnoses: **Zymbal's gland sebaceous cell adenoma**; **Zymbal's gland squamous cell papilloma**; Cutaneous squamous cell carcinoma.

Synonym(s): **Zymbal's gland adenocarcinoma**.

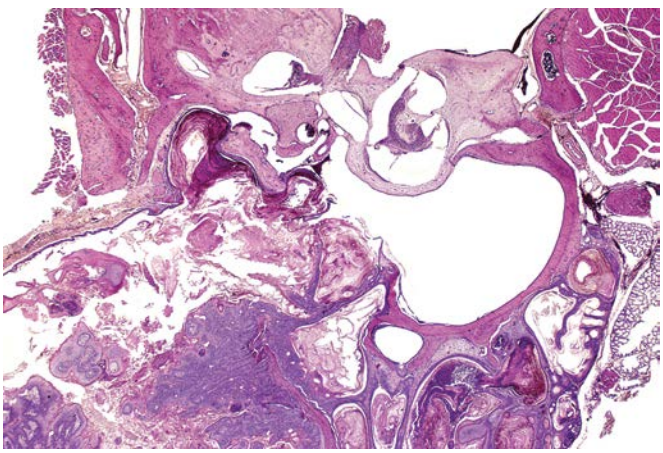


FIGURE 1 Zymbal's gland carcinoma (squamous cell subtype), invasion of middle ear, F344 rat, H&E.

References

Chandra, M., Riley, M.G., and Johnson, D.E. 1992. Spontaneous neoplasms in aged Sprague-Dawley rats. *Arch Toxicol* 66:496–502.

Rudmann, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse mammary, Zymbal's, preputial, and clitoral glands. *Toxicol Pathol* 40:7S–39S.

Links

http://journals.sagepub.com/doi/full/10.1177/0192623312454242
https://www.ncbi.nlm.nih.gov/pubmed/1444814

Zymbal's gland hyperplasia in rodents consists of a focal or rarely diffuse proliferation of sebaceous cells (sebaceous cell subtype) or duct epithelium (squamous cell subtype) in the Zymbal's (auditory) gland located near the opening of the outer ear canal. In sebaceous subtypes the lobular architecture is retained, but with enlarged or fused acini and slight compression of the adjacent tissues. Acinar cells may be hypertrophied with enlarged nuclei, multiple nucleoli, and basophilic or vacuolated cytoplasm. The squamous cell subtype of ductal epithelium consists of focal proliferation of squamous epithelium, with or without rete pegs, and formation of luminal folds or papillary projections. Hyperplasia is differentiated from neoplasia by the absence of cellular atypia or invasion and retention of acinar architecture, but hyperplasia may progress to neoplasia. Hyperplasia may be spontaneous or induced in rats and mice by trauma or inflammation or chemically by benzene, benzidines, 3,3-dimethoxybenzidine, 2-amino-3-methylimidazo[4,5f] quinolone, and aromatic amines. As this gland is unique to rodents, the presence of Zymbal's gland hyperplasia in carcinogenicity assessment is of questionable relevance to humans.

Differential diagnoses: **Zymbal's gland sebaceous cell adenoma**; **Zymbal's gland squamous cell papilloma**.

References

National Toxicology Program. 2014. Nonneoplastic Lesion Atlas. Zymbal's gland – hyperplasia. Accessed 28 September, 2017.

Rudmann, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse mammary, Zymbal's, preputial, and clitoral glands. *Toxicol Pathol* 40:7S–39S.

Links

http://journals.sagepub.com/doi/full/10.1177/0192623312454242
https://ntp.niehs.nih.gov/nnl/special_senses/zymbals/hyperpl/index.htm

Zymbal's gland sebaceous cell adenoma in rodents consists of a well-defined, but not encapsulated, normal-sized or larger than normal lobule of sebaceous cells in the Zymbal's (auditory) gland located near the opening of the outer ear canal. Unlike hyperplasia, glandular architecture is lost and replaced by a mixture of small basal-like cells, mature sebaceous cells, and transitional cells between the two forms with frequent vacuolation of cell cytoplasm and pyknotic nuclei. Lobules may be cystic and contain sebum. Hyperplasia may precede Zymbal's gland neoplasia. Adenomas may be spontaneous or induced in rats and mice by benzene, benzidines, 3,3-dimethoxybenzidine, 2-amino-3-methylimidazo[4,5f] quinolone, and aromatic amines. As this gland is unique to rodents, the presence of Zymbal's gland sebaceous cell adenoma in carcinogenicity assessment is of questionable relevance to humans.

Differential diagnoses: **Zymbal's gland hyperplasia** (sebaceous cell subtype); **Zymbal's gland carcinoma** (sebaceous gland subtype); Cutaneous carcinoma, basal cell.

Reference

Rudmann, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse mammary, Zymbal's, preputial, and clitoral glands. *Toxicol Pathol* 40:7S–39S.

A2

Link

http://journals.sagepub.com/doi/full/10.1177/0192623312454242

Zymbal's gland squamous cell papilloma in rodents consists of multiple papillary growths of cornified and stratified squamous epithelium covering connective tissue cores that extend into the lumina of the ducts of Zymbal's (auditory) gland located near the opening of the outer ear canal. Cellular atypia is usually absent, but adjacent sebaceous glands may be hyperplastic. Hyperplasia may precede Zymbal's gland neoplasia. Papillomas may be spontaneous or induced in rats and mice by benzene, benzidines, 3,3-dimethoxybenzidine, 2-amino-3-methylimidazo[4,5f] quinolone, and aromatic amines. As this gland is unique to rodents, the presence of Zymbal's gland **squamous cell papilloma** in carcinogenicity assessment is of questionable relevance to humans.

Differential diagnosis: **Zymbal's gland carcinoma** (squamous subtype).

Reference

Rudmann, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse mammary, Zymbal's, preputial, and clitoral glands. *Toxicol Pathol* 40:7S–39S.

Link

http://journals.sagepub.com/doi/full/10.1177/0192623312454242

URINARY SYSTEM

Acidophilic adenoma, see the preferred term **Oncocytoma**.

Acidophilic tumor is an obsolete term once used in rats for renal tubule neoplasms with eosinophilic staining properties. See the preferred terms **Renal tubular adenoma** and **Renal tubular carcinoma**.

Amphophilic-vacuolar (A-V) tumor is a morphologically distinct renal tubule tumor occurring spontaneously in the most commonly used strains of laboratory rat. The tumor, or its precursor tubule hyperplasia, can be encountered in young and old rats and is characterized by eosinophilic or amphophilic staining, and vacuolar cytoplasm conferring a "moth-eaten" appearance to the epithelium. The tumor cells are arranged in discrete lobules usually with central necrosis. They have a tendency to grow down the length of a nephron such that cross-sections of the neoplasm can be observed in different zones of the kidney. Large A-V tumors may have a substantial basophilic portion, but a characteristic area of vacuolar eosinophilic-amphophilic epithelium is usually also present. There is a paucity of mitotic figures in the tumor tissue, and no evidence that these neoplasms metastasize. Review of all of the cases of A-V renal tumor in the NTP archives found no evidence of test article induction. Due to their spontaneous nature, these neoplasms should not be included in tumor counts associated with chemical exposure. Limited evidence suggests that they may be familial in origin.

Differential diagnoses: **Renal tubular adenoma**; **Renal tubular carcinoma**.

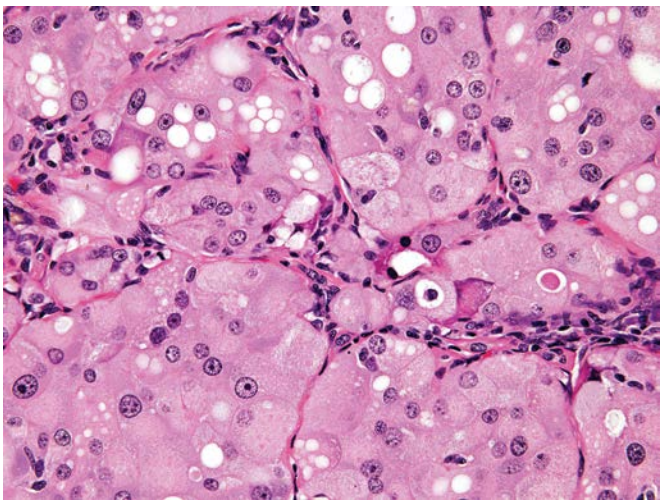


FIGURE 1 A-V adenoma, rat kidney, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

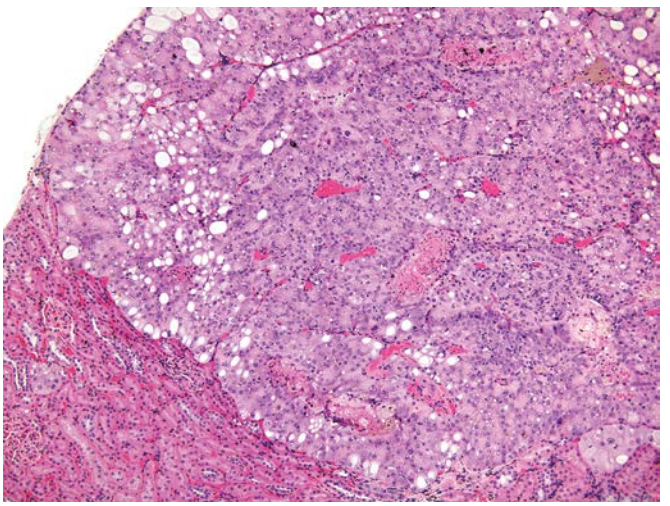


FIGURE 2 A-V carcinoma, rat kidney, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

Reference

Frazier, K. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse urinary system. *J Toxicol Pathol* 40:14S–86S.

Link

https://www.ncbi.nlm.nih.gov/pubmed/22637735

Atypical renal tubule cell hyperplasia (ATH) in the rodent is the obligate precursor of renal tubule adenoma. In rats it is characterized by a solid or complex proliferation of proximal tubule epithelial lining cells that do not exceed the limits of a single tubule. ATH can appear as several neighboring foci that represent the involvement of convolutions of a single tubule. Most of the lesions are basophilic, but amphophilic-vacuolar (A-V) tumors and clear cell tumors are preceded by A-V and clear cell variants, respectively. In the basophilic type, the lesion can show a faint hyaline sheen when stained with hematoxylin and eosin (H&E). The cells are well formed, with well-defined cell borders, and are sometimes enlarged with prominent, enlarged nucleoli. The

expansive nature of these lesions is confirmed by the presence of attenuated fibroblasts or capillaries partially encircling the lesion. This intimate encirclement by interstitial cells is an important diagnostic criterion for ATH in rodent studies.

Differential diagnoses: **Renal tubular hyperplasia**; **Renal tubular adenoma**.

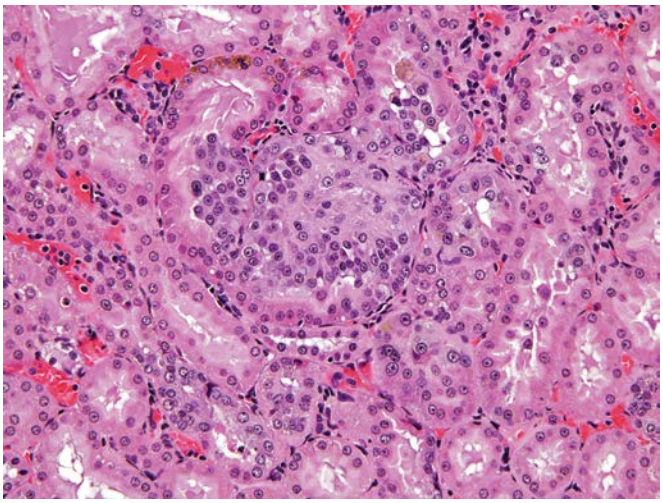


FIGURE 3 ATH, rat kidney, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

Reference

Frazier, K. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse urinary system. *J Toxicol Pathol* 40:14S–86S.

Link

https://www.ncbi.nlm.nih.gov/pubmed/22637735

Atypical urothelial cell hyperplasia is a focal lesion consisting of disordered pleomorphic urothelial cells and should be regarded as a precursor of urothelial cell neoplasia. Chemicals carcinogenic for the renal pelvis urothelium can cause this lesion.

Differential diagnosis: **Urothelial hyperplasia**.

Reference

Frazier, K. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse urinary system. *J Toxicol Pathol* 40:14S–86S.

Link

https://www.ncbi.nlm.nih.gov/pubmed/22637735

Bowman's capsular hyperplasia represents an alteration from the attenuated form of Bowman's capsule cells in the kidney to a more cuboidal shape. As cuboidal cells are less space-occupying than flattened cells, this invariably involves an increase in the number of Bowman's capsule cells, and therefore involves hyperplasia of the lining as well.

Reference

Frazier, K. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse urinary system. *J Toxicol Pathol* 40:14S–86S.

Link

https://www.ncbi.nlm.nih.gov/pubmed/22637735

Bowman's capsular metaplasia represents an alteration from the attenuated form of Bowman's capsule cells in the kidney to a more cuboidal shape. This involves an increase in the number of Bowman's capsule cells, and therefore involves hyperplasia of the lining as well. This metaplastic change in Bowman's capsule can occur as rats age, but it is also seen with exposure to toxic agents such as lead salts. Male mice normally have cuboidal capsule cells.

Reference

Frazier, K. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse urinary system. *J Toxicol Pathol* 40:14S–86S.

Link

https://www.ncbi.nlm.nih.gov/pubmed/22637735

Decidual-like reaction in the urinary bladder, see the preferred term **Urinary bladder mesenchymal proliferative lesion**.

Embryonal nephroma, see the preferred term **Nephroblastoma**.

Epidermoid carcinoma, see the preferred term **Urinary bladder mesenchymal proliferative lesion**.

Juxtaglomerular cell hypertrophy and hyperplasia in the kidney occurs following administration of angiotensin 1-converting enzyme (ACE) inhibitors (e.g., captopril, enalapril, and quinapril), NSAIDs (nonsteroidal anti-inflammatory drugs), and angiotensin II type 1 receptor antagonists,

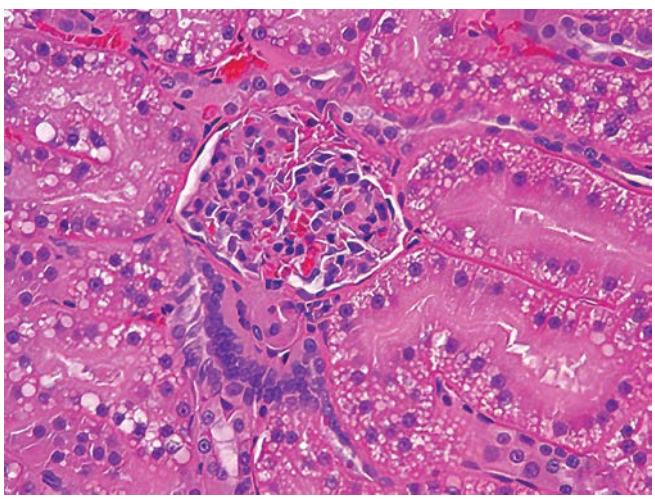


FIGURE 4 Juxtaglomerular cell hypertrophy and hyperplasia, rat kidney, H&E.

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such as losartan. In response, the renin-secreting myoepithelial cells of the juxtaglomerular apparatus can increase in size and number, causing physiological effects. Large oral doses of captopril have produced juxtaglomerular cell hypertrophy and hyperplasia in mice, rats, and monkeys, which is reversible after cessation of exposure. There can be interspecies differences in the juxtaglomerular cell response, with those in rats being milder than those observed in macaques.

Reference

Frazier, K. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse urinary system. *J Toxicol Pathol* 40:14S–86S.

Link

https://www.ncbi.nlm.nih.gov/pubmed/22637735

Malignant cell epithelioma, see the preferred term **Renal tubular carcinoma**.

Mesangial cell hyperplasia is an increase in the number of mesangial cells in the glomerulus of the kidney. It rarely occurs as a separate entity but more frequently is an accompaniment of various glomerular diseases during their progressive phases, such as in immunologically mediated glomerular injury. It is one component of the nephrotic syndrome induced by puromycin. Mesangial cell hyperplasia is not associated with tumor development.

Reference

Frazier, K. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse urinary system. *J Toxicol Pathol* 40:14S–86S.

Link

https://www.ncbi.nlm.nih.gov/pubmed/22637735

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Reference

Frazier, K. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse urinary system. *J Toxicol Pathol* 40:14S–86S.

Link

https://www.ncbi.nlm.nih.gov/pubmed/22637735

Mesangioproliferative glomerulonephritis is a diffuse renal glomerular lesion characterized by hyperplasia and/or hypertrophy of mesangial cells, accompanied by increased mesangial matrix. Glomerular capillary loops are minimally affected. This glomerular alteration has been induced in rats by Habu snake venom.

Reference

Frazier, K. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse urinary system. *J Toxicol Pathol* 40:14S–86S.

Link

https://www.ncbi.nlm.nih.gov/pubmed/22637735

Mesenchymal bladder tumor, see the preferred term **Urinary bladder mesenchymal proliferative lesion**.

Mesenchymal cell tumor, see the preferred term **Renal mesenchymal tumor**.

Mixed mesodermal tumor, see the preferred term **Renal mesenchymal tumor**.

Nephroblastematosis is a small aggregate of densely basophilic blastemal cells (i.e., cells capable of growth and regeneration into organs or body parts) infiltrating the interstitial space of the outer zones of the kidney, usually without organoid differentiation but with rosette formation in the larger lesions. It is believed to derive from the metanephric blastema, usually first becoming apparent in the outer stripe of the outer medulla or deep cortex, and is presumed to be a precursor of nephroblastoma.

Synonym(s): **Nephrogenic rest**.

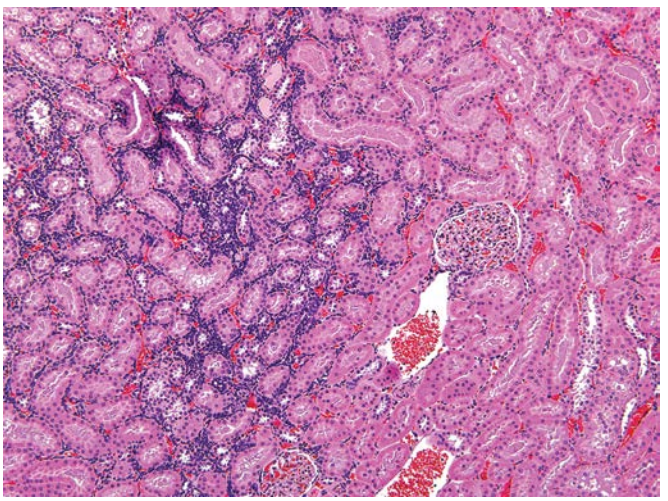


FIGURE 5 Nephroblastematosis, rat kidney, H&E.

Reference

Frazier, K. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse urinary system. *J Toxicol Pathol* 40:14S–86S.

Link

https://www.ncbi.nlm.nih.gov/pubmed/22637735

Nephroblastoma is an embryonal tumor of the kidney consisting in the rat of aggregates of densely basophilic blastemal cells, primitive tubule or rosette formation, mature ducts, and occasionally, primitive glomerular structures. Blastema (i.e., cells capable

of growth and regeneration into organs or body parts) is always present in the tumor, but primitive tubule or rosette formation may be scant. The most common morphology in the rat consists of dense clusters of blastemal cells condensed around a mature, duct-like profile. In some cases, mature ducts can be traced to, and found to be continuous with, the urothelial lining of the renal pelvis. Blastemal cells, which have very little cytoplasm, can appear in an alveolar pattern. When seen, glomerular bodies consist of very small, dense cells supported by an eosinophilic stalk and surrounded by a layer of flattened cells. The neoplasm occurs mostly in young adult rats and is often responsible for the death of the animal. Nephroblastomas are usually observed as spontaneous neoplasms. They have been induced experimentally in the offspring of female rats injected intraperitoneally with the direct-acting nitrosourea and *N*-nitroso-ethylurea, both during the late stage of gestation. The equivalent tumor in humans is usually referred to as Wilm's tumor. Nephroblastoma is extremely rare in the mouse, but has been recorded in hamsters, rabbits, dogs, and nonhuman primates.

Differential diagnoses: **Renal mesenchymal tumor**; **Renal sarcoma**.

Synonym(s): **Embryonal nephroma**.

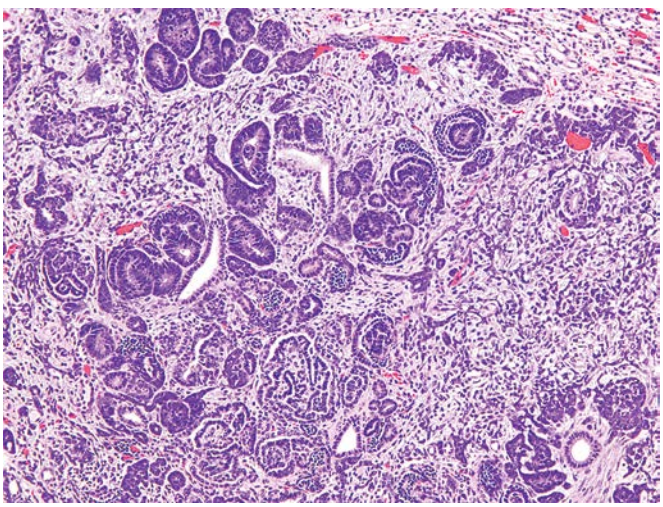


FIGURE 6 Nephroblastoma, rat kidney, H&E. (Reproduced with permission of Society of Toxicology from Frazier, K. et al. 2012. *J Toxicol Pathol* 40:14S–86S.)

Reference

Frazier, K. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse urinary system. *J Toxicol Pathol* 40:14S–86S.

Link

https://www.ncbi.nlm.nih.gov/pubmed/22637735

Nephrogenic rest, see the preferred term **Nephroblastematosis**.

Oncocytic adenoma, see the preferred term **Oncocytoma**.

Oncocytic hyperplasia refers to small, compact, proliferative lesions located in the cortex or outer stripe of the outer medulla of the kidney. They are spontaneous lesions in rats consisting of oncocytic cells, i.e., epithelial cells with granular or

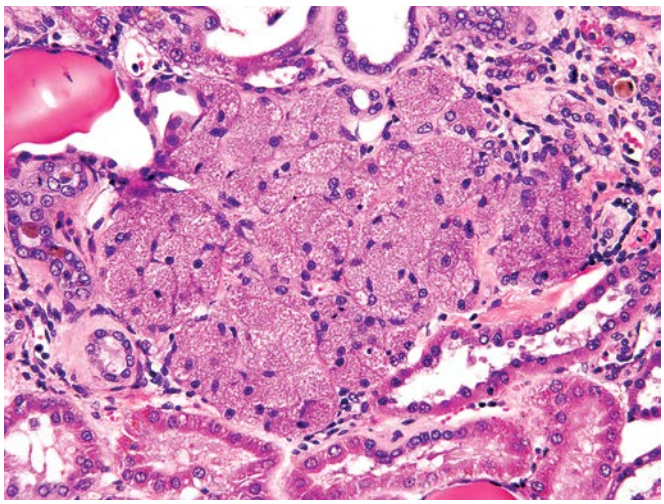


FIGURE 7 Oncocytic hyperplasia, rat kidney, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

ground-glass cytoplasm, usually with chromophobic or faintly basophilic staining properties. Ultrastructurally the granules are enlarged, misshapen mitochondria with numerous cristae. They are believed to originate from the collecting duct system, mainly from collecting tubules. Discrimination between oncocytic hyperplasia and oncocytoma can be difficult. In the F344 rat, oncocytic proliferations occur at a rate of approximately 0.1%.

Differential diagnosis: **Renal tubular hyperplasia**.

Oncocytoma is a discreet, benign proliferation of oncocytic cells (i.e., epithelial cells with abundant, granular, eosinophilic cytoplasm due to presence of numerous large mitochondria of varied sizes) that appear following progression of hyperplasia, causing compression of the surrounding renal tissue. As oncocytomas are unlikely to be induced by compound exposure, they are not included in tumor counts for regulatory purposes in human hazard and risk assessment.

Differential diagnosis: **Renal tubular adenoma**.

Synonym(s): **Acidophilic adenoma**; **oxyphilic adenoma**; **oncocytic adenoma**.

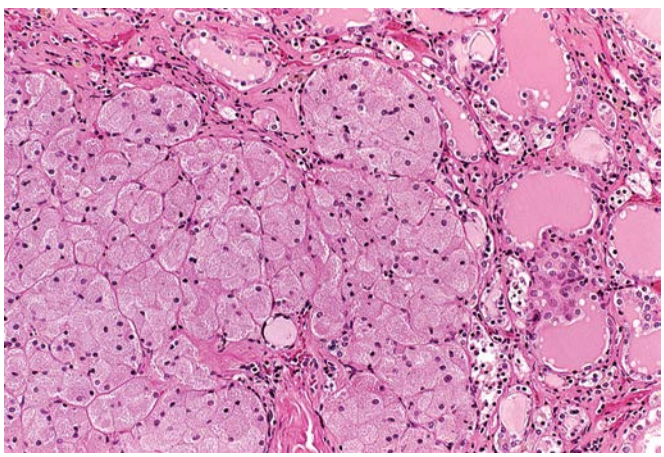


FIGURE 8 Oncocytoma, rat kidney, H&E. (Reproduced with permission of Society of Toxicology from Frazier, K. et al. 2012. *J Toxicol Pathol* 40:14S–86S.)

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Reference

Frazier, K. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse urinary system. *J Toxicol Pathol* 40:14S–86S.

Link

https://www.ncbi.nlm.nih.gov/pubmed/22637735

Oxyphilic adenoma, see the preferred term **Oncocytoma**.

Renal cell adenoma, see the preferred term **Renal tubular adenoma**.

Renal cell carcinoma, see the preferred term **Renal tubular carcinoma**.

Renal epithelioma, see the preferred term **Renal tubular adenoma**.

Renal lipomatous tumor is represented by lipoma and liposarcoma. Lipoma is a small interstitial aggregate of mature adipocytes of benign appearance, while liposarcoma tends to be a larger, locally invasive malignant neoplasm containing hemorrhage and cystic spaces and consisting of adipoblasts, adipocytes, and undifferentiated mesenchymal cells. These tumors have not been induced by administration of pharmaceuticals or chemicals.

Reference

Jones, T., Hard, G., Mohr, U. (eds.) 1998. *Monographs on Pathology of Laboratory Animals. Urinary System*, 2nd ed. Berlin: Springer-Verlag, pp. 139–146.

Link

https://rd.springer.com/book/10.1007/978-3-642-80335-2

Renal mesenchymal tumor (RMT) is a neoplasm of the rat kidney composed of a heterogeneous population of neoplastic mesenchymal cell types. The main neoplastic components are fibroblast-like spindle cells, stellate cells mimicking primitive mesenchyme, and usually, smooth muscle fibers. Abnormal deposits of collagen are also prominent. Occasional tumors include striated muscle, hemangiomatous areas, cartilage, and osteoid. A feature of these neoplasms is that the engulfed, pre-existing tubules survive within the tumor tissue as basophilic hyperplastic tubule profiles or dilated tubules, sometimes assuming a cystic appearance. In addition, RMT frequently invades the renal pelvis and hilus where pre-existing urothelium survives as tracts or islands of epithelium within the mesenchymal tumor tissue. The neoplasm is capable of metastasizing via the regional lymph nodes to the lung, or by seeding onto adjacent visceral organs, and is only induced by genotoxic chemicals.

Differential diagnoses: **Nephroblastoma**; **Renal sarcoma**; **Sarcoma, NOS** (not otherwise specified).

Synonym(s): **Stromal nephroma**; **mesenchymal cell tumor**; **mixed mesodermal tumor**.

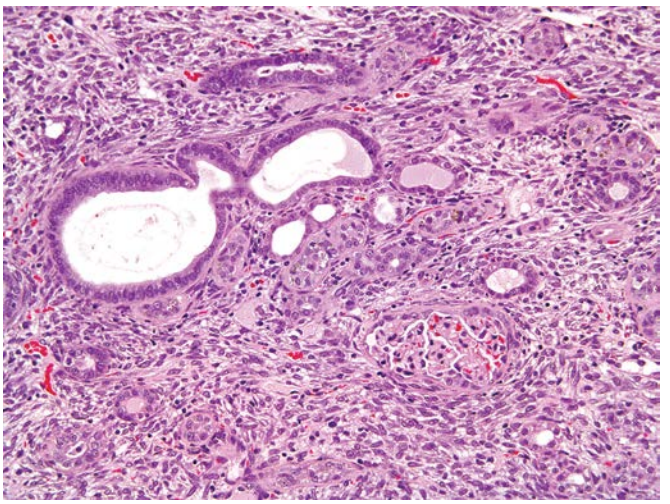


FIGURE 9 RMT, rat kidney, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

Reference

Frazier, K. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse urinary system. *J Toxicol Pathol* 40:14S–86S.

Link

https://www.ncbi.nlm.nih.gov/pubmed/22637735

Renal sarcoma is a rare kidney tumor in the rat consisting of a monomorphic population of spindle-shaped (fibroblast-like) sarcoma cells without the survival of engulfed, pre-existing tubule profiles, and no conspicuous collagen formation. The sarcoma cells usually adopt a fascicular growth pattern. It is an invasive tumor with the potential to metastasize. This tumor has been induced in both rats and mice by a single injection of polyoma virus.

Differential diagnoses: **Fibrosarcoma**; **Sarcoma, NOS** (not otherwise specified); **Renal mesenchymal tumor**; **Nephroblastoma**.

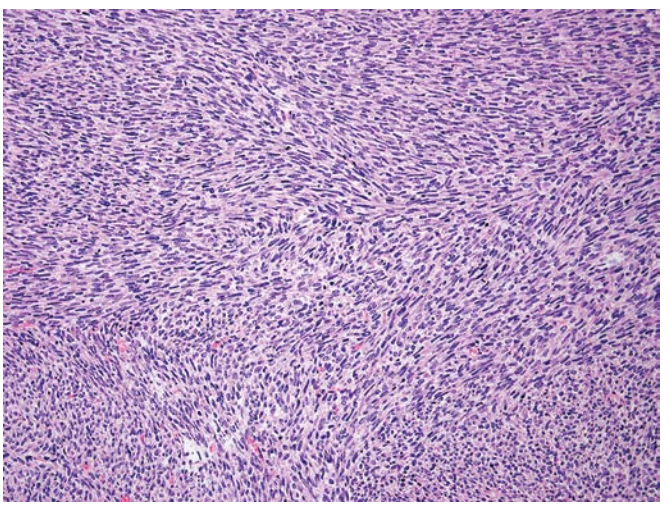


FIGURE 10 Renal sarcoma, rat kidney, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

Reference

Frazier, K. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse urinary system. *J Toxicol Pathol* 40:14S–86S.

Link

https://www.ncbi.nlm.nih.gov/pubmed/22637735

Renal tubular adenoma (RTA) is a small neoplasm arising from the renal tubule epithelial lining. It is developmentally preceded by the expansion of atypical tubular cell hyperplasia (ATH). RTA represents an extension of proliferation beyond the entity of a single tubule, and often shows attempted tubule differentiation and capillary ingrowth. It may be organized into lobules, occasionally with a small focus of degeneration, but generally lacks areas of cell pleomorphism. Renal tubular adenomas do not metastasize but possess the potential to progressively enlarge into carcinomas. These adenomas have been induced by chemicals which produce alpha 2u-globulin nephropathy (jet fuels, d-limonene, lindane, and others).

Differential diagnoses: **Amphophilic-vacuolar (A-V) tumor**; **Atypical renal tubule cell hyperplasia**.

Synonym(s): **Renal epithelioma**; **renal cell adenoma**.

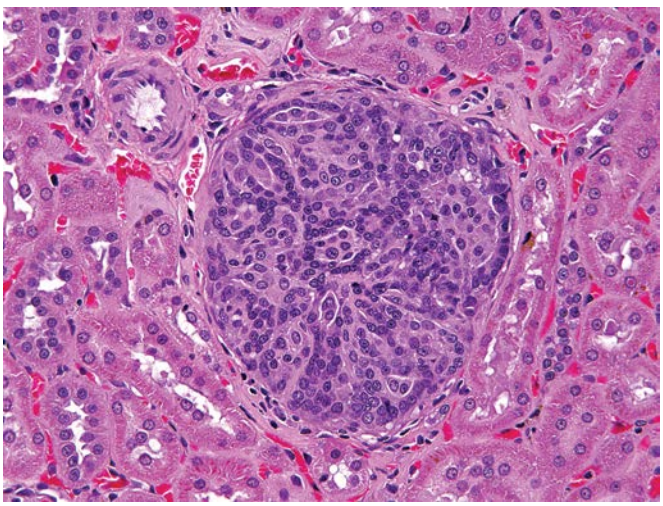


FIGURE 11 Renal tubular adenoma, rat kidney, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

Reference

Frazier, K. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse urinary system. *J Toxicol Pathol* 40:14S–86S.

Link

https://www.ncbi.nlm.nih.gov/pubmed/22637735

Renal tubular carcinoma is a large malignant tumor of tubule origin, most likely originating from proximal tubules, and developing progressively through the sequence of atypical tubule cell hyperplasia (ATH) and renal tubule adenoma (RTA). The most common form is basophilic, but clear, chromophobe, and amphophilic-vacuolar (A-V) cell types are also sometimes encountered. Renal tubular carcinoma is distinguished from adenoma by its larger size, prevalence of mitotic figures, areas of cell pleomorphism, and areas of degeneration and/or hemorrhage. Anaplastic morphology is sometimes seen as has been observed with carcinomas induced by the mycotoxins, fumonisin B1, and ochratoxin A. Renal tubular carcinomas can grow by expansion but can also be locally invasive. Accordingly, these neoplasms are capable of metastasis, particularly when of large dimensions approaching 2 cm diameter in the rat. The lung is a common site for metastases, the latter being morphologically similar to the parent tumor.

Differential diagnosis: **Renal tubular adenoma**.

Synonym(s): **Renal cell carcinoma**; **malignant cell epithelioma**.

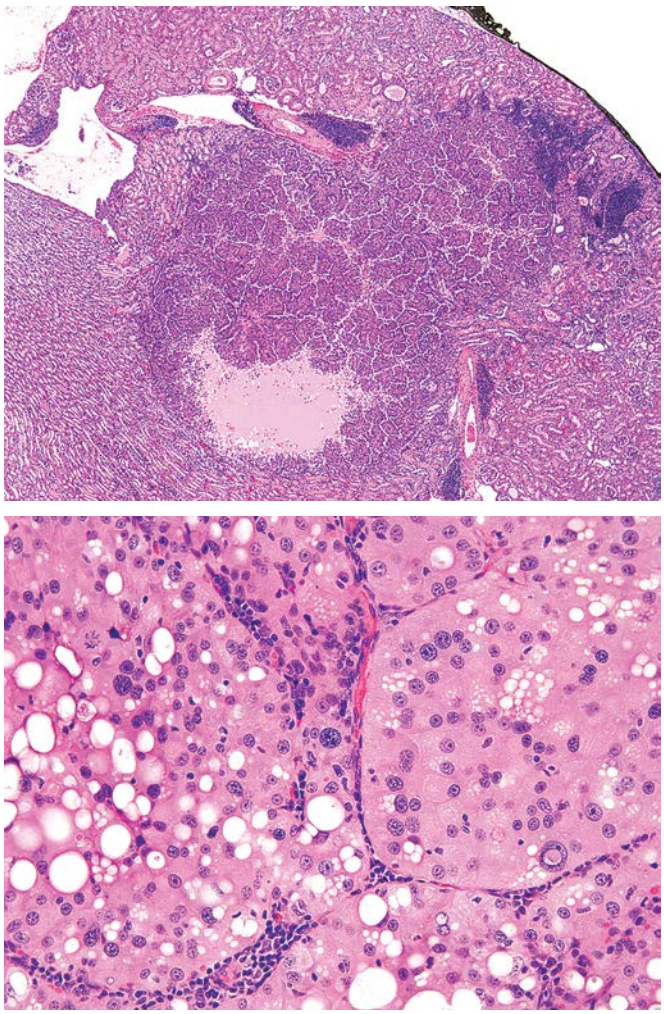


FIGURE 12 Renal tubule carcinoma, rat kidney, H&E. (Reproduced with permission of Society of Toxicology from Frazier, K. et al. 2012. *J Toxicol Pathol* 40:14S–86S.)

Reference

Frazier, K. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse urinary system. *J Toxicol Pathol* 40:14S–86S.

Link

https://www.ncbi.nlm.nih.gov/pubmed/22637735

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Renal tubular hyperplasia is a proliferative increase in the epithelial lining cells of kidney tubules. It is most frequently encountered in the proximal tubules and collecting duct system. In the proximal tubule, hyperplasia can either represent an increase in the number of lining cells without any alteration of the single cell layer (simple renal tubule hyperplasia), or a solid or stratified cystic proliferation with altered cellular detail (atypical renal tubule cell hyperplasia; ATH). ATH is an obligate precursor of renal tubule adenoma. In end-stage chronic progressive nephropathy (CPN) there appears to be a third form of cell proliferation with complex tubule cell increase (i.e., CPN tubule proliferation), which appears to be an adaptive response of the failing kidney and is not a preneoplastic lesion.

Differential diagnoses: **Atypical renal tubule cell hyperplasia**; **Oncocytic hyperplasia**.

References

Frazier, K. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse urinary system. *J Toxicol Pathol* 40:14S–86S.

Seely, J.C. and Frazier, K.S. 2015. Regulatory forum opinion piece: Dispelling confusing pathology terminology; recognition and interpretation of selected rodent renal tubule lesions. *J Toxicol Pathol* 43:457–463.

Links

https://www.ncbi.nlm.nih.gov/pubmed/25869578
https://www.ncbi.nlm.nih.gov/pubmed/22637735

Sarcomatoid carcinoma, see the preferred term **Urinary bladder carcinosarcoma**.

Stromal nephroma, see the preferred term **Renal mesenchymal tumor**.

Transitional cell carcinoma, see the preferred term **Urothelial carcinoma**.

Ureteral leiomyosarcoma is a malignant neoplasm of the smooth muscle surrounding the ureter. It is composed of interlacing bundles and whorls of pleomorphic spindle cells arranged in crisscross patterns of bundles with blunt-ended or cigar-shaped nuclei. Eosinophilic cytoplasm contains longitudinal myofilaments and perinuclear clear space, and is immunoreactive for desmin. Necrosis, cystic change, and mineralization are commonly seen.

Differential diagnosis: **Sarcoma, NOS** (not otherwise specified).

Reference

Jokinen, M.P., Seely, J.C. 2018. Urinary bladder, ureter, and urethra. In: Suttie, A.W., Leininger, J.R., Bradley, A.E. (eds.) *Boorman's Pathology of the Rat*. Elsevier, Academic Press, pp. 167–187.

Link

https://www.ncbi.nlm.nih.gov/pubmed/26973378

Urinary bladder adenocarcinoma is characterized by glandular structures lined by one or more layers of cuboidal to columnar cells, and may contain mucous. These rare tumors arise either from the urothelium and undergo differentiation to adenocarcinoma, or via glandular metaplasia. Adenocarcinomas have moderate cellular atypia and tend to invade adjacent structures. Nuclei may be located eccentrically, and mitotic figures may be present.

Differential diagnoses: **Urothelial carcinoma**; **Adenocarcinoma**.

Reference

Frazier, K. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse urinary system. *J Toxicol Pathol* 40:14S–86S.

Link

https://www.ncbi.nlm.nih.gov/pubmed/22637735

Urinary bladder carcinogenesis is the induction of neoplasms, benign and/or malignant, by the administration of both genotoxic and nongenotoxic xenobiotics. The pathogenesis of urinary bladder carcinogens may either be direct or indirect. Direct carcinogens are those that react with DNA to form adducts, and lead to mutations and cancer. Indirect carcinogens, such as urinary solids, are those that increase the risk of cancer by producing cytotoxicity by mechanical irritation, and subsequently increase cell proliferation. The human relevance of bladder carcinogenesis must be determined by defining the mechanism inducing the neoplasm, since there are anatomic differences with regard to organ positioning and the presence of urinary solids between laboratory animals and humans.

Reference

Frazier, K. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse urinary system. *J Toxicol Pathol* 40:14S–86S.

Link

https://www.ncbi.nlm.nih.gov/pubmed/22637735

Urinary bladder carcinoma, see the preferred term **Urothelial carcinoma**.

Urinary bladder carcinosarcoma is a rare neoplasm composed of both malignant mesenchymal (e.g., fibroblasts or leiomyocytes), and malignant epithelial cells. This tumor has the same features as a malignancy of the cell type of origin but are intermixed with each other throughout the lesion.

Differential diagnosis: **Urinary bladder mesenchymal proliferative lesion**.

Synonym(s): **Spindle cell carcinoma**.

Reference

Jones, T., Hard, G., Mohr, U. (eds.) 1998. *Monographs on Pathology of Laboratory Animals. Urinary System*, 2nd ed. Berlin: Springer-Verlag, pp. 139–146.

Link

https://rd.springer.com/book/10.1007/978-3-642-80335-2

Urinary bladder leiomyosarcoma is a malignant neoplasm of the smooth muscle in the wall of the urinary bladder, and has the same features as described for **Ureteral leiomyosarcoma**.

Differential diagnosis: **Sarcoma, NOS** (not otherwise specified).

Reference

Jokinen, M.P., Seely, J.C. 2018. Urinary bladder, ureter, and urethra. In: Suttie, A.W., Leininger, J.R., Bradley, A.E. (eds.) *Boorman's Pathology of the Rat*. Elsevier, Academic Press, pp. 167–187.

Link

https://www.ncbi.nlm.nih.gov/pubmed/26973378

Urinary bladder mesenchymal proliferative lesion is a solitary or multiple proliferation of cells observed only in the mouse, and usually near the bladder trigone. The pathogenesis is uncertain but now generally accepted to be a mesenchymal proliferation (i.e., decidual-like) and not a neoplasm. The lesion is demarcated but not encapsulated, and two types of cells are observed: large, pleomorphic epithelioid cells, admixed with variable numbers of spindle cells. Vascularization, occasional necrosis, and mitoses may be noted. It is not known if these lesions can be chemically induced.

Differential diagnoses: **Urinary bladder carcinosarcoma**; **Leiomyoma**; **Leiomyosarcoma**.

Synonym(s): **Decidual-like reaction in the urinary bladder**; **mesenchymal bladder tumor**.

Reference

Frazier, K. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse urinary system. *J Toxicol Pathol* 40:14S–86S.

Link

https://www.ncbi.nlm.nih.gov/pubmed/22637735

Urinary bladder papilloma is generally a single, exophytic, benign urothelial neoplasm of the urinary bladder. Less common variants include the inverted or endophytic type. These tumors range from small to large within the bladder lumen. Papillomas are generally pedunculated, consisting of fibrovascular stalks covered by thickened layers of urothelium, and attached to the bladder mucosa. There is little cellular atypia and no invasion. Squamous or glandular metaplasia may be evident.

Differential diagnoses: **Urinary bladder polyp**; **Urothelial carcinoma**.

Reference

Frazier, K. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse urinary system. *J Toxicol Pathol* 40:14S–86S.

Link

https://www.ncbi.nlm.nih.gov/pubmed/22637735

Urinary bladder polyp is an abnormal growth of tissue that may occasionally arise in the bladder and renal pelvis. They are pedunculated, benign tumors which can become quite large. Polyps are characterized by a cellular core covered by a thin layer of urothelium. The cellularity of the polyp may be loose to dense and may contain intercellular material resembling edema fluid. The exact cause of urinary polyps is not known, but mechanical trauma, as from the parasite *Trichosomoides crassicauda*, can occur.

Differential diagnosis: **Urinary bladder papilloma**.

Reference

Frazier, K.S., Seely, J.C. 2013. Urinary system. In: Sahota, P.S., Popp, J.A., Hardisty, J.F., Gopinath, C. (eds.) *Toxicologic Pathology: Nonclinical Safety Assessment*. Boca Raton: Taylor & Francis, pp. 422–484.

Link

https://www.crcpress.com/Toxicologic-Pathology-Nonclinical-Safety-Assessment/Sahota-Popp-Hardisty-Gopinath/p/book/9781138199545

Urinary bladder spindle cell carcinoma, see the preferred term **Urinary bladder carcinosarcoma**.

Urinary bladder squamous cell carcinoma may arise from urothelium which has undergone differentiation to squamous

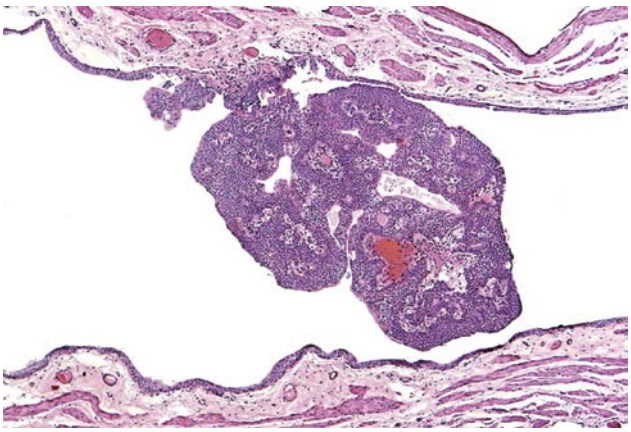


FIGURE 13 Papilloma, rat urinary bladder, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

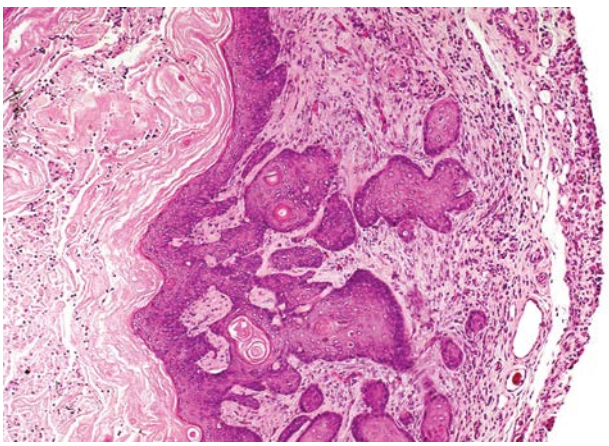


FIGURE 14 Squamous cell carcinoma, rat urinary bladder, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

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epithelium. These neoplasms tend to be highly malignant, poorly demarcated, with moderate cellular atypia, and are invasive. The diagnosis of squamous cell carcinoma should be made when the majority of the neoplasm is squamous. Variable keratinization (squamous pearls) may be present. Squamous cell carcinomas are noted less often then urothelial carcinomas, but generally appear more malignant, and metastasize more frequently.

Differential diagnosis: **Urothelial carcinoma**.

Synonym(s): **Epidermoid carcinoma**.

Reference

Frazier, K. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse urinary system. *J Toxicol Pathol* 40:14S–86S.

Link

https://www.ncbi.nlm.nih.gov/pubmed/22637735

Urothelial carcinoma is a malignant neoplasm of urothelial cells characterized by cellular anaplasia and invasion into the bladder wall. It may be well differentiated or undifferentiated, poorly demarcated, and associated with inflammation. Most neoplastic cells appear urothelial phenotypically, but some may show squamous metaplasia. Spontaneous urothelial carcinomas are uncommon in laboratory animals; however, these carcinomas have been induced by a wide variety of genotoxic chemicals such as the aromatic amines, nitrofurans, nitroureas, and cyclophosphamide. Urothelial carcinomas have been observed after long exposures to bladder calculi or other implanted materials due to increased cell proliferation.

Differential diagnoses: **Urinary bladder adenocarcinoma**; **Urinary bladder carcinosarcoma**; **Urinary bladder squamous cell carcinoma**.

Synonym(s): **Transitional cell carcinoma**; **urinary bladder carcinoma**.

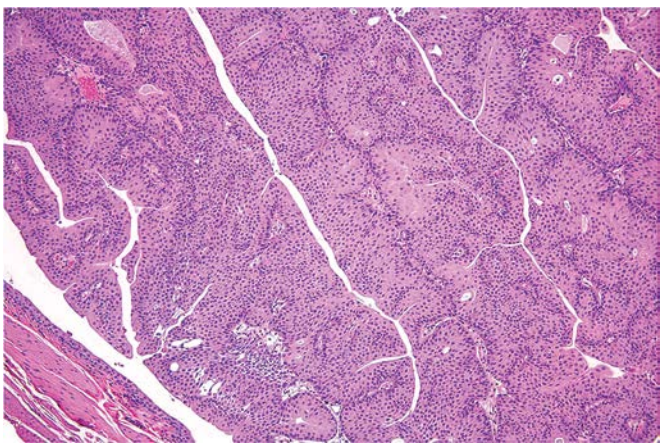


FIGURE 15 Urothelial cell carcinoma, rat urinary bladder, H&E. (Reproduced with permission of Society of Toxicology from Frazier, K. et al. 2012. *J Toxicol Pathol* 40:14S–86S.)

Reference

Frazier, K. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse urinary system. *J Toxicol Pathol* 40:14S–86S.

Links

https://www.ncbi.nlm.nih.gov/pubmed/22637735
https://www.toxpath.org/inhand.asp#pubg

Urothelial cell hyperplasia, see the preferred term **Urothelial hyperplasia**.

Urothelial hyperplasia is a nonneoplastic but potentially preneoplastic process representing an increased number of urothelial lining cells. Urothelial hyperplasia is a common response to a number of conditions including xenobiotic exposure, inflammation due to infection, mechanical trauma from calculi, or chemically induced papillary necrosis. Hyperplasia may be focal, multifocal, or diffuse. Hyperplasia may also be classified as simple, papillary, or nodular. Simple hyperplasia is generally an initial cellular response that contains normal

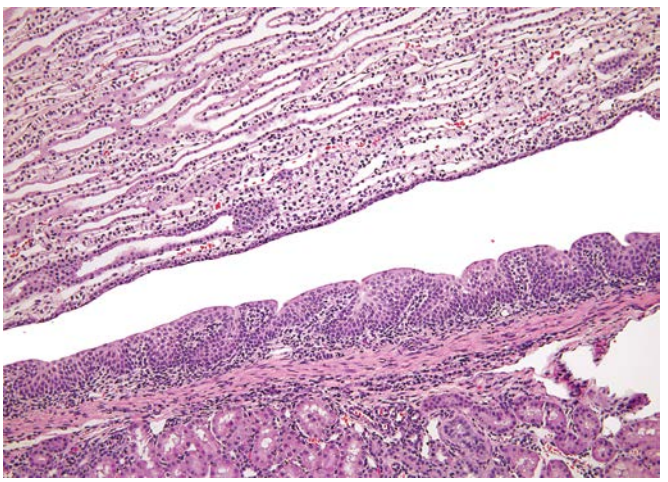


FIGURE 16 Urothelium hyperplasia, kidney pelvis, rat, H&E.

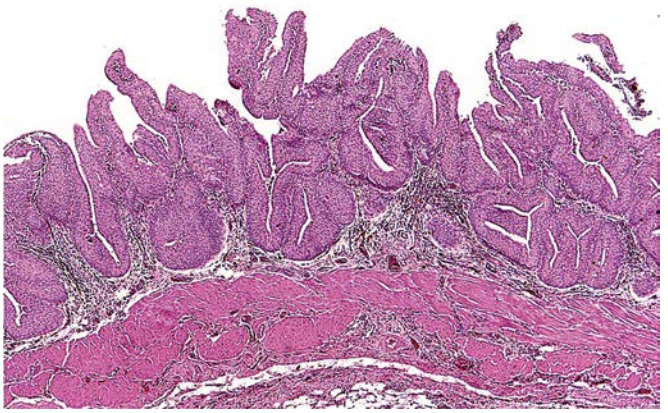


FIGURE 17 Urothelium hyperplasia, rat urinary bladder, H&E. (Reproduced with permission of Society of Toxicology from Frazier, K. et al. 2012. *J Toxicol Pathol* 40:14S–86S.)

to slightly pleomorphic cells, while papillary or nodular hyperplasia are more extensive forms of hyperplasia that may exhibit cellular atypia. Papillary hyperplasia is characterized by a folded urothelium that has delicate projections into the bladder lumen. In severe cases of papillary hyperplasia, one must differentiate the finding from papillary neoplasia. However, the nature of the hyperplastic urothelium is that normally observed with the ordered uniformity typical of transitional cells, but without pleomorphism. Nodular hyperplasia can either be visualized as exophytic or endophytic growths of hyperplastic urothelial cells into the lamina propria, but not through the basement membrane. In addition, squamous or glandular metaplasia (or mixtures of both) may be observed in hyperplastic lesions. Urothelial hyperplasia by nature should be reversible and return to normal when the initiating agent is removed.

Synonym(s): **Urothelial cell hyperplasia**.

Reference

Frazier, K. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse urinary system. *J Toxicol Pathol* 40:14S–86S.

Link

https://www.ncbi.nlm.nih.gov/pubmed/22637735

Urothelial metaplasia of normal urothelium can be squamous or glandular, or mixtures of both. It may occur in both nonneoplastic and neoplastic lesions associated with a wide variety of toxic, carcinogenic, or other stimuli. In particular, squamous metaplasia may develop into squamous papillomas and carcinomas. Glandular or mixtures of metaplastic types are much more uncommon than squamous metaplasia.

Reference

Frazier, K. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse urinary system. *J Toxicol Pathol* 40:14S–86S.

Link

https://www.ncbi.nlm.nih.gov/pubmed/22637735

Wilms tumor is the most commonly used term for nephroblastoma in humans. See the preferred term **Nephroblastoma**.



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Appendix 3: Mini-Atlas of Organ System Anatomy and Histology

Organ System Teams

BONE, MUSCLE, AND TOOTH

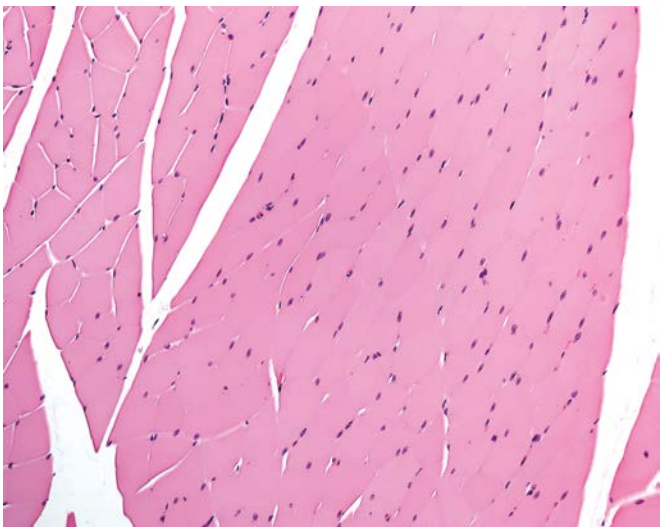


FIGURE 1 Section of normal skeletal muscle from a mouse. Cross-sections of individual myofibers with peripheral nuclei. H&E.

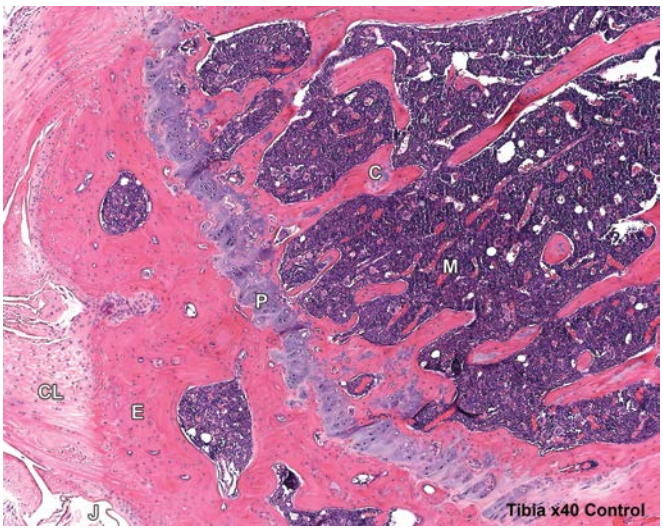


FIGURE 3 Proximal tibia from a mouse with joint cavity (J), cruciate ligaments (CL), epiphysis (E), physis (P), and metaphysis (M). Cancellous (C) or trabecular bone is labeled in the metaphysis. Decalcified bone, H&E.

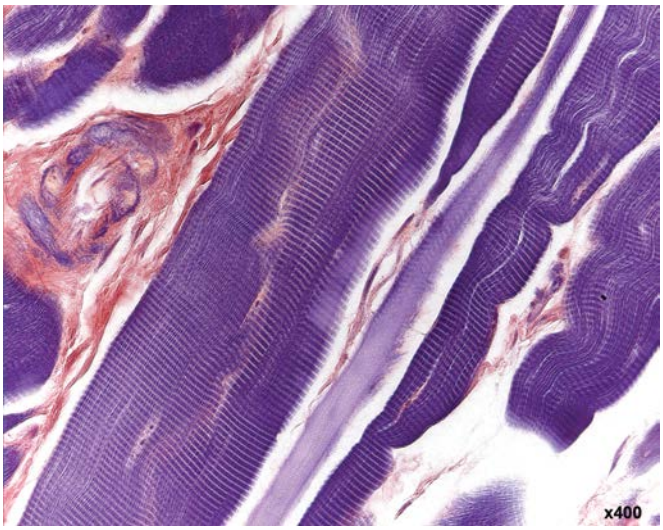


FIGURE 2 Longitudinal section of normal skeletal muscle from a mouse. Muscle fibers have been stained with phosphotungstic acid hematoxylin (PTAH) which highlights myofiber striations.

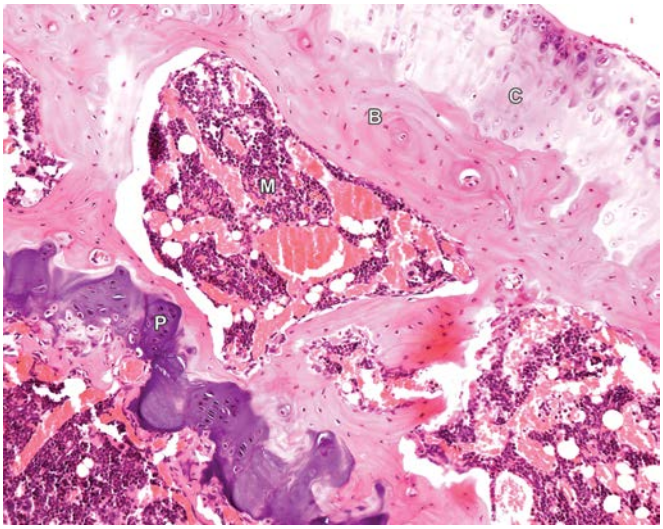


FIGURE 4 Femur from a mouse showing articular cartilage (C), subchondral bone (B), and physis (P). The physis consists of multiple zones to include the reserve, proliferative, hypertrophic and calcification zones. Bone marrow containing normal hematopoietic tissue is present (M). Decalcified bone, H&E.

A3

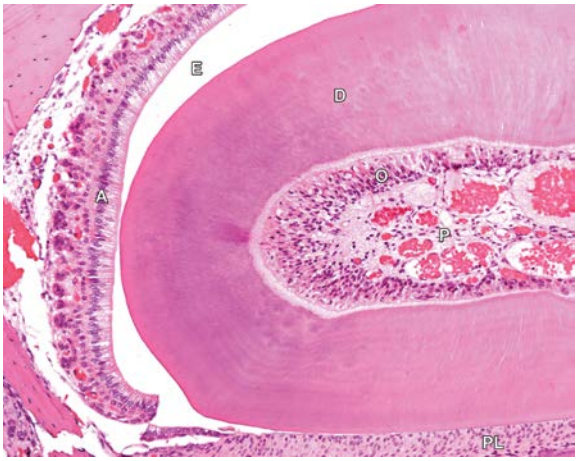


FIGURE 5 Continuously erupting tooth from a mouse. A layer of ameloblasts (A) borders the space where enamel (E) is normally present but is lost during processing. Dentin (D) consists of matrix produced by odontoblasts (O). The pulp cavity contains multiple blood vessels (P). Periodontal ligament (PL) is noted at the edge of the section. Decalcified tooth, H&E.

CARDIOVASCULAR SYSTEM

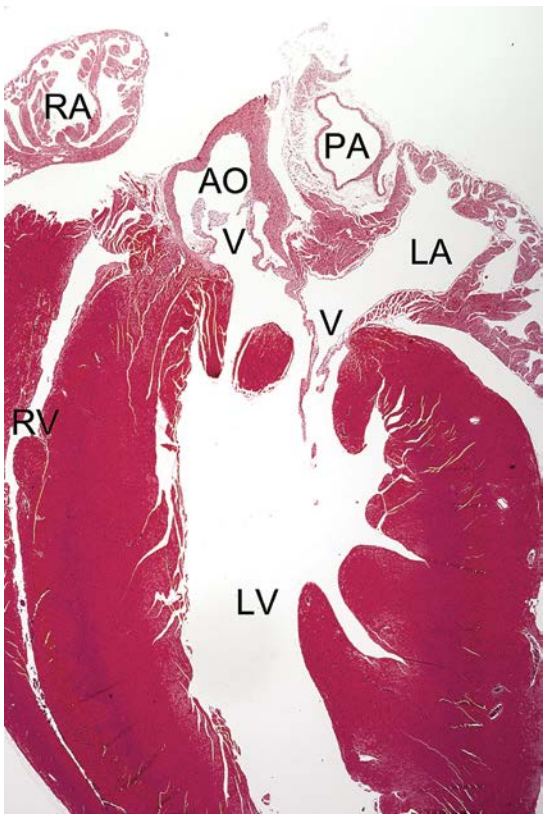


FIGURE 1 Mouse heart; H&E, normal anatomy. Oxygenated blood from the lungs flows from the left atrium (LA) through the left AV valve (V) into the left ventricle (LV), then through the aortic valve (V) into the aorta (AO), then to the general circulation. Deoxygenated blood from the general circulation returns to the right atrium (RA), through the right AV valve (not shown) into the right ventricle (RV), then through the pulmonary valve (not shown) into the pulmonary artery (PA), then to the lungs.



FIGURE 2 Rat tongue; H&E, normal anatomy. Artery (A): note thich = k muscular wall. Vein (V): note thin wall. Red dots in both vessels are red blood cells.

ENDOCRINE GLANDS

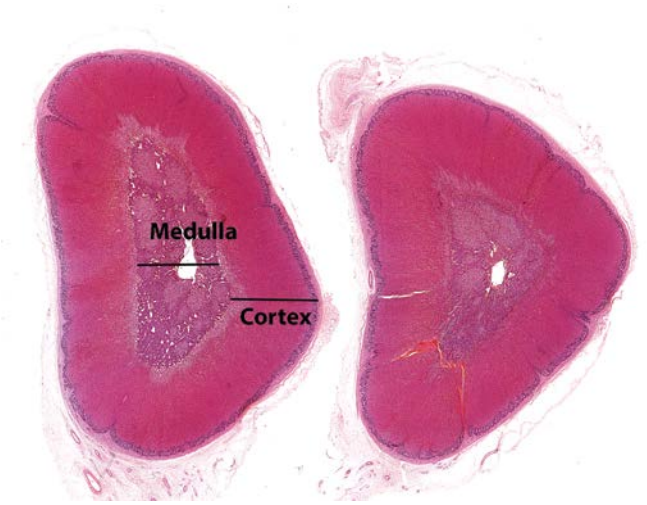


FIGURE 1 Adrenal gland of the mini pig. H&E.

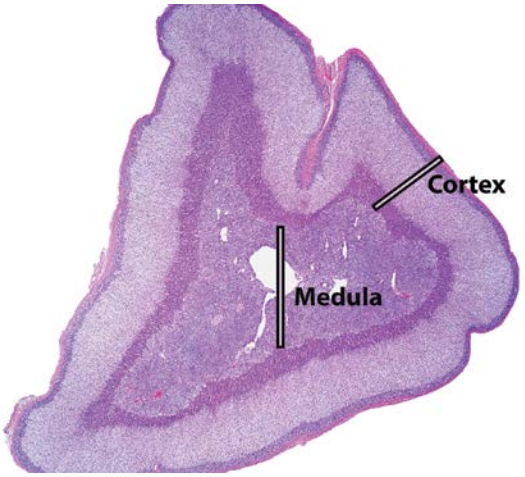


FIGURE 2 Adrenal gland, cynomolgus monkey. H&E.

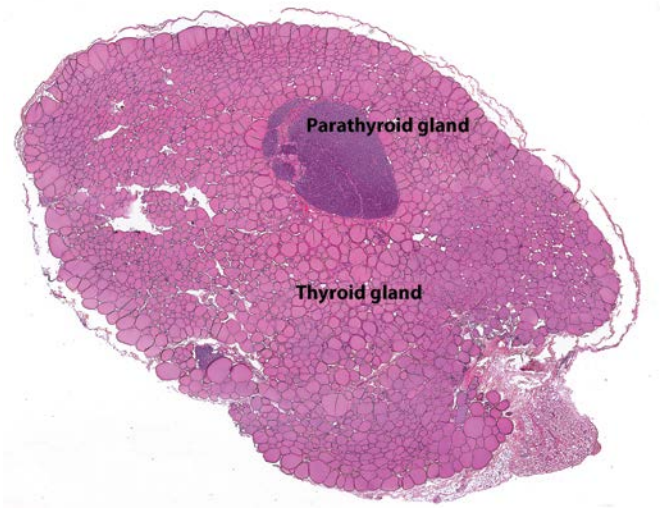


FIGURE 5 Thyroid gland and (internal) parathyroid gland of the cynomolgus monkey. H&E.

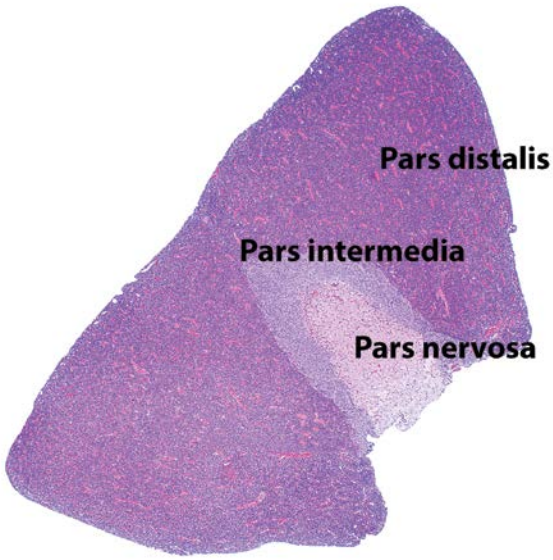


FIGURE 3 Pituitary gland, Sprague Dawley rat. H&E.

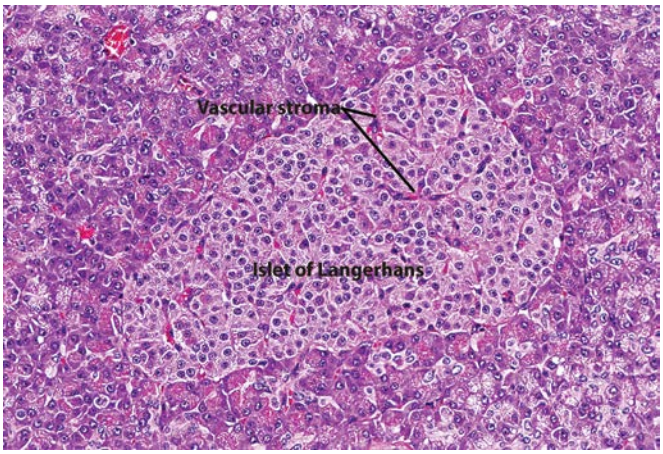


FIGURE 6 Endocrine pancreas, islet of Langerhans, cynomolgus monkey. H&E.

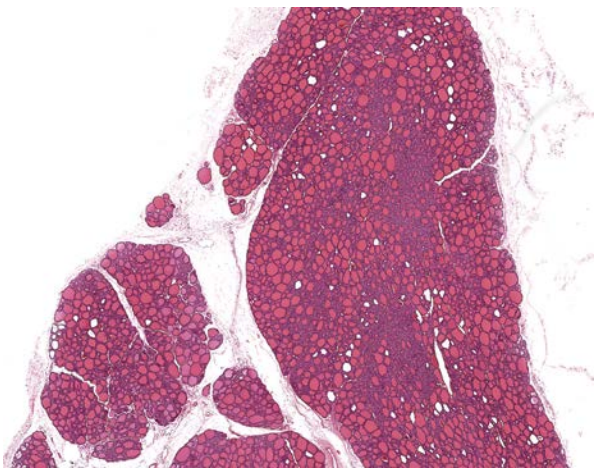


FIGURE 4 Thyroid gland, minipig. H&E.

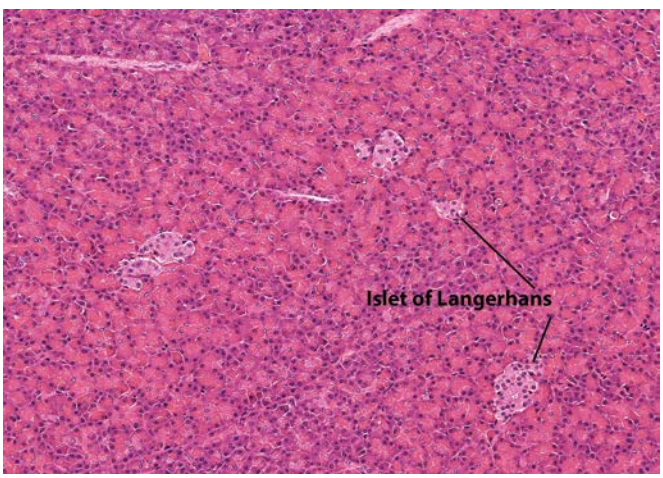


FIGURE 7 Endocrine pancreas, islet of Langerhans, minipig. H&E.

A3

GASTROINTESTINAL TRACT

The gastrointestinal tract (GIT) is composed of a tube fashioned into multiple specialized chambers and compartments that extend from oral cavity to anus. Each region contains specialized cells which produce specific chemicals/enzyme and fluids and an important immunological barrier to provide the necessary environment for digestion, absorption, metabolism, and excretion. The compartments are variably supported by the skeleton, viscera, abdominal wall, and mesentery. Its function is driven by multiple neurophysiological mechanisms, most notably that of peristalsis, which ensures the normal orad-to-aborad transit and mixing of digesta. For toxicologic pathologists, examination typically begins with the tongue as part of the upper GIT and oral cavity. The esophagus, stomach, and small and large intestines then form the other key anatomical elements. The microbiome is essential for any normal healthy mammal, and the largest part of it (by number and volume) is to be found with the GIT. Toxicologic pathology has only just started to explore the impact of xenobiotics on the resident microbiological fauna, but it will likely become an important area of consideration.

Anus is the distal opening of the gastrointestinal tract. The anus joins the rectum at the squamocolumnar junction, extending beyond the peritoneal boundary as the anal canal, which is lined by a squamous epithelium that becomes a keratinized perianal skin (perineum) at its terminus. It may be collected along with a portion of rectum and evaluated as an example of mucocutaneous transition. Internal and external sphincter muscles control the opening of the anal canal under both sympathetic and parasympathetic innervation. In dogs (and other carnivores), paired anal glands, also referred to as anal sacs or paranal sinuses, are between the sphincter muscles. These sinuses contain secretions from associated sebaceous and apocrine glands and may become impacted and inflamed (anal sacculitis). In older dogs, anal glands are a site for apocrine adenocarcinoma. In rodents, the anal tissues may be a location of melanomas in Fischer-344/N rats. In humans, anal cancer, specifically anal intraepithelial neoplasia progressing to squamous cells carcinoma, is associated with human papilloma virus (HPV) infection. Vaccination against the HPV types implicated in anal cancer may provide protection from neoplastic progression, as well as decreasing the occurrence of HPV-associated anal warts.

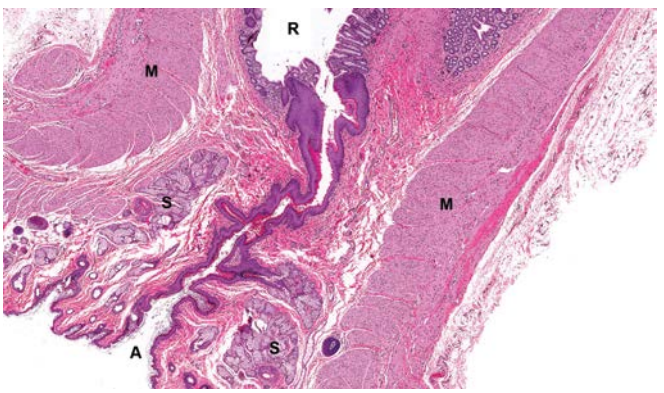


FIGURE 1 Anus, rat. H&E. 6.2×. R = rectum, A = anus, M = muscular wall, S = modified sebaceous glands.

Appendix is a blind-ending extension from the terminus of the cecum. The appendix was originally identified only in apes and humans, and was considered a vestigial, evolutionary remnant of no particular function. Recent evidence suggests this structure is present in a variety of mammals including Old and New World monkeys, apes, lemurs, rabbits, and rodents. Mice and rats are generally considered to lack a distinct cecal diverticulum; however, anatomical survey of laboratory mice found that some individuals in C3H, BALB/c, and C57/BL6 strains do indeed possess a distinct cecal appendix, whereas other individuals lack any distinction between the apex and body of the cecum. Irrespective of gross anatomical details, the terminal cecal GALT, also called the cecal patch, is recognized as the murine equivalent of the human appendix and has been employed in models of appendicitis. The terminal cecum/appendix is an important area of immunological interaction, implicated in a unique interplay between the mucosal immune system and the intestinal bacterial population, with a role in the development, signaling, and maintenance of the intestinal lymphoid tissue. In this capacity, the appendix has been implicated, in part, with the etiology of ulcerative colitis.

Brunner's gland are present primarily in the submucosa, but also in the lamina propria of the duodenum, adjacent to the pyloric-duodenal junction and until the entry of pancreatic duct. Brunner's glands occur from the proximal to mid-region of the duodenum in dogs. They are unique to mammalian species and consist of serous, mucus, and endocrine cells. These glands produce a bicarbonate-rich mucus secretion, which exerts a physiologic anti-acid function by coating the duodenal epithelium to protect it from the acid chyme of the stomach. They also secrete pepsinogen and epidermal growth factor (urogastrone) in response to the presence of acids in the duodenum which inhibit gastric acid secretion. Brunner's gland secretions coat the intestinal walls and provide an alkaline condition for the intestinal enzymes to be functional, thus enabling absorption to take place. Epidermal growth factor produced by Brunner's glands plays an important role in the repair and healing of duodenal ulcers. Scattered endocrine cells in Brunner's glands of some species (not rats) secrete somatostatin, gastrin-cholecystokinin, and peptide YY. Brunner's glands are absent in Pdx1 (pancreatic and duodenal homeobox 1) protein null mice (known as insulin promoter factor 1 [Ipf1] in humans).

Synonym(s): **Duodenal glands**; **submucosal glands**.

Cecum is the first segment of large intestine and comprised of mucosa, submucosa, muscularis mucosa, and serosa, as are present in other regions of the small and large intestine. The cecum in dog and other carnivorous species is a small diverticulum at the junction of the ileum and colon and is curved, kidney-shaped, blind-ending pouch in rodents. The cecum is the site of absorption of calcium, magnesium, water, electrolytes, vitamin K, and fatty acids.

Colon is the second segment (cecum is the first segment; see **Cecum**) of the large intestine which functions in absorption of water and nutrients to result in the formation of feces. In most laboratory animals, the colon has an ascending section, a short transverse section, and a descending section leading to the rectum; however, there are some species differences. The colon in humans, monkeys, and pigs are sacculated with ascending, transverse, descending, and sigmoid sections. Rat and dog colon is not sacculated. Guinea pigs have a complex colon with its enlarged proximal colon. The colon is devoid of villi, but mucosa is arranged in transverse or longitudinal folds. The mucosa is lined predominantly by mucus-secreting goblet cells, absorptive cells with sparse distribution of enterochromaffin cells. Goblet cells are abundant in the colonic mucosa and provide mucus secretion to the lumen contents. Aggregates of lymphoid cells, termed "lymphoglandular complexes" (part of the gut-associated lymphoid tissue [GALT] complex), are found in the mucosa and submucosa of the colon. The colon contains the largest population of microorganisms (producing vitamins B and K) in the gastrointestinal tract and is the major site of production and absorption of volatile fatty acids in the rat, dog, rabbit, pig, and human. The submucosa, tunica muscularis, and serosa of the large intestine are similar to those of the small intestine, containing a mixture primarily of lymphocytes, plasma cell, and macrophages with capillaries.

Crypts form the mucosa of the small intestine that extends down into the lamina propria along with villi which extend into the lumen. The stem cells that replenish the epithelial cells of the villi are found in the crypts. The remainder of the crypt is composed of proliferating epithelial cells which either migrate up the villi as they differentiate into absorptive cells with microvilli or goblet cells (see **Goblet cell**), or remain in the crypt and differentiate into Paneth cells (see **Paneth cell**). The enterochromaffin cells (see **Enterochromaffin cell**) are scattered in crypts.

Synonym(s): **Intestinal gland**; **intestinal crypt**.

Duodenum is the first part of small intestine. The function of the duodenum is to digest and absorb the nutrients from chyme entering from the pylorus of the stomach and to complete the chemical digestion process with addition of pancreatic enzymes, bile acids, and bile salts. Histologically, duodenum is made up of four distinct concentric layers (mucosa, submucosa, tunica muscularis, and the adventitia, or serosa). The mucosa has three components (lining epithelium, an underlying lamina propria consisting of a vascularized loose connective tissue, and a thin layer of smooth muscle, the muscularis mucosae). The mucosa of the duodenum is composed of crypts of Lieberkühn (see **Crypt**) and villi which extend into the lumen. The base of the crypt is lined by mitotically active stem cells, and the remainder of the crypt has proliferating epithelial cells which either migrate up the villi to differentiate into absorptive cells with microvilli or goblet cells (see **Goblet cell**) or remain in the crypt to differentiate into Paneth cells (see **Paneth cell**). The villous epithelium is composed of the main absorptive cells (tall columnar cells with surface microvilli), goblet cells, and few globular leukocytes and enterochromaffin cells. Villi in the duodenum are taller than those in jejunum and ileum. The lamina propria contains variable numbers of lymphocytes, macrophages, plasma cells, eosinophils, mast cells, and occasional intraepithelial lymphocytes. Paneth cells have an exocrine serous morphology and produce antimicrobial peptides. Brunner's glands (see **Brunner's glands**) are present in the submucosa immediately following the pyloric-duodenal junction until the entry of pancreatic duct.

Enteric nervous system provides intrinsic innervation of the gastrointestinal (GI) tract and consists of various types of neurons and glial cells distributed in two intramuscular plexuses that extend along the entire length of the GI tract to control motor functions, local blood flow, mucosal transport, and secretions, and modulate immune and endocrine functions. Enteric neurons and glial cells are embryologically derived from the neural crest. The enteric nervous system is the largest and most complex division of the peripheral and autonomic nervous systems, and consists of an interconnected network of neurons and glial cells grouped into two major plexuses of ganglia: the myenteric (Auerbach's) plexus; and the submucosal (Meissner's) plexus, and contains full reflex circuits, including sensory neurons, interneurons, and motor neurons, which control muscle activity, transmucosal fluid fluxes, local blood flow, and other functions. The myenteric plexus extends from the upper esophagus to the internal anal sphincter and includes the myenteric interstitial cells of Cajal that serve as a pacemaker and which create the bioelectrical slow wave potential that leads to contraction of the smooth muscle. They are also implicated in the formation of GI stromal tumors of humans and rats. The submucosal plexus is not present in the esophagus, and contains only very few ganglia in the stomach, but is prominent in the small and large intestines. The enteric nervous system also makes use of more than 30 neurotransmitters, most of which are identical to the ones found in the central nervous system, such as acetylcholine, dopamine, and serotonin.

Enterochromaffin cell is an endocrine cell present more frequently in stomach and small intestine than large intestine. These cells are most often seen in the basal parts of the gastric glands of the fundus, particularly in the rat, and produce a variety of endocrine and paracrine hormones such as serotonin, histamine, and histamine-related enzymes such as histidine decarboxylase. These cells are argyrophilic in histologic sections stained with silver techniques. Enterochromaffin cells are characterized ultrastructurally by the presence of numerous rounded or oval, vesicular, electron-lucent granules frequently containing a small eccentric electron dense core. Gastrin stimulates release of histamine from enterochromaffin cells of the body mucosa, which increases acid secretion through activation of parietal cell histamine H2 receptors.

Synonym(s): **Argentaffin cell**; **APUD (amine precursor uptake and decarboxylation) cell**.

A3

Esophagus is a tube-like structure through which food passes from the pharynx to the stomach by rhythmic muscular contractions called peristalsis. The wall of the esophagus consists of mucosa, submucosa (connective tissue), two layers of muscle fibers between layers of fibrous tissue, and an outer layer of connective tissue. The mucosa consists of stratified squamous epithelium of around three layers of squamous cells. The muscle fibers of the esophagus in many mammals are striated initially, but then becomes smooth muscle in the caudal region as it joins to the stomach. In the dog, it is composed of striated muscle throughout its length, except near the junction with the stomach, where smooth muscle fibers are present. Primates have a mixture of smooth and striated muscle in the muscularis of the esophagus. Serous glands are present, especially in dogs, in the submucosa.

Goblet cells are specialized, simple columnar epithelial cells distributed throughout the intestinal mucosal epithelium. Goblet cells secrete gel-forming glycoprotein mucins as well as other components of mucous. Goblet cells are modified simple columnar cells, with apical accumulation of large mucin granules which stain a strong magenta hue when stained with PAS, outlying the "goblet" shaped secretory region. These granules exit the cell via exocytosis as well as via apocrine secretion in response to external stimuli, including microbial factors, growth factors, inflammatory cytokines, and autonomic neural pathways via expression of adrenergic and cholinergic receptors on the cell surface. Secreted mucous forms a layer, which in addition to providing lubrication, serves as a protective, bacteria-free barrier between gut contents and epithelium. In the small intestine of humans, this mucous is unattached to the underlying epithelium and forma a monolayer, whereas in the large intestine it forms a bi-layered gel, with the thicker inner layer providing a bacteria-free environment and the luminal layer harboring gut microflora. Goblet cells are found in increasing numbers aborally: they are sparse in the duodenum, becoming progressively more numerous in the colon.

Gut-associated lymphoid tissue/mucosa-associated lymphoid tissue (GALT/MALT) are general terms describing the gastrointestinal collection of organized, mucosa-associated B-cell follicles and their overlying, specialized epithelium (M-cell epithelium), and larger intestinal lymphoid aggregates which are the origin of cells that traffic to areas where they effect mucosal immunity (i.e., by producing IgA antibodies). This lymphoid tissue is commonly referred to as Peyer's patches (PP) in the small intestine and isolated lymphoid aggregates or follicles (ILFs) in the large intestine (much less frequently in the small intestine). In most species the PP (GALT) are concentrated into the ileum; however, in mice the GALT tissue is more evenly distributed along the length of the ileum and jejunum. In the GALT, gut antigens are exposed to the underlying follicles embedded in the mucosa via M-cell–containing follicle-associated epithelium. Once exposed, antigen presentation and T/B-cell stimulation occurs, whereby they become memory and effector cells and migrate via the blood to specific sites (the gut lamina propria, for example) via chemokine stimulation and vascular adhesion molecule specificity. Once localized, these immune cells have niche-specific markers and activity. The lamina propria of the intestine in humans, for example, contains few B lymphocytes but many IgA and IgM plasmablasts and plasma cells. The distribution and composition of GALT varies considerably by species, age, and local intestinal morphology (normal or presence of infection/inflammation). The primate appendix and avian bursa of Fabricius are also considered part of the GALT complex. The large intestine of pigs contains lymphoglandular complexes where the glands of the intestine penetrate the surrounding lymphoid aggregates. In dogs, ruminants, and pigs, the PP are large and continuous along the distal small intestine, and comprise the primary lymphoid tissue responsible for antigen-independent B-cell development. Other GALT-like elements include lymphocyte-filled villi in the small intestine rats and humans, and cryptopatches in the small intestine of mice. Reptiles and fish do not have PP, rather the gut immune system is composed of leukocytes scattered in the epithelium along with occasional non-organized lymphoid aggregates.

Ileocecocolic junction (ICC) is the transition between the small (distal ileum) and large intestine. In some species, this transition is more accurately described as ileocecal (rodents, rabbits, and humans), ileocolic (dogs), or ileocecocolic (swine), depending on the point of convergence of these three anatomic structures. Functionally, this junction acts as a sphincter or valve, allowing intermittent and coordinated movement of chyme into the large intestine, and preventing reflux from the large intestine back into the ileum. In zebrafish, no stomach, small intestine, or large intestine can be distinguished; however, epithelial and goblet cell differences in morphology or number suggest functional differentiation along the tract. In rodents, the cecum is sensitive to antibacterial effects, becoming dilated due to treatment-related dysbiosis. In mice, clinafloxacin treatment has led to dilation, torsion, and rupture at the ileocecocolic junction. In hamsters, natural infection with *Helicobacter* spp. has been linked to inflammation, hyperplasia, and dysplasia at the ileocecocolic junction, and hamsters are proposed as a natural model of *Helicobacter*-associated inflammatory bowel disease (IBD) and possibly neoplasia. In dogs, intussusception is the most common reason for surgical resection of the ileocolic junction, while in older nonhuman primates this region is associated with obstruction secondary to adenocarcinoma formation.

Ileum is the terminal section of the small intestine, transitioning continuously from the jejunum and opening to the cecum at the ileocecal (or ileocolic) valve, which serves to prevent reflux from the large intestine. The ileum is attached to the cecum for some portion of its length by the ileocecal fold, in addition to its mesenteric attachment (distinguishing it grossly from the jejunum, which only has a mesenteric attachment). Histologically, the jejunum and ileum have a similar structure, with an absorptive, villus/crypt mucosa; however, the villi become shorter in the ileum, and goblet cell numbers increase moving distally. The ileum is an important site for bile salts and vitamin B_{12}; however, its absorptive role is less than in the duodenum and jejunum, hence the shorter villi, diminished relative surface

area, and lower levels of brush-border enzymes compared to the rest of the small intestine. Both the jejunum and ileum contain PP (GALT) embedded along the antimesenteric aspect within the submucosa and mucosa. In mice, this GALT tissue is evenly distributed along the length of the ileum and jejunum, whereas in other species it tends to be more prominent in the ileum. Villar epithelial cells originate from crypt stem cells, with a turnover rate from crypt to villus tip that varies between species and is modified by factors such as intestinal microbiota, diet, drug administration, circulatory disturbance, and so forth. Mice and rats have been recorded with a 2- to 3-day turnover rate compared to 3–6 days in humans. The crypts of dogs and pigs do not contain Paneth cells, whereas humans, nonhuman primates, and rodents do. While rich in detoxifying systems such as glucuronosyltransferase and cytochrome P450s, the enzyme concentration in the ileum is typically lower than in the duodenum and jejunum. In humans, the ileum (as well as stomach and colon) does not produce enterokinase.

Intestinal villi (singular: villus) are small, finger-like projections that extend into the lumen of the small intestine. Each villus is approximately 0.5–1.6 mm in length (in humans) and has many microvilli projecting from the surface of the epithelium (enterocytes) which collectively form the striated or brush border. Villi increase the internal surface area of the intestine, making available a greater area for absorption. An increased absorptive area is important, as digested nutrients (including monosaccharide and amino acids) pass into the semipermeable villi through diffusion, which is effective only at short distances. Increased surface area (contact with the lumen contents) decreases the average distance needed for travel (diffusion) by intraluminal nutrient molecules for absorption. The villi are well vascularized for transport of absorbed nutrients into the blood and/or lymphatics.

Intestine is the lower part of the alimentary canal from the end of the stomach to the anus. The word derives from the Latin *intestina*, meaning "internal or inward." The intestines are further divided as small intestine (duodenum, jejunum, ileum), and large intestine (cecum, colon, rectum), each with different structural and functional attributes.



FIGURE 2 Gastrointestinal tract, rat. S = stomach, SI = small intestine, C = cecum, LI = large intestine, M = mesentery. (Photograph courtesy of Kenard Lee Jr.)

Jejunum is the midportion of the small intestine, transitioning continuously from the duodenum proximally to the ileum distally. The jejunum and ileum have similar morphologic features, however jejunal villi are longer and narrower as compared to those in the ileum. The lymphatic drainage from jejunum is to the middle mesenteric lymph nodes, although individual variations exist whereby there may be overlap between intestinal segments and draining lymph nodes. The jejunum's principle function is to absorb nutrients, and epithelial enterocytes (absorptive cells with many surface microvilli) comprise the principle epithelium lining the villi. This results in a large surface area for absorption. It has been estimated the mucosal surface area of the human small intestine is ~30–40 m^2. Apart from its crucial function in digestion and absorption, the epithelium of the small intestine mucosa must maintain a barrier to the intestinal lumen contents while serving as a site for antigen sampling, uptake, and presentation to the mucosal immune system.

Lacteal is a specialized lymphatic vessel located in the center of each villus in the small intestine that functions in immune surveillance and the transport dietary lipid in the form of chylomicrons from the intestine to the blood. Lacteals form a submucosal network in the small intestine which ramify and flow into larger collecting lymphatic vessels leading to regional lymph nodes. With respect to immune function, disruption of intestinal lymphatic vasculature in mice results in failure of immune surveillance and death. From the lymph nodes, larger lymphatic ducts converge at the thoracic duct and empty into the subclavian vein, permitting systemic circulation of chylomicrons and immune cells prior to arrival of lymphatic duct contents in the liver. Bypassing the liver from venous blood from small intestine has made this lymphatic route a potential means for drug delivery, however much has yet to be understood in regard to the mechanisms of uptake across the lacteal (lymphatic) endothelium. Though often considered a passive process, intravital microscopy has tracked uptake across the enterocyte and entry into the lacteals, which are actively contracted by surrounding villus smooth muscle controlled by the autonomic nervous system. Molecular pathways of lacteal function are also under investigation; for example, adult lacteals appear to reside in a constantly regenerative state, under the control of NOTCH signaling.

Lamina propria is a layer of loose reticular connective tissue matrix containing fibroblasts, leukocytes, and other immune cells, glands secreting into the lumen, lymphoid cell aggregates, lymphatics, and capillaries. The intestinal mucosa covers the luminal surface of the lamina propria and comprises an epithelial layer supported and anchored to the lamina propria. The deeper surface of the laminal propria is bordered by the muscularis mucosae that separate the lamina propria from the submucosa and tunica muscularis.

Large intestine is the part of the gastrointestinal tract between the end of the small intestine and the anus. The mucosa of the large intestine is specialized for maximizing ion and water absorption and for the condensation of digesta into fecal

matter, where it is stored before being eliminated. The designation "large" is a reflection of the increased luminal diameter compared to the small intestine and not the length, which is often shorter than the small intestine.

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Mucosa comprises the innermost layer of the intestine and consists of an epithelium on a basal lamina which anchors it the underlying matrix of loose connective tissue. This matrix (lamina propria) contains cells and structures specific to each region of the tract and may be bounded by a thin muscle layer (muscularis mucosa). Collectively, these elements comprise the mucosa, although different intestinal segments may not have all layers; the proximal oral cavity for example does not have a muscularis mucosa where the submucosa abuts underlying bone. Distal from the oral cavity, the mucosa yields to the next layer of the intestinal tube: the submucosa, surrounded by a muscularis layer, and finally an adventitia or serosa comprising the outermost surface. The type of mucosal epithelium and contents of the lamina propria vary by location and species. For example, the mucosa of the small intestine forms finger-like projections known as villi, which extend into the lumen and increase the surface area, while the surface is more flattened in the large intestine. Between species, the esophageal epithelium of swine, equids, ruminants, rats, and mice is keratinized, while that of carnivores and humans is not. Similarly, the intestinal epithelium of cats, dogs, and pigs does not contain Paneth cells, whereas the epithelium of most other species does.

Oral cavity (mouth) consists of two regions, the vestibule and the oral cavity proper. The vestibule is the area between the teeth, lips, and cheeks. The oral cavity is bounded at the sides and in front by the alveolar process (containing the teeth) and at the back by the isthmus of the fauces. Its dorsal aspect (roof) is formed by hard palate and soft palate, while the ventral portion (floor) is formed by the mylohyoid muscles and tongue. Mucous membrane covers the surfaces of the oral cavity borders/structures. Secretions into the oral cavity are from the submaxillary and sublingual salivary glands and, to a lesser degree, from the glands in the tongue and mucous membranes.

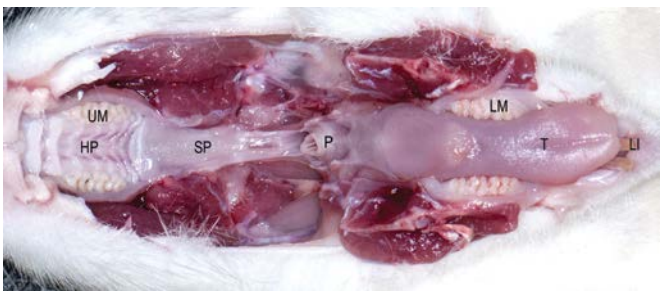


FIGURE 3 Oral cavity, rat, disarticulated at temporomandibular joint. T = tongue, HP = hard palate, SP = soft palate, P = pharynx, UM = upper molars, LM = lower molars, LI = lower incisors. (Photograph courtesy of Kenard Lee Jr.)

Oxyntic cells are specialized epithelial cells that secrete hydrochloric acid (HCl) and intrinsic factor. These cells are located in the gastric glands found in the lining of the fundus in the body of the stomach. They contain an extensive secretory network (canaliculi) from which the HCl is secreted by active transport into the stomach. The enzyme hydrogen potassium ATPase (H^+/K^+ ATPase) is unique to these cells and transports the H^+ against a concentration gradient of about 3 million to 1, which is the steepest ion gradient in the human body. These cells are primarily regulated via histamine, acetylcholine, and gastrin signaling from both central and local modulators.

Synonym(s): **Parietal cells**; **delomorphous cells**.

Paneth cells are specialized epithelial cells found in the mucous membrane lining and crypts of the small intestine, with a few also present in the cecum and appendix. The crypts of dogs and pigs do not contain Paneth cells, whereas humans, nonhuman primates, and rodents do. In the mouse, Paneth cells are especially prominent in the jejunum. They are identified microscopically by their location just below the intestinal stem cells in the intestinal glands (crypts of Lieberkühn) and presence of the large eosinophilic refractile granules that fill most of their cytoplasm. These granules consist of several compounds that are known to be important in antimicrobial effects, immunity, and host-defense such as α-defensins, lysozymes, and secretory phospholipase A_2 ($sPLA_2$). When exposed to bacteria or bacterial antigens, Paneth cells secrete these compounds into the lumen of the intestinal gland, thereby contributing to maintenance of the gastrointestinal barrier.

Synonym(s): **Davidoff's cell**.

Pericryptal fibroblast (sheath) is a distinct and highly organized system of fibroblasts, collagen, and mucopolysaccharide ground substance in the zone immediately subjacent to the epithelium of the intestine. The PCFS forms a virtually complete layer around the small intestinal and colonic crypt.

Pharynx is the posterior portion of the oral cavity lumen that includes the opening of the esophagus and larynx. The pharynx is similar across animal species. In larger mammals, the pharynx is part of the digestive system and also of the conducting zone of the respiratory system, and is conventionally divided into three sections: the nasopharynx, oropharynx, and laryngopharynx.

Rectum is the final straight portion of the large intestine in most mammals. In some laboratory animal species (mice and rats) the rectum and colon are morphologically similar, differentiated by the presence (rectum) or absence (colon) of perineum. In many mammals, the rectum is followed by the anal canal, before the gastrointestinal tract terminates at the anus.

Salivary glands in mammals are exocrine glands that produce saliva. Saliva is primarily composed of water and contains mucin, amylase, electrolytes, lysozymes, and growth factors (epidermal growth factor [EGF]; nerve growth factor [NGF]). The functions of the salivary gland secretions include lubrication of food to aid in swallowing, control of pH in the oral cavity, modulating oral microbial flora, and initiation of

starch digestion by amylase production. The secretory activity is under sympathetic and parasympathetic control. The multiple nerve control for the salivary glands includes the salivary nuclei of the medulla oblongata, the appetite center of the hypothalamus, and reflex pathways of the upper digestive tract. Most mammals have three pairs of major salivary glands and numerous minor salivary glands in the oral cavity and tongue. The parotid salivary glands, located most ventrally, produce a serous, watery secretion. The mandibular (maxillary, submandibular) salivary glands have mixed serous and mucous acini with mixed secretion. Sexual dimorphism of mandibular salivary gland is noted in rodents, with the tall columnar epithelium-lined granular ducts being more prominent in males. This sexual dimorphism is not evident at the time of birth and develops later with sexual maturity, at about 7 weeks of age in rats and 20 days of age in the mouse. The sublingual salivary gland, which is closely associated with the mandibular salivary gland anatomically, produces predominantly mucoid secretions. In dogs, the parotid is a mixed-type salivary gland whose secretion contains both acidic and neutral mucus in contrast to the mostly neutral secretions of rodents. In primates, parotid salivary glands are serous or mixed, the mandibular salivary glands are mixed, and the sublingual salivary glands are mostly mucous type. Lingual salivary glands, which are serous and mucinous type, are minor salivary glands present at the base of the tongue.

Small intestine is the part of the gastrointestinal tract between the stomach and the large intestine. The mucosa of the small intestine is specialized for maximizing digestion and absorption of nutrients. It is highly folded to form microscopic finger-like projections (villi) which increase the surface area to increase the surface area for absorption. The mucosal lining also contains specialized cells that produce substances which help digestion and provide immune defenses and hormones to control coordination of digestive process of the intestine, gallbladder, and pancreas. The small intestine has three distinct regions—the duodenum, jejunum, and ileum. The duodenum (first part of the small intestine) begins at the termination of the stomach (pylorus) and curves around the pancreas, where it joins the jejunum. An important anatomical feature of the duodenum is the ampulla of Vater where the bile duct and pancreatic duct, controlled by sphincter of Oddi, empty their contents into the small intestine. The second segment, the jejunum, is the longest segment of the small intestine, with the third and final segment being the ileum, which is much shorter than the jejunum and similar in length to the duodenum. Although there are few distinct anatomic features to delineate between these three segments of the small intestine, they are adapted to perform specific functions. For example, the duodenum plays an important role in control of gastric emptying as well as the flow of bile duct contents into the intestine. The intestinal villi are longest in the duodenum of some species, there are Brunner's glands only at this site in the small intestine and the duodenum is also a major site for absorption of iron. The jejunum is a major site for absorption of the vitamin folic acid, and the distal ileum is the most important site for absorption for the vitamin B_{12} and bile salts. An important anatomic feature of the small intestine is also its highly integrated nervous system, which lies within the wall of the intestine (the enteric nervous system). The enteric nervous system plays a very important role in coordinating much of the functions of the small intestine, including its muscular activity of propulsion (the moving of intestinal contents).

Synonym(s): **Small bowel**.

Stomach is a muscular, dilated segment of the gastrointestinal tract. In humans and many laboratory animal species it is involved in the second phase of digestion, following mastication (chewing), and is located between the esophagus and the small intestine. It secretes digestive enzymes and gastric acid to aid in food digestion. The cardiac sphincter between the esophagus and the stomach prevents the movement of gastric contents back up the esophagus, while the pyloric sphincter controls the passage of partially digested food (chyme) from the stomach into the duodenum, where peristalsis occurs to move this through the rest of the intestines (Figure 4).

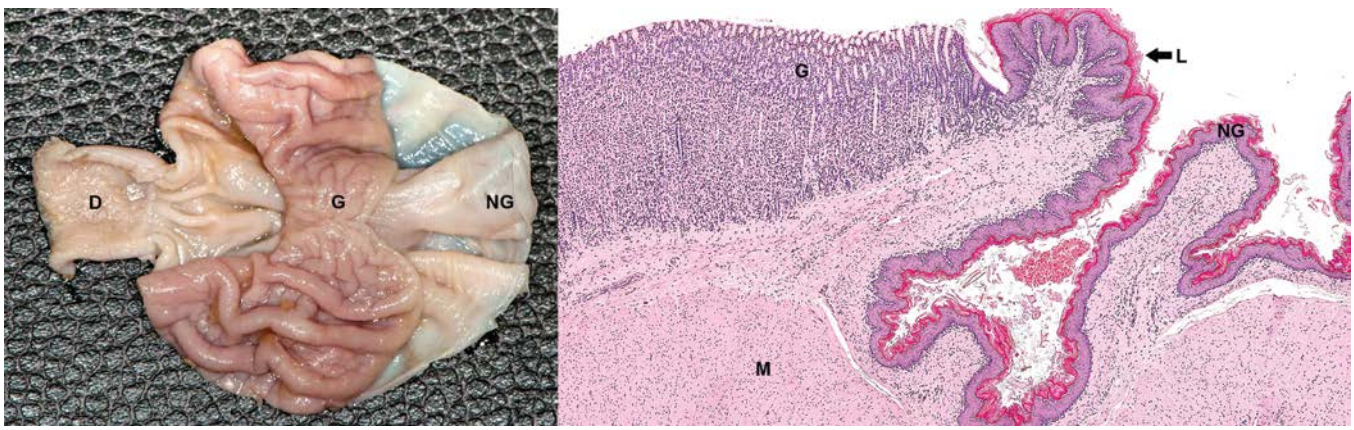


FIGURE 4 Stomach, rat. NG = nonglandular stomach, G = glandular stomach, D = duodenum. Stomach, rat. H&E. 10×. L = limiting ridge, G = glandular mucosa, NG = nonglandular mucosa, M = muscular wall. ([Left] Photograph courtesy of Kenard Lee Jr.)

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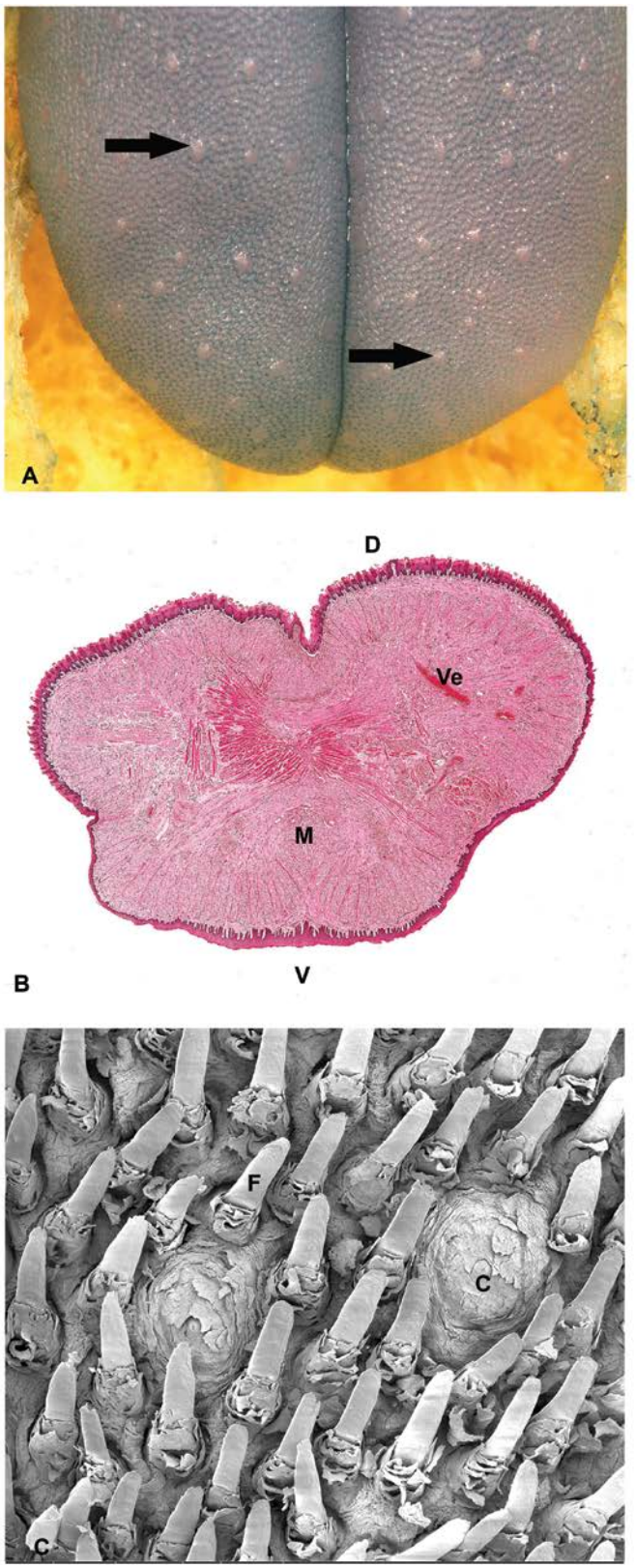


FIGURE 5 Tongue, rat. (A) Stained with blue food coloring. Arrows = taste buds. (B) Cross-section, mid-tongue. H&E. 3.2×. D = dorsal, V = ventral, M = muscle, Ve = vein. (C) Scanning electron micrograph, 500×. F = filiform papillae, C = circumvallate papillae.

Taste buds are sensory organs around papillae on the upper surface of the tongue, soft palate, upper esophagus, cheek, and epiglottis that contain the taste receptors. They are involved in detecting the five elements of taste perception: salty, sour, bitter, sweet, and umami; through the combination of these elements animals can detect "flavors." These tastes can be detected by any area of the tongue via small openings in the tongue epithelium, called taste pores, where parts of the food dissolved in saliva come into contact with the taste receptors, which are located on top of the taste receptor cells that constitute the taste buds. The taste receptor cells provide sensory responses to the gustatory areas of the brain via the seventh, ninth, and tenth cranial nerves.

Tongue is a muscular organ in the mouth of most animals that manipulates food for mastication and is used in the act of swallowing. It is the primary organ of taste in the gustatory system. The tongue's upper surface is covered in taste buds within numerous lingual papillae richly supplied with nerves and blood vessels. A major function of the tongue is for speech in humans and vocalization in other animals (Figure 5).

HEMATOPOIETIC SYSTEM

Bone Marrow

Organization

Bone marrow is localized in the adult animal in medullary cavities of bone and although present at multiple sites, it is considered to be a single system. It is variably distributed within the medullary cavity of long and flat bones and makes up approximately 3% of the body weight of adult rats. In young animals and in disease states, extramedullary hematopoiesis is present in various organs, but most notably the spleen.

Organs for evaluation are generally the sternum, femur/knee joint, and ribs. For evaluation of the bone marrow, it is recommended to examine both a smear and section.

Function

Bone marrow is the major tissue for all blood cell formation/hematopoiesis. It is also a primary lymphoid tissue and produces lymphocytes and lymphocyte precursors that further mature in the thymus or bursa equivalents for respectively T- and B-cell lineages.

Development

Hematopoietic progenitors arise during embryogenesis within the extraembryonic yolk sac. These cells form the hematopoietic stem cells (HSCs), which are the source of the cellular components of blood throughout the lifespan of the animal. This is done by self-renewal and subsequent regulated differentiation into the different cell lineages, such as erythroid, myeloid, megakaryocytic. HSCs are closely associated with blood vessels, sinusoidal endothelial cells, perivascular cells, and osteoclasts. Figure 1 depicts erythroid maturation; Figure 2 represents a normal bone marrow picture in the rat.

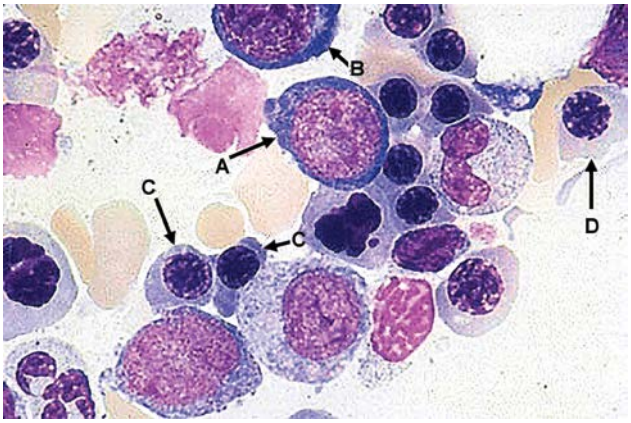


FIGURE 1 Erythroid maturation: A = rubriblast (or prorubricyte), B = basophilic rubricyte, C = polychromatophilic rubricyte, D = metarubricyte.

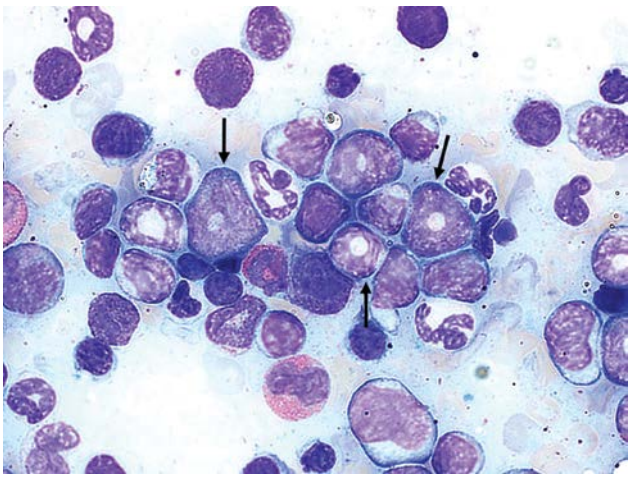


FIGURE 2 Normal bone marrow, rat. Note the ring-form neutrophils (arrows).

Microanatomy

Bone marrow is organized in microniches, hematopoietic islands, and cords, intermixed with a complex network of vascular sinuses supported by stromal cells, reticular fibers, and extracellular matrix. These form a spongiform structural network of the hematopoietic space.

Sampling and Diagnostic Considerations

Hematopoietic cellularity of bone marrow is dependent upon anatomic site, age, sex, and strain of the animal. Here concurrent controls are optimal for comparison.

Changes in bone marrow should always be interpreted together with the results of clinical pathology/hematology evaluation of peripheral blood; bone marrow is the source of peripheral blood cells and they are therefore interrelated. Also, other conditions of the animals should be considered such as inflammation, infection, and neoplasia.

LIVER, GALLBLADDER, AND EXOCRINE PANCREAS

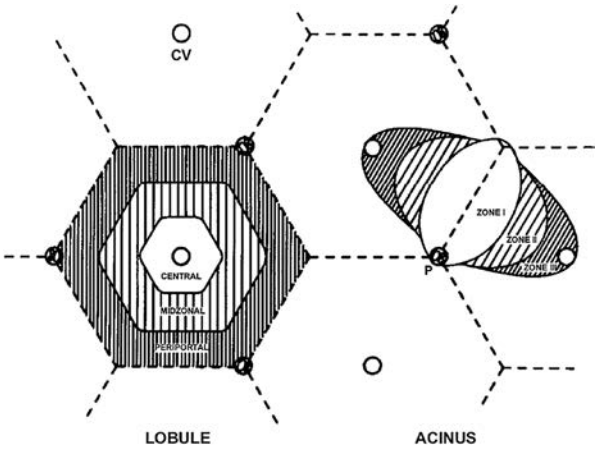


FIGURE 1 Liver lobule schematic, P = portal triad, CV = central vein. (Liver acinus zones shown for comparison.) (Reproduced with permission of Elsevier from Cattley and Cullen, 2013.)

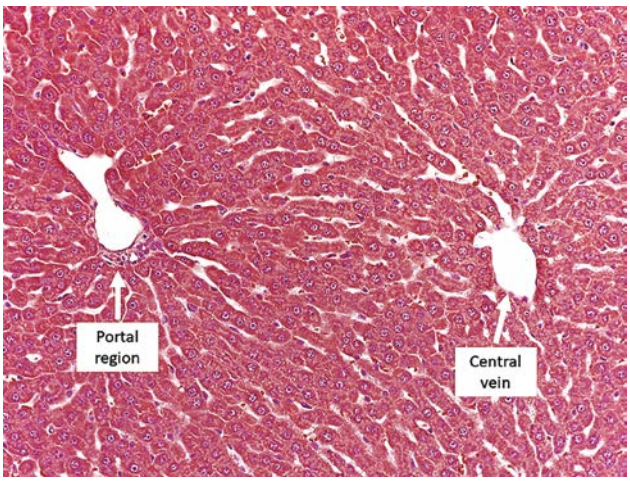


FIGURE 2 Liver lobule histology, H&E. (Figure courtesy of R. Cattley, Auburn University.)

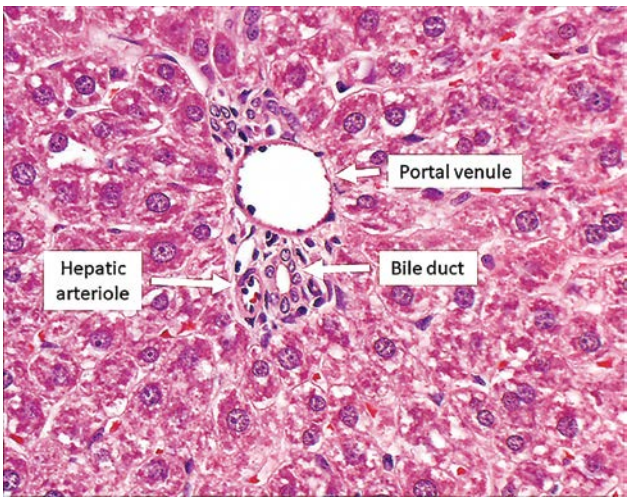


FIGURE 3 Liver portal region histology, H&E. (Figure courtesy of R. Cattley, Auburn University.)

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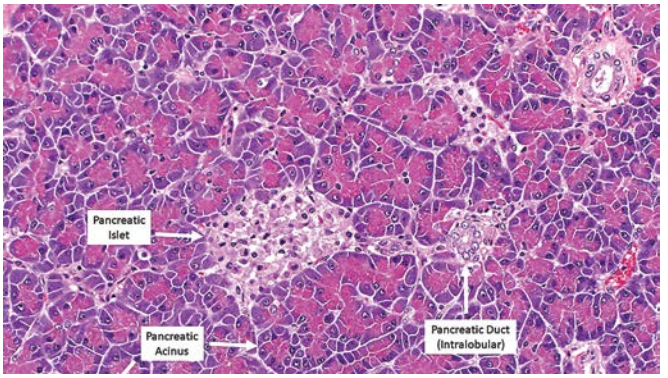


FIGURE 4 Pancreas histology, H&E. (Figure courtesy of R. Cattley, Auburn University.)

LYMPHOID SYSTEM

Normal Microanatomy

Lymphoid tissue refers to all of the tissues and organs that comprise the lymphoid system. Broadly, lymphoid tissue can be divided into primary lymphoid tissues—those where T- and B-lymphocytes originate and develop, and secondary lymphoid tissues, where T- and B-lymphocytes mature and become activated. The primary lymphoid tissues are the thymus, where T cells develop, and the bone marrow in mammals and bursa of Fabricius in birds, where B lymphocytes develop (B lymphocytes are named for the avian *b*ursa of Fabricius). Secondary lymphoid tissues are numerous and include the lymph nodes, the spleen, and all the various mucosa-associated lymphoid tissues (MALT), which are organized lymphoid tissues found in submucosal locations throughout the body. **Palatine tonsils** are large and well-developed examples of MALT in the nasooropharyngeal region. Organized lymphoid tissue around ducts (duct-associated lymphoid tissue) and in skin are functionally similar to MALT. Pathogens come in contact with the immune system in mucocutaneous epithelial tissues such as skin, the gastrointestinal (GI) tract, eye, and upper respiratory tract, where dendritic cells recognize the pathogen and present its antigens to cells in lymphoid tissues, thus initiating both cell-mediated and humoral immune responses. Lymphatic vessels are found throughout the body, and connect peripheral tissues to lymph nodes, which function to respond to tissue-based pathogens, while the spleen functions to respond to bloodborne pathogens. Naïve mature lymphocytes traffic or recirculate throughout the body, leaving the circulation via specialized postcapillary venules, termed high endothelial venules (HEVs), in lymph nodes and MALT, and return to the circulation via lymphatics and the thoracic duct. HEVs are lined by tall cuboidal endothelial cells and are predominantly found in the paracortex, or T lymphocyte zone, but are also found to a lesser extent in the cortex, or B lymphocyte zone.

B lymphocytes are one of the two major classes of lymphocytes (T lymphocytes are the other major class). B lymphocytes develop in the bursa of Fabricius of birds and in the bone marrow of mammals. B lymphocytes function in humoral adaptive immunity by recognizing antigen, and with T lymphocyte help (T cell-dependent) or no T lymphocyte help (T cell-independent) differentiating into plasma cells, which secrete antibodies, also termed immunoglobulins (Igs). B lymphocytes can also function as antigen-presenting cells (APCs) (like dendritic cells and macrophages). B lymphocyte development occurs in distinct stages, from the common lymphoid precursor (CLP) to pro-B cells to large and small pre-B cells, and finally to the immature translational B cell stages of T1 and T2. Immature B cells then migrate to secondary lymphoid tissues, such as lymph node and spleen, to mature into follicular or marginal zone B cells. Finally, mature B cells become activated, undergo immunoglobulin gene rearrangement, clonal expansion, and then form plasmablasts and ultimately plasma cells.

T lymphocytes are produced in the bone marrow from hematopoietic stem cells, and then migrate to the thymus where they undergo cell division to create a large population of immature T cells. T cells can either be helper T cells or cytotoxic T cells based on whether they express CD4 (helper) or CD8 (cytotoxic) glycoprotein. The earliest T cells are double negative in that they express neither CD4 nor CD8 and are thus called double negative ($CD4^-CD8^-$) cells. As the T cells

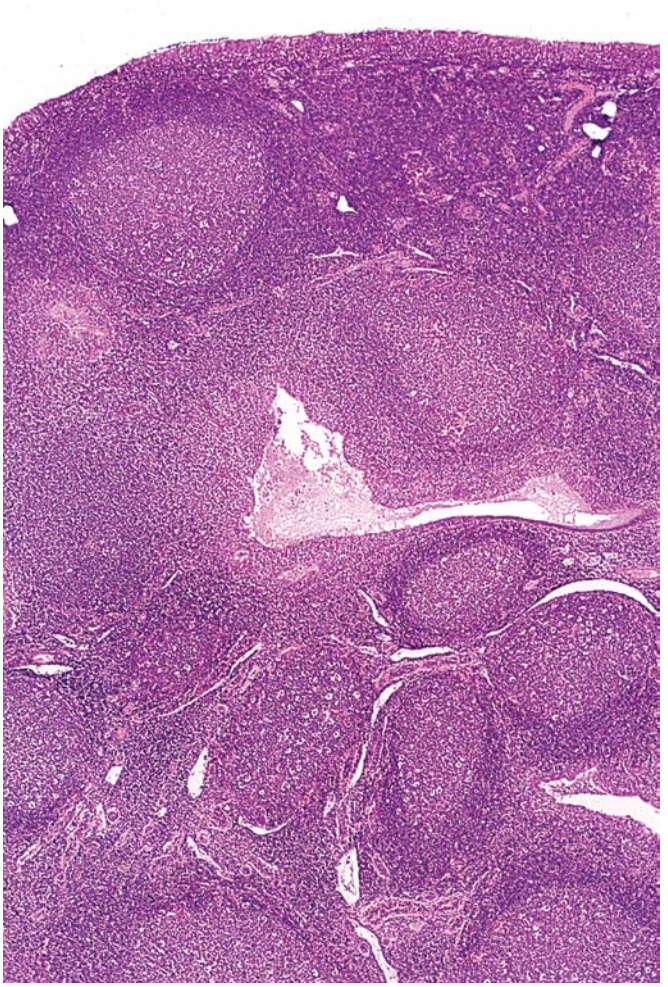


FIGURE 1 Palatine tonsils with prominent germinal centers in a dog.

migrate from the periphery through the cortex, they mature to become double positive T cells ($CD4^+CD8^+$). As maturation of these double positive cells continues, they undergo positive and negative selection.

As the T cells continue to mature in the thymus, they will eventually become single positive T cells ($CD4^+CD8^-$ or $CD4^-CD8^+$). Only single positive T cells can leave the thymus and populate the peripheral lymphoid tissues such as the lymph nodes, MALT, spleen, tonsils, and so forth. Naïve T cells, or those that have not yet encountered foreign antigen in the peripheral lymphoid tissues, can be activated by recognition of MHC-peptide complexes on the APCs with subsequent proliferation and differentiation into effector or memory T cells. These activated T cells then become involved in T cell-mediated immunity in the peripheral lymphoid system to eliminate bacterial, viral, or parasitic infections as well as malignant cells. Cytotoxic T lymphocytes can kill cells infected with virus, bacteria, or protozoa as well as allografts such as transplanted heart, lung, and kidney, and cancer cells. T helper cells secrete cytokines that can activate B cells to produce antibodies and activate macrophages to destroy ingested microbes. They also help activate cytotoxic T cells to kill infected target cells. To date, four types of T helper cells have been identified: Th1, Th2, Tfh, and Th17. A subpopulation of cells, called T regulatory (Treg) cells, is thought to be derived from the same cell lineage as T helper cells. These cells are immunosuppressive and will downregulate induction and proliferation of the T effector cells, or those that actively respond to a stimulus. Thus a previous name for these cells was "suppressor T cell" because they help to maintain immunological tolerance. Natural killer T (NKT) cells also originate in the thymus from double positive T cells and represent a combination of T cell and natural killer (NK) cell attributes. They express a TCR complex and several NK cell markers. They do not recognize MHC but do recognize a glycolipid antigen presented by a molecule called CD1d. NKT cells will reciprocally activate APCs upon lipid/glycoprotein presentation. Once activated, these cells can produce Th1- and Th2-related cytokines and can perform functions ascribed to both T helper and cytotoxic T cells.

Dendritic cells (DCs) are bone marrow-derived cells of the monocyte lineage that are key components of both adaptive and innate immune responses. DCs are morphologically characterized by having multiple cytoplasmic projections, or dendrites, which give these cells their name. DCs are found in regions of environmental contact, such as mucocutaneous tissues including skin, GI tract, and respiratory tract as well as in both primary lymphoid tissues, such as thymus, and in secondary lymphoid tissues, such as lymph node, MALT, and spleen. DCs function in antigen presentation and are thus important in the initiation of cell-mediated immune responses, such as those responsible for allergic contact dermatitis and the inflammatory response to other noxious stimuli, including toxins. Upon antigen capture and activation, DCs very quickly deliver antigenic signals to draining lymph nodes, homing to the outer paracortical region to contribute to B-cell responses as well as to T-cell activation. All DCs express major histocompatibility class (MHC) I and MHC II molecules as well as immune activation costimulatory molecules. There are several different subpopulations of DCs that differ by their tissue location, the cell surface markers that they express, and their functionality.

Tissue-resident macrophages are large phagocytic cells that exist as permanent populations of macrophages established in almost all tissues and body cavities in utero. These macrophages exhibit tissue-dependent phenotypical, functional, and transcriptional differences and contribute to innate and adaptive immunity, tissue development, and tissue repair and homeostasis. Tissue-resident macrophages are long-lived and self-renewing, become activated and proliferate locally, and are not derived from circulating bone marrow-derived monocytes. Monocytes are independently maintained and may transform into macrophages within tissues, but monocytes contribute minimally to tissue-resident macrophage populations and activity.

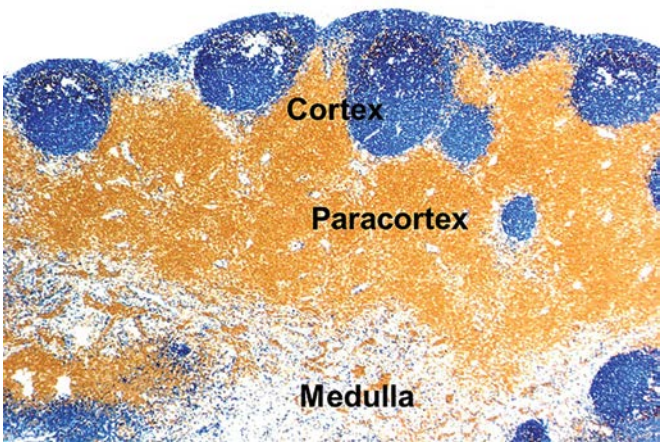


FIGURE 2 Lymph node and lymphoid follicle. Lymph node from a cynomolgus monkey stained for CD20 (blue) and CD3 (brown), illustrating the outer cortex consisting of B cell containing lymphoid follicles, the subjacent paracortex containing T cells, and an inner medulla, which consists of cords containing largely plasma cells, and sinuses lined by macrophages and fibroblastic reticular cells (FRCs).

Lymph nodes are discrete encapsulated secondary lymphoid organs found throughout the body. Their organized structure consists of an outer cortex, which contains multiple lymphoid follicles made up primarily of B cells with lesser numbers of APCs and T cells, and an inner medulla, which consists of cords containing largely plasma cells, and sinuses lined by macrophages and fibroblastic reticular cells (FRCs). In between the cortex and medulla is the paracortex, which consists almost entirely of T lymphocytes. Afferent lymphatic vessels drain distal tissues transporting extracellular fluids, leukocytes, APCs, and byproducts of inflammation to proximal lymph nodes. Lymph enters the lymph node via afferent lymphatics that pierce the capsule and empty into the subcapsular sinus. Paracortical sinuses then traverse the cortex and paracortex. Medullary sinuses converge in the

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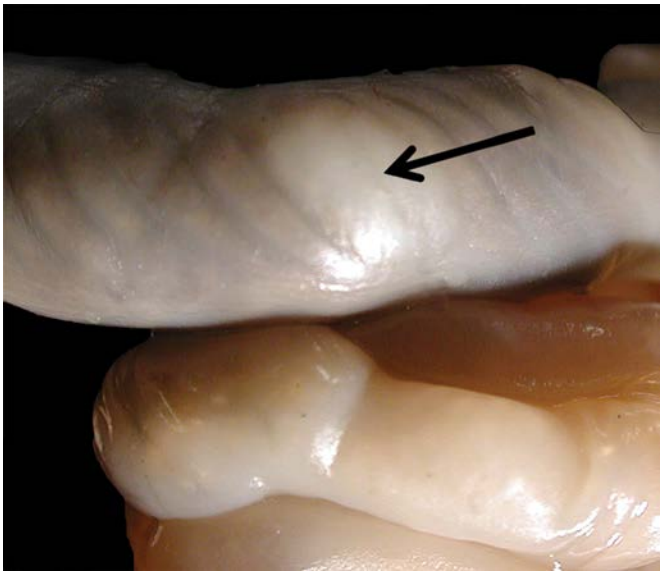


FIGURE 3 Gross image of rat intestine illustrating Peyer's patches (grossly evident raised white areas).

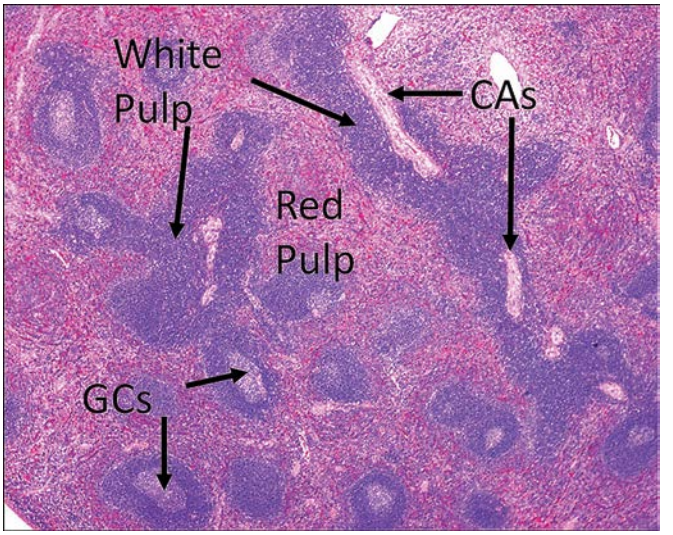


FIGURE 4 Spleen, splenic white pulp, splenic red pulp. Normal spleen from a cynomolgus monkey illustrating white pulp containing follicles with central germinal centers (GCs) and central arterioles (CAs).

hilus, exiting the lymph node via efferent lymphatic vessels. Efferent lymphatic vessels eventually connect to the thoracic duct, which empties into the vena cava allowing lymph and migrating lymphocytes to rejoin circulating blood. Fixed tissue macrophages and FRCs line sinuses, phagocytize particulate matter, and secrete cytokines. Lymph nodes dramatically change in size and morphology in response to antigenic and proinflammatory stimulation. APCs arrive from distal sites, move to follicles in the cortex to encounter B cells, and to the deep cortical unit of the paracortex to encounter T cells. Follicles remodel from primary to secondary follicles, and paracortical areas expand. Lymphocyte trafficking originates with egress of lymphocytes from cortical and paracortical zones into sinuses exiting the lymph node and eventually rejoining circulation via the thoracic duct. Lymphocytes exit circulation, surveille tissues via migration, home to sites of inflammation, and colonize other lymphoid organs as well as return to the lymph node of origin. Lymphocyte reentry to the lymph node occurs via lymphatic drainage or via circulation by transmigration across high endothelial venules (HEVs), where endothelium express unique surface proteins directing lymphocyte homing. The vascular supply of the lymph node enters and exits through the hilus. HEVs are postcapillary venules with distinct endothelial cell morphology. HEVs are found primarily in the cortex, with fewer in the paracortex. The stroma of the lymph node is composed of FRCs and a meshwork of reticular fibers. The reticular network provides a framework for organized lymphoid structures, cell migration, and conduits for cytokine gradients.

Lymphoid follicles are found in secondary lymphoid tissues, including the spleen, lymph nodes, and MALT. Lymphoid follicles are made up primarily of a central zone consisting of B cells, with lesser numbers of APCs throughout, and T cells are the periphery. Lymphoid follicles are defined as primary prior to antigenic stimulation and secondary following antigenic stimulation with formation of a central germinal center (see following). Follicular morphology differs in different secondary lymphoid tissues but is best illustrated in the spleen, where the innermost portion of the lymphoid follicle contains B lymphocytes and is divided into a central region, termed the germinal center, which contains proliferating and differentiating B lymphocytes surrounded by concentric zones of more mature B lymphocytes starting with (from innermost to outermost) the mantle zone, the inner marginal zone, a band of myofibroblasts, and the outer marginal zone that lies outside the band of myofibroblasts. Immediately outside the B lymphocytes of the central lymphoid follicle is the central splenic arteriole, which is surrounded by the periarteriolar lymphoid sheath, consisting of T lymphocytes. In lymph nodes, lymphoid follicular structure is simplified compared to follicles in the spleen. In lymph nodes, lymphoid follicles made up of largely of B lymphocytes are found in the outer cortex, while T lymphocytes reside in the paracortex, which is found between follicles and between the cortex and inner lymph node medulla.

Fully formed lymph node-like lymphoid follicles with germinal centers may form as tertiary lymphoid structures in nonlymphoid tissues or in lymphoid tissues without follicles, particularly thymus and bone marrow. These induced lymphoid follicles are structurally and functionally similar to lymph node follicles and are frequently associated with a chronic immune response in autoimmunity, transplantation, neoplasms, and diseases.

MALT consists of small clusters of loosely organized or mature lymphoid follicles, or large discrete tonsils associated with mucosal tissues. Mucosal lymphocytes and tonsils form an extensive system of secondary lymphoid tissue protecting all mucosal surfaces by interacting with antigens and secreting immunoglobulins and interacting with

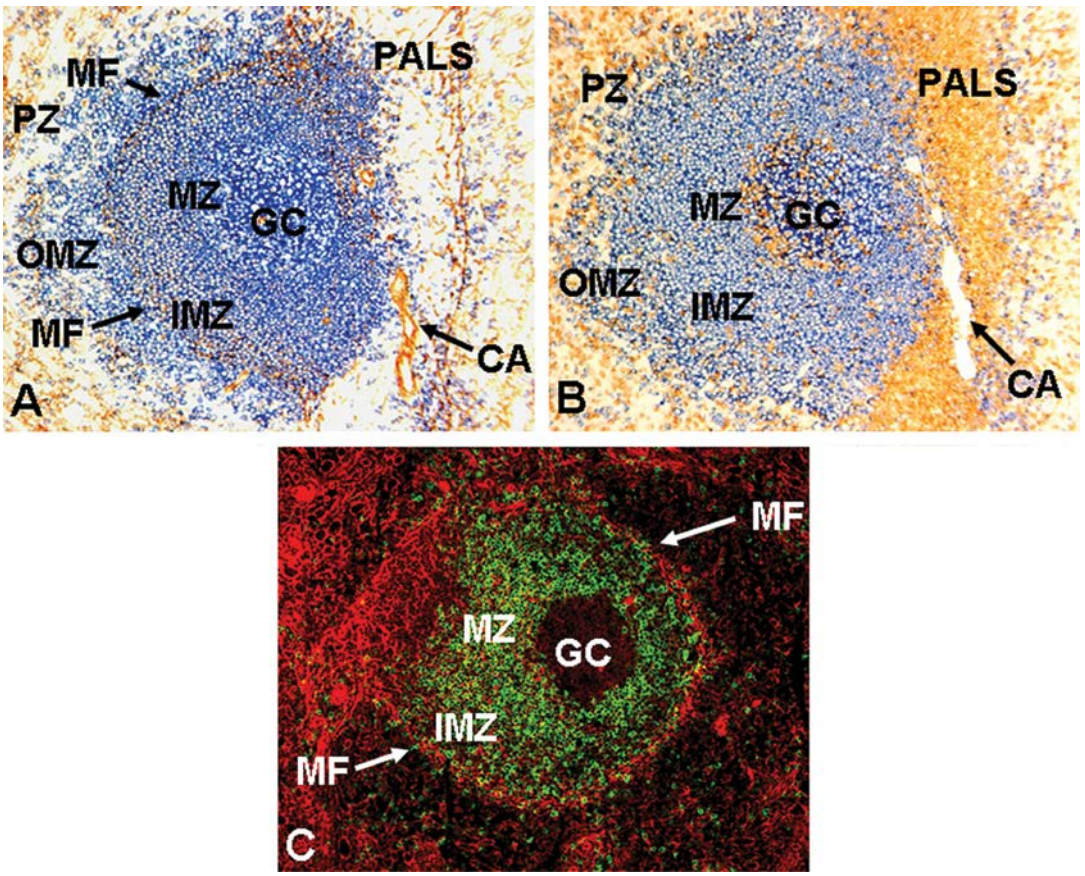


FIGURE 5 Lymphoid follicle and splenic marginal zone. Splenic lymphoid follicle from a cynomolgus monkey stained for (A) the B-cell marker CD20 (blue) and α-smooth muscle actin (SMA/brown), (B) CD20 (blue) and the T lymphocyte marker, CD3 (brown), and (C) IgD (green) and F-actin (red). Panel A illustrates that the lymphoid follicle is composed of a central germinal center (GC) surrounded by the mantle zone (MZ), the inner marginal zone (IMZ), a band of smooth muscle actin (SMA)$^+$ myofibroblasts (MF), and the outer marginal zone (OMZ) outside the SMA$^+$ band. Panel B illustrates the periarteriolar lymphoid sheath (PALS) of CD3$^+$ T cells that surrounds the central arteriole (CA) adjacent to the CD20$^+$ lymphoid follicle. Panel C illustrates how IgD expression differentiates between the germinal center (IgD$^-$), mantle zone (IgD strongly$^+$), and the IMZ (IgD weakly to moderately strongly$^+$). CA = central arteriole, GC = germinal center, MZ = mantle zone, IMZ = inner marginal zone, MF = myofibroblasts, OMZ = outer marginal zone, PALS = periarteriolar lymphoid sheath, PZ = peripheral zone. Bars = 100 μm. (Reproduced with permission from the American Society for Investigative Pathology from Vugmeyster et al. 2006. *Am J Pathol* 168:476–489.)

the systemic immune system. Only a few sites of MALT are formed in utero and present at birth, such as **Peyer's patches** of the small intestine and the nasopharynx nasal/nose-associated lymphoid tissue (rodents), nasopharyngeal tonsil (other mammals), and adenoid (humans). In most mucosal tissues, MALT is induced in the postnatal period after antigenic exposure. Although not in mucosal locations, duct-associated lymphoid tissue around ducts in glandular tissues, and skin-associated lymphoid tissue are functionally similar and are frequently included as part of the MALT system. In all cases, antigenic exposure drives development of the loosely organized MALT toward mature lymphoid follicles with germinal centers. These organized lymphoid follicles may be grossly visible on the serosa of the hollow organs. Histologically, the follicles frequently push up the mucosa of the luminal surface, with the mucosa being a specialized overlying follicle-associated epithelium (FAE). FAE is formed by membranous/microfold (M) cells that are frequently interspersed by leukocytes. M cells lack apical microvilli and secretory capacity and selectively sample antigens and particles which would normally be excluded by the mucosal barrier. In MALT, B cells exceed the number of T lymphocytes, and subsequent to antigenic exposure, B cells release mostly IgA into the mucosal secretions, and T- and B-lymphocytes and macrophages migrate to other lymphoid tissues to produce a systemic immune system.

The **spleen** is both the largest secondary lymphoid tissue and a component of the mononuclear phagocyte system. It is located in the left anterior quadrant of the abdominal cavity in nearly all vertebrates. The lymphoid tissue compartment is referred to as the **white pulp**, while the other compartment, termed the **red pulp**, consists of vascular sinuses lined by discontinuous endothelium and separated by cords comprised of macrophages which are part of the monocyte phagocyte system. The splenic white pulp consists of lymphoid follicles

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containing B and T lymphocytes surrounded by a marginal zone containing dendritic cells, macrophages, and recirculating B lymphocytes. Outside the lymphoid follicles and **marginal zones** lies the red pulp, consisting of venous sinuses delineated by splenic cords comprised of macrophages and other phagocytic cells and divided by a trabecular fibrovascular stromal network that extends into the red pulp parenchyma from the splenic capsule. The white pulp functions as part of the secondary lymphoid system, while the red pulp functions to phagocytize pathogens as well as to remove senescent red blood cells from the circulation. The red pulp is also often the site of extramedullary hematopoiesis, particularly in murine rodents.

The **splenic marginal zone** is a distinct anatomic region that surrounds the central lymphoid follicle and contains mature B lymphocytes. In mouse, the marginal zone B cells are delineated from the lymphoid follicles by a marginal sinus containing metallophilic macrophages that delineate the follicular B cells from the marginal zone. In contrast, primate splenic white pulp lacks marginal zone sinuses, and has large B-cell lymphoid follicles with a prominent smooth muscle actin-positive band of myofibroblasts that divides the outer marginal zone from the rest of the follicle. In addition, mouse marginal zone B cells do not recirculate, are naïve B cells, and are found only in the spleen, while human (and very likely all primates) marginal zone B cells recirculate, consist primarily of memory B cells, and are found in other anatomic sites. There are data to suggest that marginal zone B lymphocytes are important in the T lymphocyte independent immune response as well as in the development of autoimmunity; hence their depletion has ramifications for both the therapy of autoimmune conditions as well as for potentially increased susceptibility to T lymphocyte independent pathogens, such as *Streptococcus pneumoniae*.

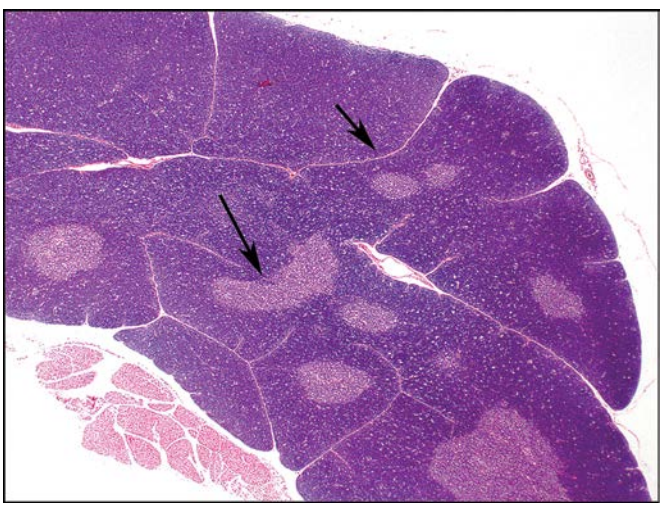


FIGURE 6 Normal thymus from a 3-month-old Sprague Dawley rat illustrating the darker staining cortex (arrow), the paler staining medulla (longer arrow), and the septae (short arrow).

The **thymus** is located on either side of the midline in the anterior portion of the thoracic cavity ventral to the base of the heart and the aortic arch. It is composed of two lobes connected by a narrow isthmus and invested by a thin capsule. Each lobe contains numerous lobules that are divided by septae. The lobules vary in size, but each contains a darkly basophilic **cortex** and a paler-staining, more eosinophilic **medulla**. Not readily apparent in both the cortex and medulla is a framework of simple cuboidal reticular epithelial cells that provide both structure and nurture functions for the developing T lymphocytes. Macrophages are also present that aid in the maturation of T lymphocytes and that remove apoptotic debris. The thymic cortex is densely cellular, containing mostly T lymphocytes. The thymic medulla contains fewer T lymphocytes than the cortex and also contains macrophages and a robust epithelial component, which is responsible for its pale eosinophilic staining properties with H&E. These epithelial cells are important for the further development and maturation of T cells as they arrive from the cortex and become single positive cells; either $CD4^+CD8^-$ or $CD4^-CD8^+$ cells. Macrophages within the medulla can function to remove cellular debris or can function as dendritic interdigitating (antigen-presenting) cells. The medulla also contains Hassall's corpuscles. These are remains of the epithelial tubes that grow out from the third branchial pouches of the embryo to form the thymus. They are composed of concentric or lamellated type IV reticular epithelial cells and can sometimes show keratinization and contain cellular debris. These structures appear in fetal life and will increase with age or with increased cellular destruction. Although the true function is unclear, they are thought to be involved in the removal of apoptotic thymocytes and the maturation of developing thymocytes.

NERVOUS SYSTEM

The nervous system is anatomically complex with numerous structures and substructures with functionally distinct subdivisions (Figure 1). It is responsible for obtaining and processing information from the external environment (such as sight, smell, touch, taste), and coordinating response to these stimuli as well as maintaining function and coordination of all the other systems necessary for the maintenance of life (such as movement, respiration, heartbeat, and gastrointestinal motility). On the most superficial level, the central nervous system (CNS) consists of the brain and spinal cord, while the peripheral nervous system (PNS) consists of the peripheral nerves and ganglia. The autonomic nervous system (also called visceromotor nervous system) has components in both the CNS and PNS, interacts closely with the hormonal (or endocrine) systems, and innervates smooth muscle, cardiac muscle, or glands that make up the visceral system. The enteric nervous system is a fairly autonomous subdivision of the autonomic nervous system that controls the gastrointestinal tract.

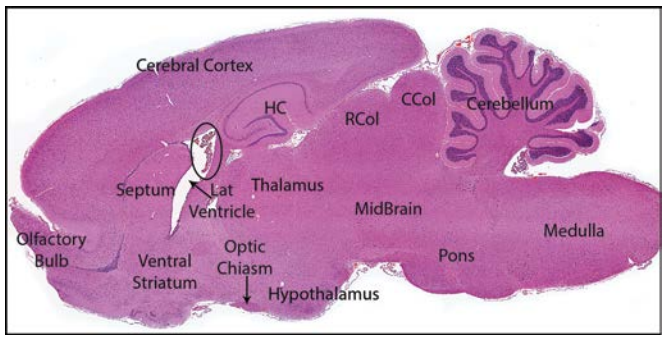


FIGURE 1 Parasagittal histologic section of the rat brain. Selected major regions and structures are indicated. Choroid plexus within the lateral ventricle is encircled. CCol, caudal colliculus; HC, hippocampus; RCol, rostral colliculus. Rat. H&E.

The primary effector cells of the nervous system are neurons, which are the cells responsible for processing and responding to information. Neurons have an axon that transmits information to and from the neuronal cell body and serves as a conduit for movement of nutrients and elimination of waste necessary to maintain the health of the axon and neuron. Neurons also have dendrites that communicate with other neurons, forming an interlinked matrix. Functionally related groups of neurons reside within distinct groups that are referred to as nuclei (also called ganglia in some anatomy texts) within the brain and spinal cord, and within ganglia in the PNS. Each neuron, nucleus, and ganglion has a specialized function or functions, and functionally related nuclei are interconnected by bundles of axons that together are referred to as tracts. Regions of the CNS in which neuronal cell bodies reside make up the "gray matter," while regions containing the interconnecting tracts that are enriched in myelinated processes make up the "white matter." Since neurons are terminally differentiated cells, damage to a specific class or group of neurons can have permanent effects.

The nuclei (also called ganglia) within the CNS are all named, with much research dedicated to their respective functions and interrelationships. The nuclei have a similar general location and similar functions within all animals, including humans. However, the shape of the brain and the relative proportions of substructures vary greatly between species, depending on the functional needs of each species. For example, humans have relatively tiny olfactory bulbs, but these take up approximately one third of the rodent brain. Numerous brain atlases have been published for a variety of species and are the best source of information about the location of these nuclei (e.g., Paxinos et al. 2009; Paxinos and Franklin 2012; Paxinos and Watson 2014; Snider and Niemer 1961). Likewise, numerous textbooks (and research papers) have been devoted to functional neuroanatomy, which describe the location and function of various tracts and substructures within both the CNS and PNS. These functional neuroanatomy textbooks are the best sources of information regarding specific functional tracts (e.g., the olfactory tracts and nuclei) and the nuclei associated with these tracts. Cross-referencing between the brain atlases and the functional neuroanatomy textbooks will guide researchers in understanding structure-function relationships in the brain, spinal cord, and PNS.

It is critical to understand that although a single nucleus (or ganglion) may be a very small part of the nervous system or brain as a whole, damage to this single nucleus can have profound functional consequences. An example of this is the specificity of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) for the dopaminergic neurons in the substantia nigra, producing permanent Parkinson-like symptoms in the young people taking this street drug for recreational purposes. Based on what brain structures are known or suspected to be affected by test materials, toxicity studies should be designed so that these pertinent regions are adequately represented in the examined histologic sections. Similarly, once affected brain areas have been identified, consideration should be given to structural-functional relationships to ensure that related areas are also adequately evaluated. This illustrates the importance of brain atlases and a knowledge of functional neuroanatomy for the assessment of potential neurotoxicants.

In the PNS, groups of functionally related neurons are found within ganglia. Dorsal root ganglia along the spinal cord contain the cell bodies of sensory nerves responsible for receiving and transmitting sensory information between peripheral sensory receptors and the CNS (Figure 2). Peripheral autonomic ganglia are paravertebral or within the viscera and are important for coordinating movement and responses of the viscera, which are generally beyond conscious control.

The autonomic nervous system (also called visceral or visceromotor nervous system) controls whole-body homeostasis by ensuring that tissues receive adequate nutrients, oxygen, and electrolytes while maintaining temperature and the



FIGURE 2 Dorsal root ganglia (encircled) in a transverse section through the vertebral spine of a rodent. The dorsal nerve roots that connect the ganglia with the spinal cord are out of the plane of this histologic section. Mouse. H&E.

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consistency of the extracellular fluid and osmolarity, all while responding rapidly to a constantly changing environment. There are two overlapping control mechanisms for these functions—the hormonal (endocrine) system, which has slower but more prolonged effects, and the visceromotor system, which has rapid but short-term effects. These two systems are closely interrelated, so that both systems respond to emotional state as well as sensory stimuli from the external environment. The autonomic nervous system generally innervates smooth muscle within blood vessels, viscera, or glands, or cardiac muscle in the heart. The autonomic nervous system has two main divisions, the sympathetic and parasympathetic systems. The sympathetic system is generally responsible for rapid mobilization of resources and responses necessary for protection from an external danger (the fight-or-flight response.) Sympathetic preganglionic neuronal cell bodies are principally located in the T1 to L2 (thoracolumbar) segments of the spinal cord, with axons extending to synapses within paravertebral or prevertebral ganglia. The postganglionic axons then innervate smooth muscle, cardiac muscle, and secretory cells. The parasympathetic system is generally responsible for restoring and maintaining normal homeostatic functioning. The parasympathetic preganglionic neuronal cell bodies are principally located in the sacral spinal cord and visceral efferent nuclei of cranial nerves III, VII, IX, and X (craniosacral) with axons extending to synapse within ganglion cell clusters in the walls of viscera (Figure 3) or the cranial nerve autonomic ganglia (III, ciliary; VII, pterygopalatine or submandibular; IX, otic). Parasympathetic postganglionic axons are short with synapses on immediately adjacent tissue.

The nervous system also has a complex neuronal support system (Figure 4). As in other organs, a rich blood supply provides nutrients and oxygen and removes waste products. In addition, many specialized support cells (collectively called glia, or glial cells) have distinct functions. Astrocytes are the most numerous glial (support) cells within the CNS. Astrocytes have numerous cell processes, giving them a star shaped appearance (hence the name astrocytes), that often end in expansions called end feet. These astrocytic end feet surround brain capillaries and completely line the interface of the CNS with blood vessels (where they are a critical part of the blood-brain barrier), the ependymal lining of the ventricular system, and the leptomeninges (Figure 5). Astrocytes process neuronal metabolic waste and metabolize certain toxins in order to protect the neurons. They also recycle electrolytes released by neurons during transmission of a nerve impulse and also metabolize and recycle many neurotransmitters. Astrocytes are involved in cell-cell communication and monitor the extracellular matrix of the CNS. Astrocytes are involved in healing damage within the CNS and will become larger (astrocyte hypertrophy) or proliferate in response to noxious stimuli (astrocytosis). Microglia are the primary immune effector cell within the CNS and are thought to derive from the monocyte-macrophage cell line. Like monocytes and macrophages in other organs, microglia secrete cytokines in response to inflammatory stimuli, serve as antigen-presenting cells, and maintain homeostasis by phagocytosing and removing cell debris from metabolism or following injury. Microglia constantly migrate throughout the CNS to accomplish their immune surveillance functions. When activated, microglial cells increase in both number and size (Figure 6). Myelin consists of multiple concentric layers of cell membranes derived from oligodendroglia in the CNS, and Schwann cells in the PNS (Figure 7) that wrap around axons to insulate them, and speed transmission of nerve impulses. Unmyelinated axons also are present and run in canals between Schwann cells.

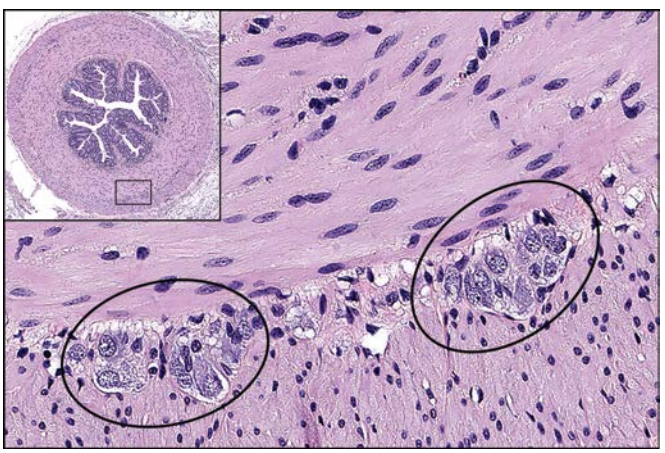


FIGURE 3 Myenteric ganglia (encircled) of the parasympathetic nervous system are located between the smooth muscle layers in the gastrointestinal tract. Rat. H&E.

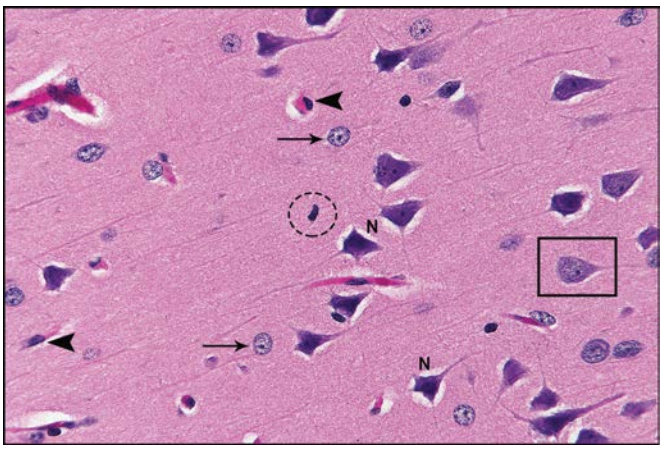


FIGURE 4 Cell types in normal cerebral cortical gray matter. Most neuronal cell bodies exhibit dark neuron artifact (N). A neuron not displaying this artifact is bounded by the rectangle. Astrocyte nuclei are indicated by black arrows. A microglial cell nucleus is within the hatched circle. Capillary endothelial cell nuclei are indicated by the black arrowheads. Monkey. H&E.

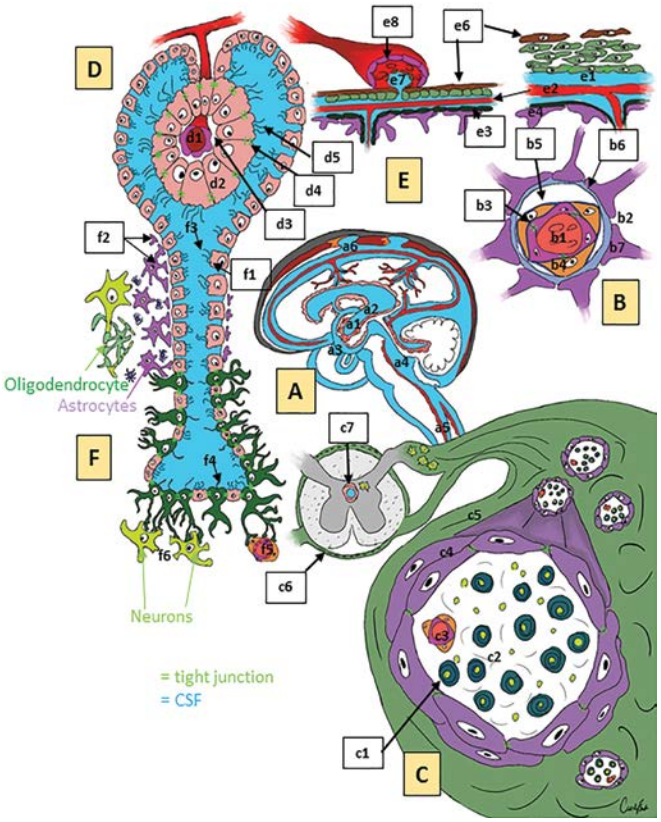


FIGURE 5 **(A)** Cerebrospinal fluid (CSF) circulation in brain of a cynomolgus macaque. CSF is produced as an ultrafiltrate of plasma by the choroid plexus (a1, D) in the lateral (a2), third (a3), and fourth (a4) ventricles. CSF flows throughout the ventricular system, the central canal of the spinal cord (a5), and over the surface of the brain and spinal cord where it serves as a shock absorber and cushion. It is reabsorbed into venous sinuses at the arachnoid villi (a6, E). **(B)** Blood-brain barrier (BBB). The BBB is the barrier between the lumen of capillaries (b1) within the brain parenchyma and the brain interstitial fluid (b2). The primary constituents of the BBB are the tight junctions between capillary endothelial cells (b3), with contribution from pericytes (b4), and the basement membranes surrounding these capillaries (b5) as well as the glia limitans (b6) and astrocyte foot processes (b7), and microglia surrounding parenchymal vessels. It is important to note that the BBB is functionally distinct from the blood-CSF barrier (D and E), and therefore measurement of a substance within the CSF does not equate to a measurement of that substance within the brain parenchyma. **(C)** Blood-nerve barrier is the barrier between blood and axons of the peripheral nerves. In the peripheral nervous system (PNS), Schwann cells form myelin (c1) around axons, and unmyelinated axons run in canals between Schwann cells and their basal lamina. External to the Schwann cells is the endoneurium (c2) that consists of type III collagen fibrils, and occasional fibroblasts, surrounding the Schwann cells and axons. Within the endoneurium are endoneurial capillaries (c3) with tight junctions, surrounded by pericytes, similar to the BBB. Exchange between these capillaries and the endoneurial interstitium is the primary point of exchange between the vasculature and peripheral nerves. Surrounding each group (fascicle) of axons is the perineurium (c4), formed of several concentric layers of specialized fibroblasts with a basal lamina, and tight junctions between fibroblasts. Together the endoneurial capillary tight junctions and the perineurial fibroblast tight junctions are the primary constituents of the blood-nerve barrier. The third layer is the epineurium (c5), a dense connective tissue sheath with abundant type I collagen and typical fibroblasts that surrounds the entire nerve fiber and eventually becomes continuous with the arachnoid (c6) surrounding the spinal cord. **(D)** Blood-CSF barrier and CSF production at choroid plexus. The choroid plexus functions to produce CSF and consists of a network of interconnected capillaries (d1) projecting from the roof of the lateral, third, and fourth ventricles, surrounded by the specialized choroid plexus epithelium (d2). The capillaries within the choroid plexus are lined by a fenestrated endothelium that allows the passage of large molecules and fluid into the interstitial pericapillary space (d3). The specialized choroid plexus epithelia have tight junctions (d4) at their apical borders to form the blood-CSF barrier at this level, and active transport mechanisms that result in the formation of CSF with higher concentrations of sodium, chloride, and magnesium and lower concentrations of potassium, calcium, glucose, and proteins when compared to plasma. The apical border (in contact with CSF) of the choroid plexus epithelium has a brush border and motile cilia (d5), which are important for the circulation of CSF within the ventricular system. **(E)** Blood-CSF barrier and CSF resorption at arachnoid villi. CSF surrounds and cushions the external surface of the brain within the subarachnoid space (e1, A). Large blood vessels (not capillaries; e2) also course through this space; these vessels have tight junctions and do not participate in exchange of materials. The pia mater (e3) and astrocyte foot processes (e4) form the barrier in contact with the brain surface, which also follow the large blood vessels as they penetrate into the brain parenchyma. The arachnoid membrane (e5) is formed of several layers of fibrocytes, the innermost of which have tight junctions. These are surrounded by the thick fibrous membrane of the dura mater (e6). Arachnoid villi (e7) are projections of the subarachnoid space through the arachnoid and dural membranes into dural venous sinuses (e8). These villi are fenestrated, allowing resorption of CSF and return to the venous circulation. **(F)** Ependymal barrier (CSF-brain barrier) at ependyma lining ventricles. Unlike the BBB (B) and blood-CSF barrier (D), the ependymal barrier does not have tight junctions but does serve as a partial barrier between the CSF and the brain parenchyma. Large molecules such as proteins can pass between ependymal cells (f1) into the extracellular space. There is not a continuous basal lamina between the ependymal cells and subjacent glial processes (f2; foot processes of astrocytes), allowing further diffusion into the extracellular matrix around glial processes. The ependymal cells have microvilli and multiple motile cilia on their apical borders (f3) in contact with the CSF that are critical for circulation of CSF within the ventricular system. Ependymal cells also line the central canal of the spinal cord (a5, c7). Within the ependymal layer, primarily at the base of the third ventricle (hypothalamus), are patches of specialized ependymal cells called tanycytes (f4). Tanycytes are joined by tight junctions between adjacent tanycytes and ependymal cells. Tanycytes have basal processes that extend through the subjacent astrocyte processes to form end feet on parenchymal blood vessels (f5), which may be fenestrated, or directly on specialized neurons (f6), thus allowing transport of substances (hormones) between the ventricles and the blood vessels, or specialized neurons of the thalamus/hypothalamus. Tanycytes have a single motile cilium at their apical pole. (Copyright 2018 Caroline Frank. Used by permission.)

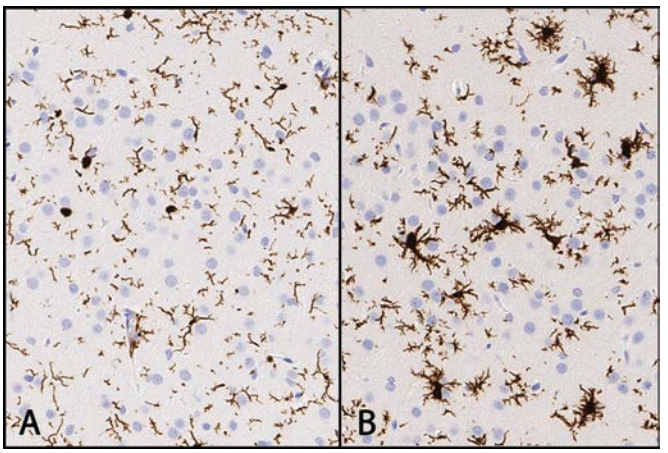


FIGURE 6 Immunolabeling for iba-1 expression in microglia. (A) Normal quiescent microglia. (B) Reactive hypertrophic microglia. Brain. Rat. Iba-1 immunohistochemistry.

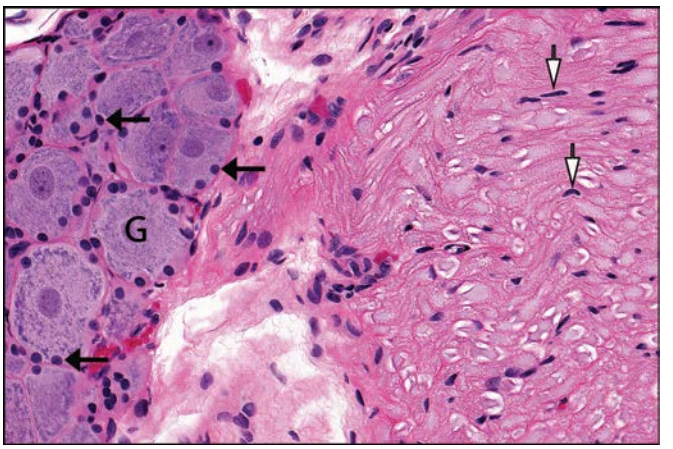


FIGURE 8 Dorsal root ganglion. Ganglionic neuronal cell body (G); satellite cells (black arrows); Schwann cell nuclei (white arrow). Monkey. H&E.

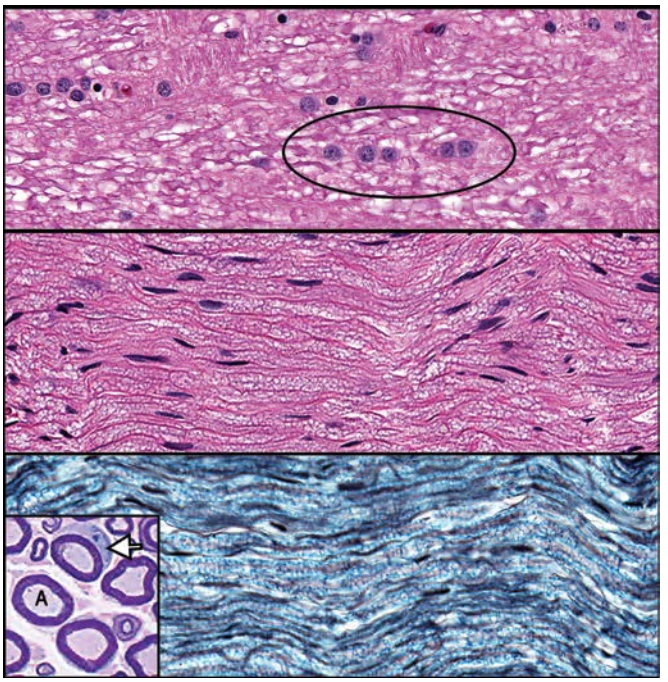


FIGURE 7 Top: Spinal cord white matter. A row of oligodendrocyte nuclei is encircled. Monkey. H&E stain. Middle: Sciatic nerve. Schwann cell nuclei are thin, dark, and elongate. The myelin sheaths are eosinophilic. Axons within the myelin sheaths are eosinophilic but not easily discernable at this magnification. Monkey. H&E stain. Bottom: Luxol fast blue (myelin)/Holmes silver nitrate stain (axons). The linear and somewhat wavy gray-black structures are axon profiles. Inset: Toluidine blue stain. Axons (A) in cross-section encircled by dark blue myelin sheaths. A Schwann cell nucleus is indicated by the white arrow. Rat.

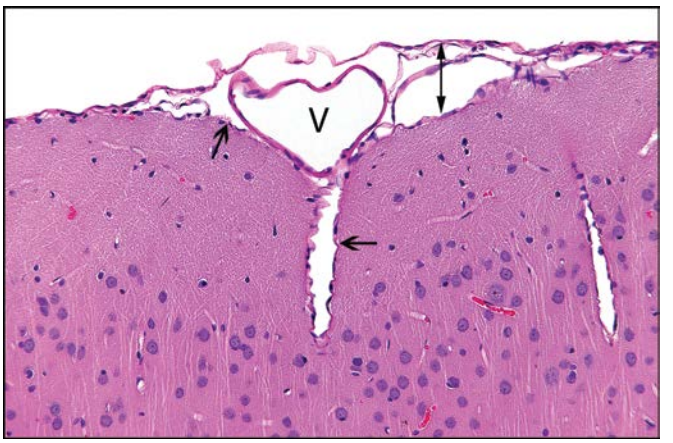


FIGURE 9 Leptomeninges overlying the cerebral cortical surface of a rodent. Pia mater (black arrows). A thin-walled blood vessel (V) is within the pia arachnoid (double arrow). Mouse. H&E.

There are also satellite cells that surround neurons, but the functional significance is unclear (Figure 8). In the CNS, satellite cells are oligodendroglia, but are simply called satellite cells in the PNS.

The external surface of the brain and spinal cord is covered with meninges and enclosed within a protective covering of bone (the skull and vertebrae, respectively). Meninges are composed of three major layers—the first (innermost) layer is the pia mater on the surface of the brain, which follows all the contours; the second is the arachnoid mater, which holds the cerebral spinal fluid (CSF) and forms a barrier between the CSF and external structures. Together the pia and arachnoid mater are called the leptomeninges (Figure 9). The third and outermost layer of the meninges is the dura mater, which forms a thick fibrous covering around the CNS. The dura mater is adhered to the internal surface of the skull, but within the vertebrae of the spinal column there is a separation called the epidural space. Nerves and blood vessels that traverse the meninges do so within a cuff of dura, which in nerves becomes continuous with the external surface of the epineurium.

Also critical to the support and function of the CNS is the circulation of cerebrospinal fluid (CSF) within the ventricular system of the brain, the central canal of the spinal cord, and the subarachnoid space over the external surfaces of the brain and spinal cord. The ventricular system is a communicating

series of CSF-filled spaces within the center of the lobes of the brain and continuous with the central canal of the spinal cord and subarachnoid space surrounding the brain and spinal cord. Ventricles are lined by ependymal cells and the choroid plexus (a region of specialized ependymal cells in close contact with capillaries), which produce the CSF (primarily by the choroid plexus epithelium, with lesser contribution from ependymal cells). These cells actively transport some substances into CSF, which are passively followed by water, while excluding others. Compared to blood plasma, CSF has higher concentrations of sodium, chloride, and magnesium, and lower concentrations of potassium, calcium, glucose, and proteins. Normal CSF has very little protein (~14–45 mg/dL in humans) including immunoglobulins, relative to plasma, and very few cells. Ependymal cells also have cilia, which participate in movement and circulation of the CSF within the ventricular system. CSF provides nutrition and support to the brain parenchyma, and serves to cushion and protect the brain, spinal cord, and the delicate structures protruding from or into the brain and spinal cord. Essentially, the brain and spinal cord are suspended within this CSF. CSF produced in the ventricles exits into the subarachnoid space located between the dura and the pia lining the external surface of the brain and spinal cord, where it is reabsorbed into venous sinuses via the arachnoid villi.

Peripheral nerves are composed of bundles of axons, some myelinated and some unmyelinated. The myelin is produced from the cytoplasmic membranes of Schwann cells. These Schwann cells and axons are embedded within the endoneurium, which is an extracellular matrix composed of type III collagen and some fibroblasts. Within the nerve, bundles of axons (fascicles) are surrounded by the perineurium, which is composed of multiple layers of specialized fibroblasts with tight junctions and a basement membrane. These tight junctions between perineurial fibroblasts form the blood-nerve barrier. The nerve fascicles are bundled together and surrounded by an external connective tissue layer called the epineurium. Axons within peripheral nerves can be from sensory nerves that transmit sensory information back to the CNS ("afferent" nerves) from motor nerves that carry stimulatory signals to the motor endplates on skeletal muscle ("efferent" nerves), or can be autonomic. Therefore peripheral nerves can be referred to as sensory nerves (containing primarily sensory axons), motor nerves (containing primarily motor fibers), or mixed (containing both motor and sensory fibers).

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REPRODUCTIVE SYSTEM AND MAMMARY GLAND

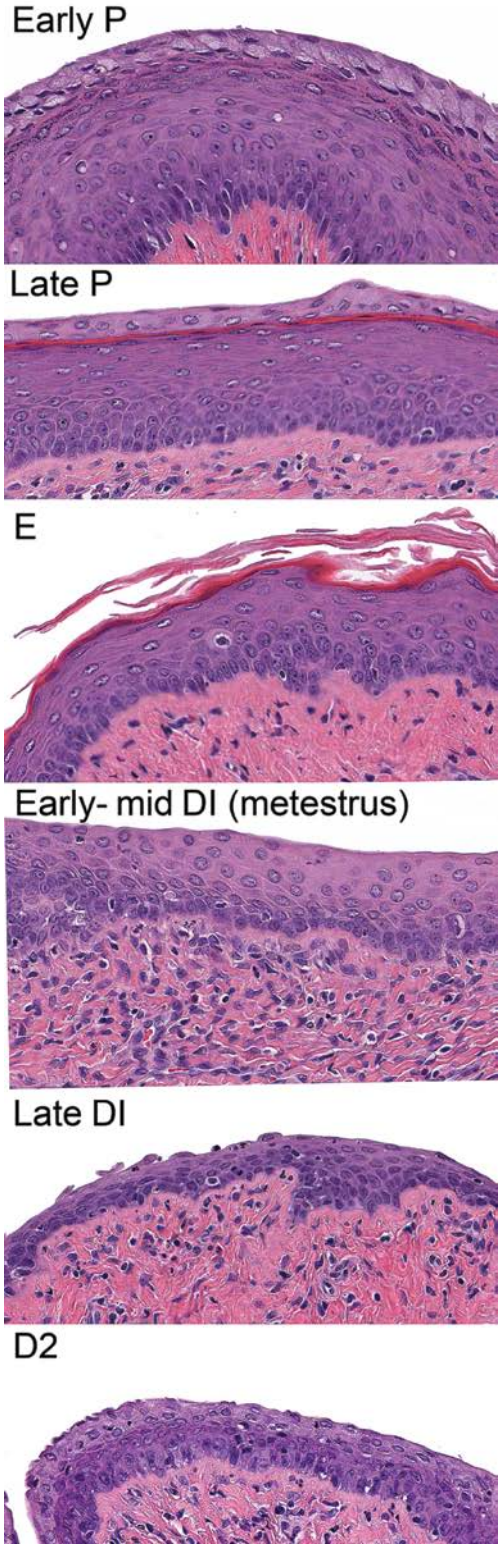


FIGURE 1 Estrous cycle–dependent changes in the vaginal epithelium, SD rat, H&E (P = proestrus, E = estrus, D1 = early diestrus or metestrus, D2 = diestrus). (Reproduced with permission of the Academic Press from Rudmann et al. 2013, in *Haschek and Rousseaux's Handbook of Toxicologic Pathology*. 3rd ed.)

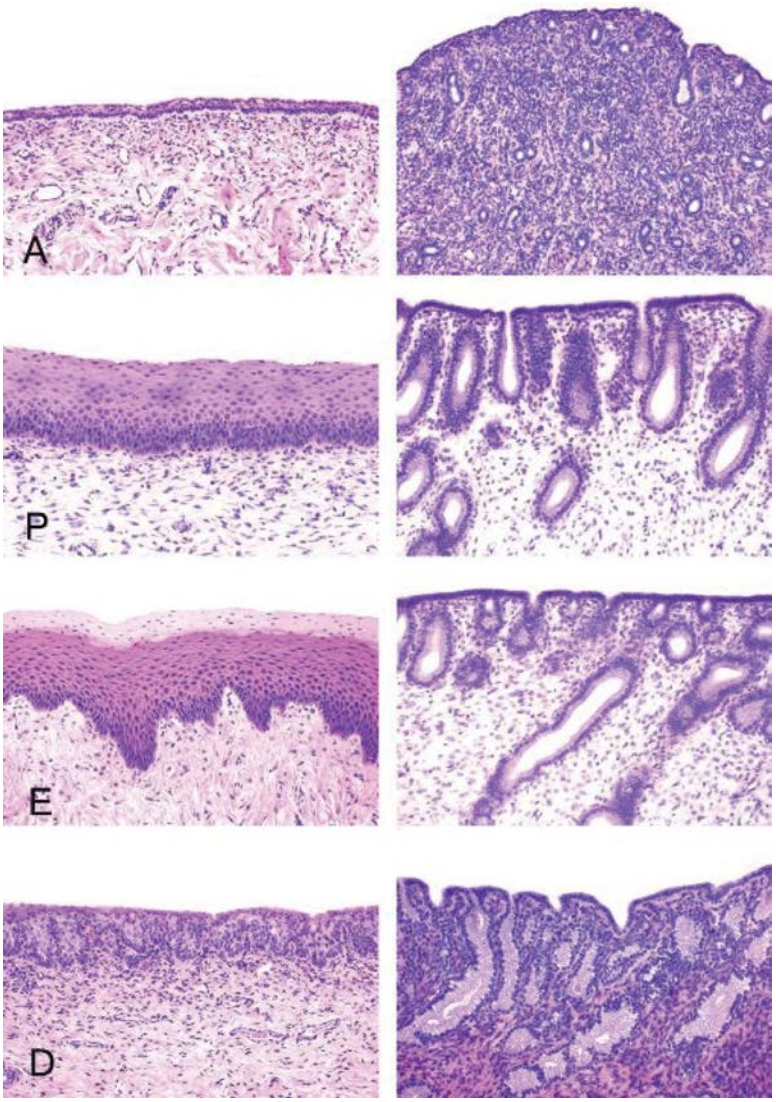


FIGURE 2 Estrous cycle–dependent changes in the vagina and uterus in the dog, H&E (A = anestrus, P = proestrus, E = estrus, D = diestrus). (Reproduced with permission of the Academic Press from Rudmann et al. 2013, in *Haschek and Rousseaux's Handbook of Toxicologic Pathology*. 3rd ed.)

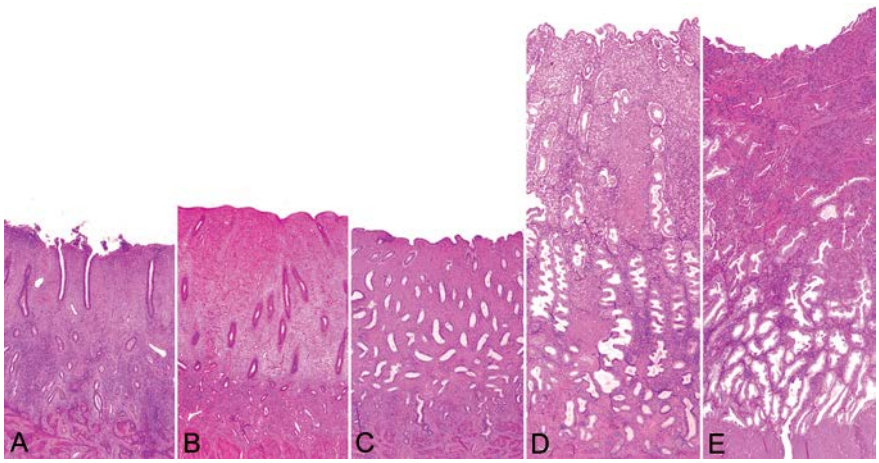


FIGURE 3 Estrous cycle–dependent changes in the uterus in the monkey, H&E (A = regenerative phase, B = follicular phase, C = periovulatory/early luteal phase, D = luteal phase, E = early menstrual phase). (Reproduced with permission of the Academic Press from Rudmann et al. 2013. in *Haschek and Rousseaux's Handbook of Toxicologic Pathology*. 3rd ed.)

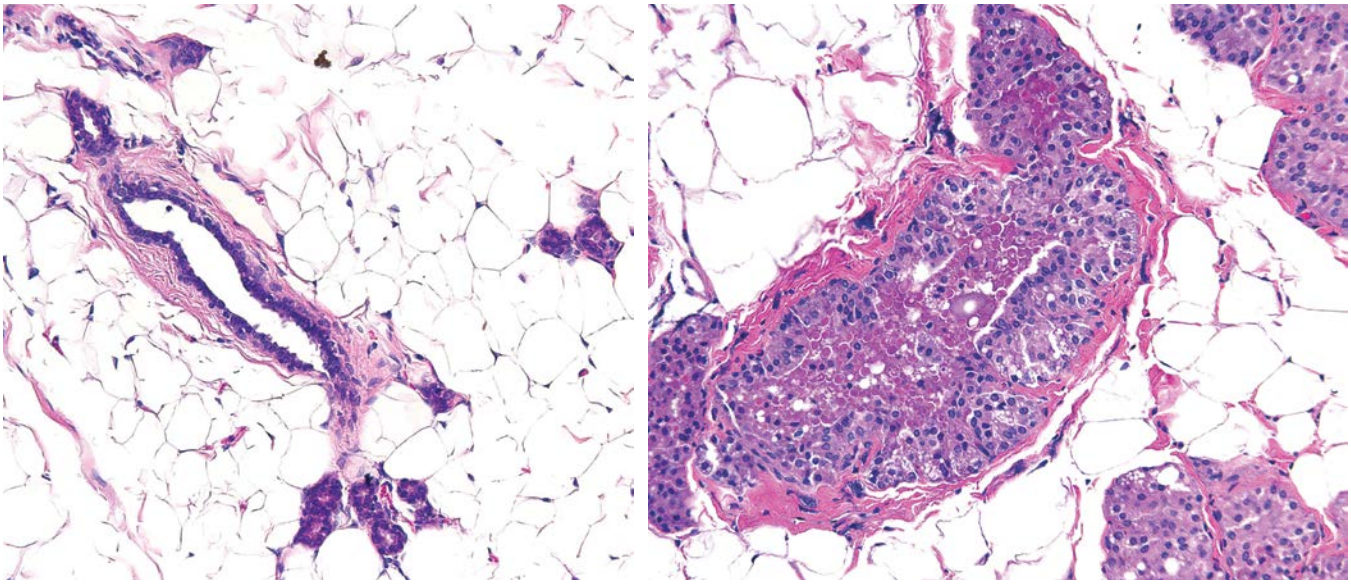


FIGURE 4 Mammary gland, female (left) and male (right) rat, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

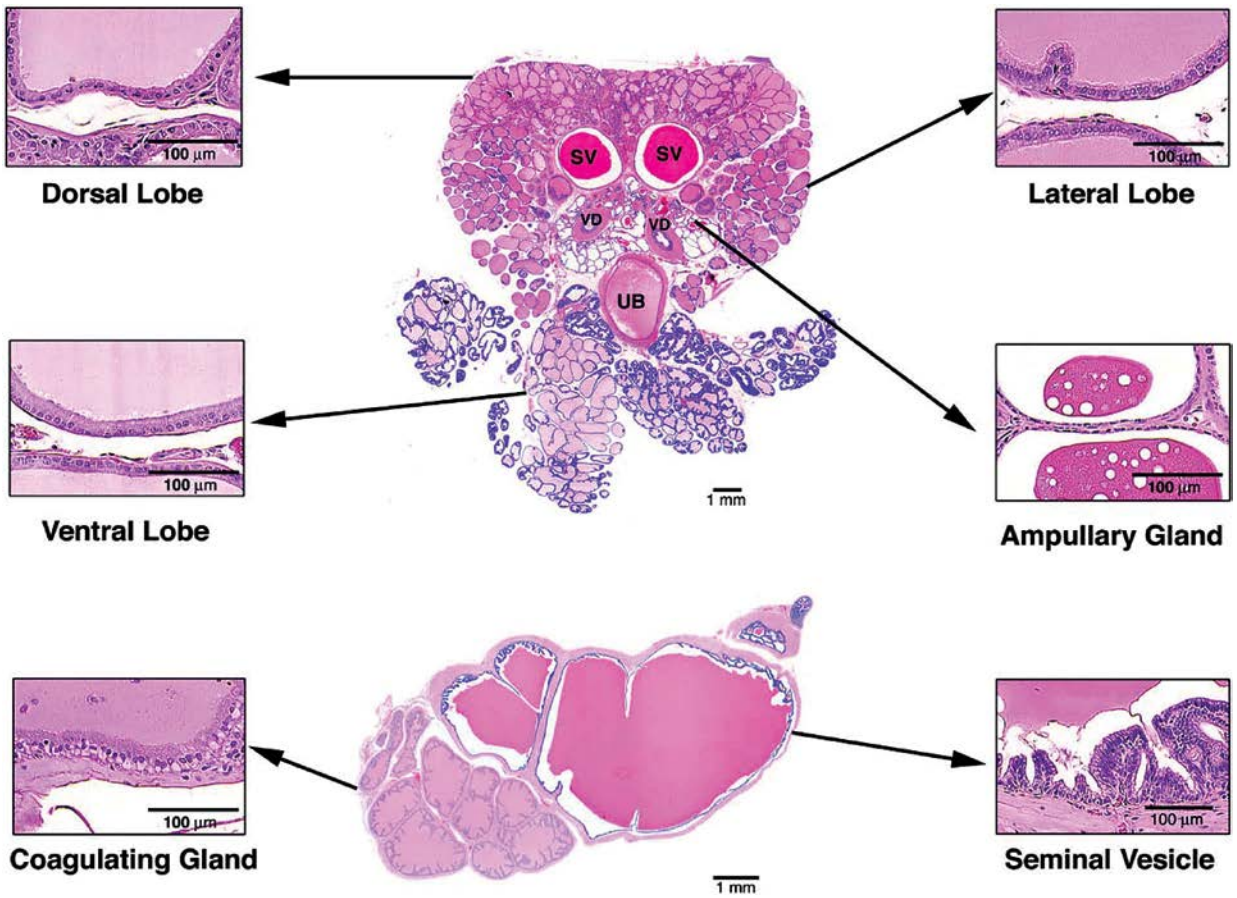


FIGURE 5 Normal anatomy and histology, rat accessory glands, H&E. (Reproduced with permission of Society of Toxicologic Pathology from Creasy et al. 2012.)

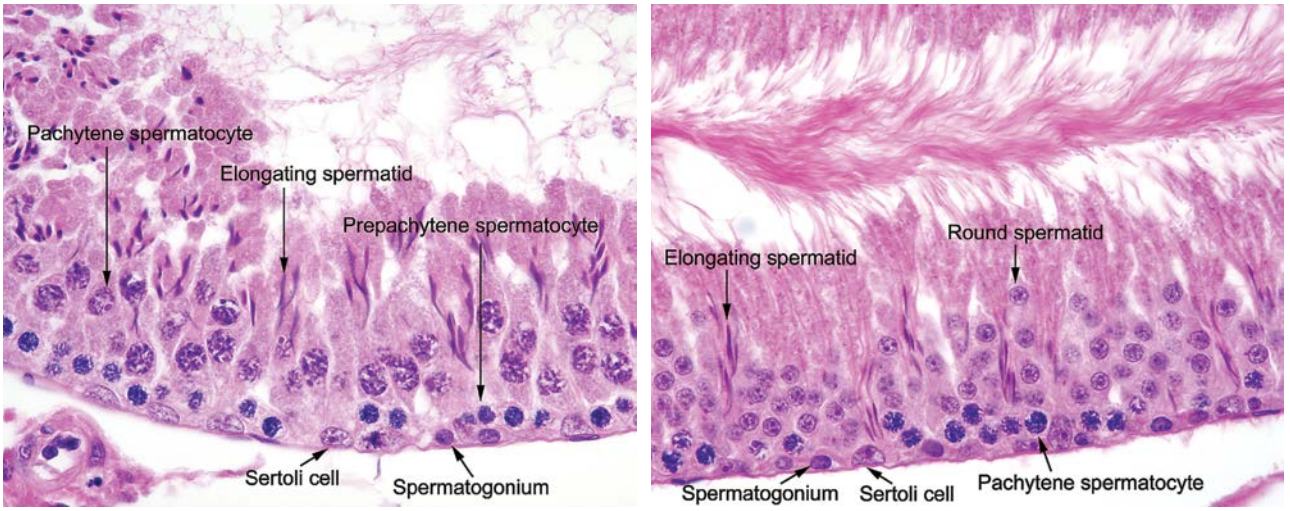


FIGURE 6 Germ cells of spermatogenesis phases, testis, rat, H&E. (Reproduced with permission of Society of Toxicologic Pathology from Creasy et al. 2012.)

RESPIRATORY SYSTEM

Alveolar macrophages play an important role in innate immunity in the lung, and act as antigen-presenting cells. This second function, when combined with their mobility (via transepithelial migration to the lymphatic system) means they are an important link between innate and adaptive immunity. In sections taken from lungs fixed by formalin instillation, alveolar macrophages appear rounded and often "free-floating" in the alveolar airspace. This is an artifact of the fixation technique, and in healthy lungs fixed with formalin vapor they appear flattened, and typically concentrate at alveolar septal junctions. Ultrastructurally they are characterized by the presence of numerous mitochondria and secondary lysosomes. Activated macrophages have been subdivided into classically activated (M1), which have largely antiproliferative, inflammatory, and cytotoxic activity, and alternatively activated (M2), which have a generally anti-inflammatory impact and are involved in initiation of wound healing and tissue remodeling. The activation state is dynamic, and an individual macrophage may switch between states depending on its environment. There is also evidence of regulation of the alveolar macrophage inflammatory response by direct interaction with the airway epithelium. Markers of an activated state include inducible nitric oxide synthase for M1 macrophages and arginase 1, Fizz1, and Ym1/2 for M2 macrophages. CD68 IHC is commonly used as a general marker for alveolar macrophages.

Bronchi are the larger conducting airways of the respiratory system, with the first generation branching from the distal trachea, and each subsequent generation becoming progressively narrower. The walls of bronchi are supported by cartilage, and interspecies differences in their arrangement and epithelial lining exist. In humans and nonhuman primates, branching is dichotomous, while in the rat and mouse, it is monopodial. In nonhuman primates, goblet cells and basal cells predominate in the bronchial epithelium, whereas the club cell is the principal nonciliated cell seen at this level in other laboratory animals. Club cells are also common throughout the respiratory tree in mice.

Bronchioles are the most distal conducting airways and are characterized by thin walls, which in most laboratory species are devoid of cartilage. The bronchioles of rhesus monkeys, in addition to containing cartilage, also contain large bundles of smooth muscle that are not seen in other laboratory animals. The main secretory cell at this level is the club cell, and goblet cells are not normally present.

Clara cell, see the preferred term **Pulmonary club cell**.

Pulmonary club cells (formerly known as Clara cells) are a cell type that is generally confined to the terminal and respiratory bronchioles, although in the mouse they are found throughout the airways, including the trachea. The cells have a characteristic apical bleb, which suggests apocrine secretion capability. In most species, club cells contain large amounts of drug-metabolizing enzymes, and are also thought to be involved in the synthesis of airway surfactant; however, in the dog, the cell cytoplasm is mostly occupied by glycogen granules. The cells are readily identified immunohistochemically with a CC16 antibody.

Synonym(s): **Clara cell**.

Pulmonary surfactant is a mixture of approximately 90% lipids (mostly phospholipids), and approximately 10% proteins (A–D) and is responsible for reducing alveolar surface tension. It is synthesized and secreted by the alveolar type II cells as lamellar bodies which unravel to form tubular myelin. The tubular myelin subsequently disaggregates to form an alveolar surface film. Most surfactant is recycled by type II cells, with the remainder being catabolized by alveolar macrophages. Of the surfactant proteins, SP-B and SP-C become incorporated into the phospholipid membranes and stabilize the alveolar surface film; SP-A has a role in the formation of tubular myelin, while SP-D regulates the size of the surfactant lipid pool. In addition, SP-A and SP-D are components of the innate immune system,

functioning as collectins (i.e., collagenous $Ca2^{+}$-dependent defense lectins), binding to a broad spectrum of microorganisms.

Respiratory bronchiole is the most distal bronchiole and represents a transition between the functions of air conducting and gas exchange. It is present in nonhuman primates and carnivores but not other laboratory species. These airways are characterized by alveolar air spaces opening directly from their walls such that they have a conducting function but also contribute directly to gas exchange.

Type I pneumocytes form thin epithelial barrier (<0.1 μm in places) across which gas exchange occurs in the alveoli. Type I pneumocytes cover approximately 98% of the alveolar surface, and they also function to regulate solute and water movement between blood and the airspace. These cells are terminally differentiated and normally lack mitotic activity. Aquaporin-5 is an ATI-specific marker in the lung parenchyma.

Type II pneumocytes are located at the intersections of alveolar walls, act as progenitors for type I pneumocytes, produce and secrete surfactant, and are involved in transepithelial fluid and electrolyte transport. By transmission electron microscopy (TEM), type II pneumocytes are characterized by the presence of cytoplasmic lamellar and multivesicular bodies, and numerous microvilli are present on their apical surface. These cells may be demonstrated by alkaline phosphatase histochemistry or immunohistochemistry.

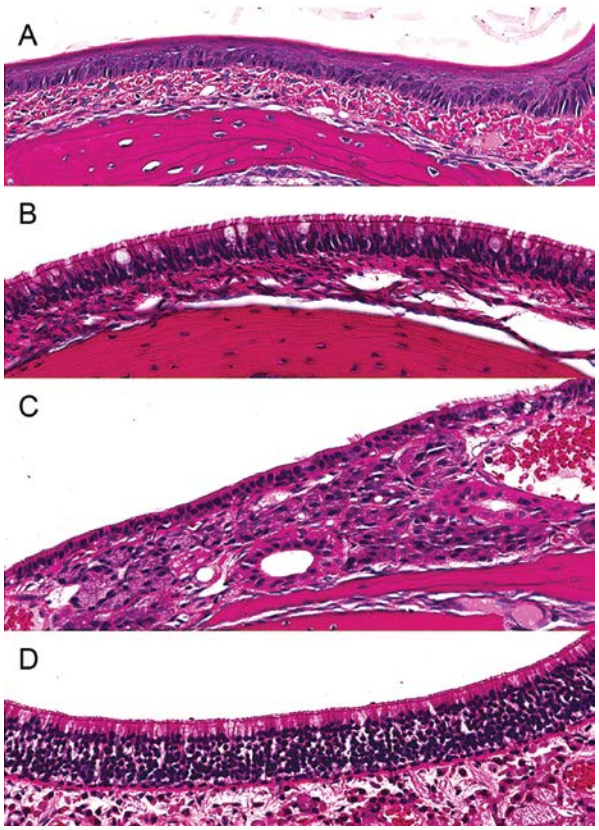


FIGURE 1 Nasal cavity epithelia, H&E: (A) squamous; (B) respiratory; (C) transitional; (D) olfactory.

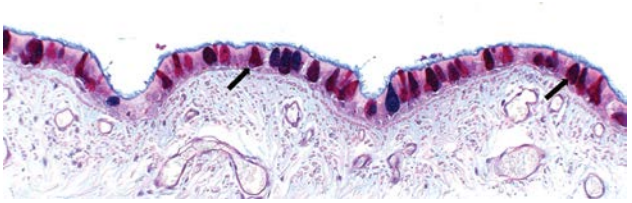


FIGURE 2 Respiratory epithelium, bronchus, dog, PAS/AB. Note numerous goblet cells (arrows) and surface cilia (blue).

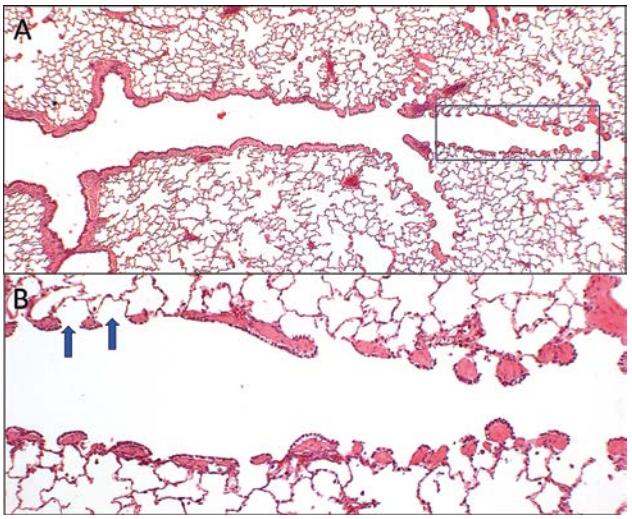


FIGURE 3 (A) Low power image of airway in dog lung, H&E. Bronchiole (left of image) branches into respiratory bronchioles (respiratory bronchiole illustrated by inset). (B) High power image of respiratory bronchiole from inset in panel A. Note alveoli opening directly from wall of respiratory bronchiole (arrows).

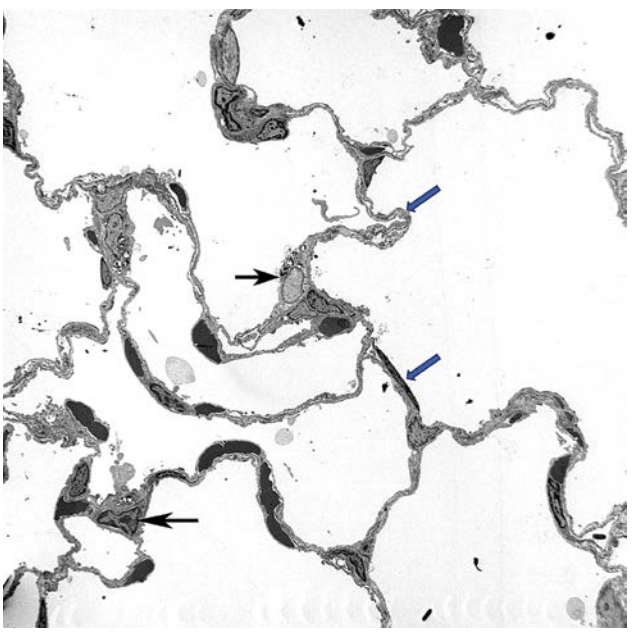


FIGURE 4 Alveolar structure, TEM, 1500×. Note thin epithelial barrier of type I pneumocytes (blue arrows), facilitating gas exchange, and type II pneumocytes found at intersections of alveolar walls (black arrows).

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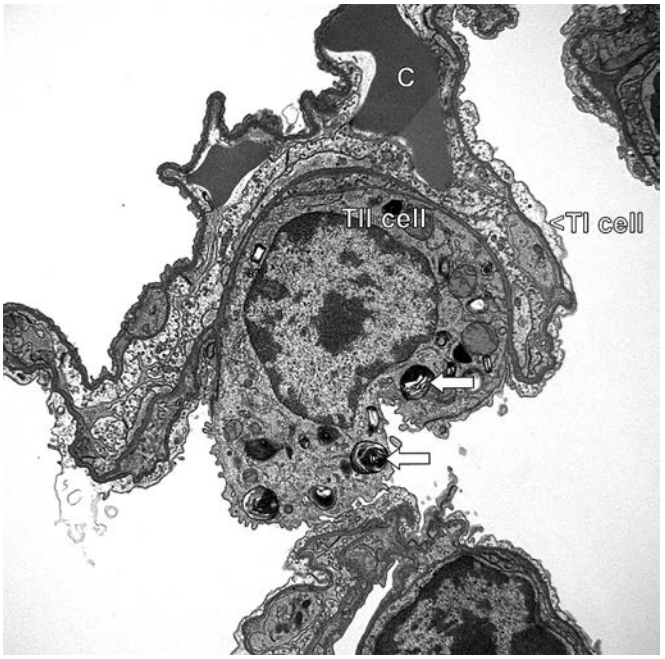


FIGURE 5 Type II pneumocyte (TII cell), TEM, 8000×. Note typical cytoplasmic lamellar bodies (arrows), capillary lumen with erythrocyte (C), and adjacent to capillary endothelium, the epithelial barrier formed by a type I pneumocyte (TI cell).

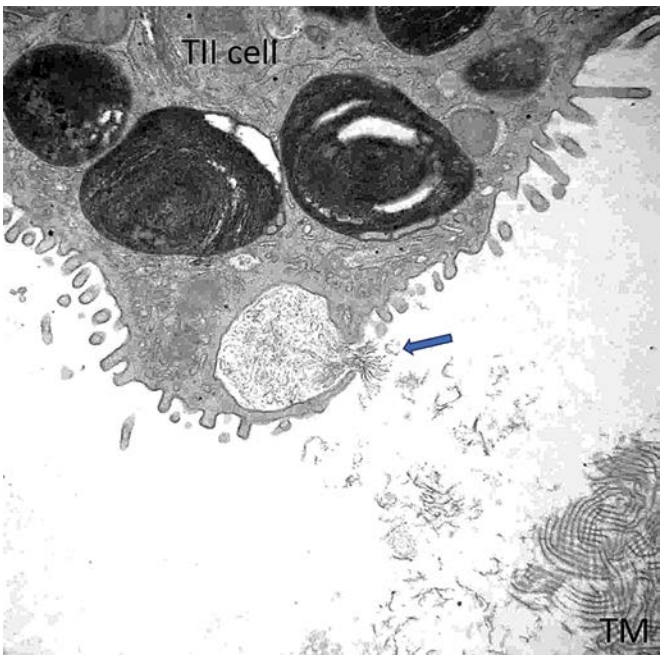


FIGURE 6 Type II pneumocyte (TII cell), TEM, 20,000×. Secretion of surfactant material (arrow), with typical appearance of secreted tubular myelin (TM) in bottom right of image.

SKIN

The skin is comprised of four interdependent elements: the epidermis, dermis, subcutis, and adnexa.

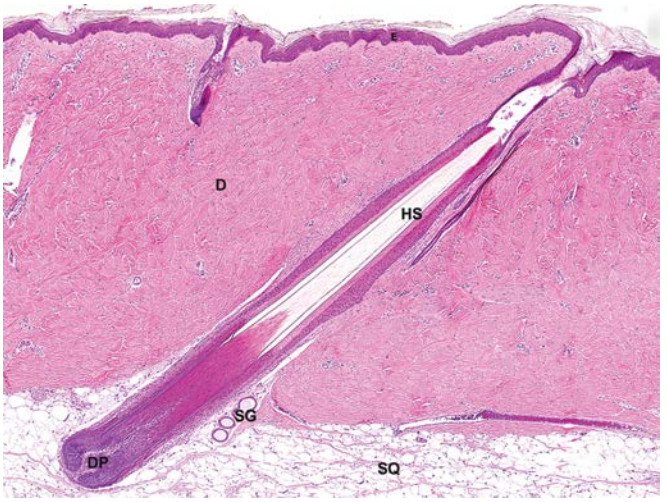


FIGURE 1 Skin from a pig, H&E. E = epidermis, D = dermis, DP = dermal papilla, HS = hair shaft, SG = sweat gland, SQ = subcutis.

Epidermis is composed of multiple, organized layers with distinct features. The innermost layer is the stratum basale where the stem cells reside (also called stratum germinativum) and in normal skin where mitoses occur. Layers external to the basilar layer progress through postmitotic differentiation to produce, in order, the stratum spinosum (spiny cell layer), stratum granulosum, and finally the most superficial layer (stratum corneum), which is composed of anuclear cornified (keratinized) cells. In some skin areas where the keratinized layer is especially thick, such as the pads of the feet, there is also the stratum lucidum within the stratum corneum (also known as the corneal cell layer, keratinized cell layer, or squamous cell layer) at the external surface.

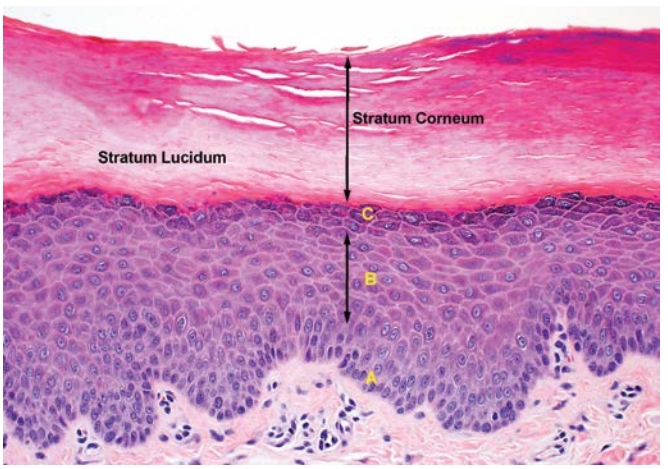


FIGURE 2 Layers of epidermis: A = stratum basale; B = stratum spinosum; C = stratum granulosum; stratum corneum includes a stratum lucidum. Rat foot pad, H&E.

The relative thickness of these layers varies depending on the regions of the body and between species, and is generally thicker in regions with little or no hair relative to densely haired regions. The stratum basale is characterized

by cuboidal to columnar cells, with open-faced nuclei and a relatively high rate of mitosis, that are attached to the basal lamina of the epidermis or to hair follicles. Mitoses within the stratum basale replace and renew this layer, and mitoses between the stratum basale and stratum spinosum generate layers above the stratum basale (suprabasal layers) as the epidermis continually turns over. Mitoses above the stratum basale (suprabasilar mitoses) are considered abnormal and indicate an increased rate of (dysregulated) epidermal turnover. The stratum spinosum progresses from polyhedral to rhomboid-shaped cells that still have nuclei and intercellular adhesions with the development of desmosomes that give the layer a characteristic "spiny" appearance. The stratum granulosum has rhomboidal to flattened squamous cells with pyknotic nuclei and intracytoplasmic keratohyalin granules; this layer becomes progressively more dehydrated closer to the external surface with a loss of nuclei. When present, the stratum lucidum consists of homogenous squamous cells without keratohyalin granules that do not stain well with hematoxylin-eosin on histologic section. The stratum lucidum is only apparent in very thick epidermal regions such as the footpads, palms, or the nasal region of animals, as in dogs. The stratum corneum is characterized by several layers of dehydrated, anucleated, squamous, cornified (keratinized) cells. There are two main types of keratin: soft keratin that is present as a component of the majority of skin surfaces with continual renewal and loss by desquamation, and hard keratin that is present in skin appendages such as hair, hooves, and nails and contains high quantities of cysteine with numerous disulfide bonds for strength. The latter is generally not lost by desquamation. The layers of the epidermis have been described as a "brick" (cell), and "mortar" (intercellular lipid) arrangement, with the thicker "bricks" at the bottom, and progressively thinner "bricks" at the top. The stratum corneum is the primary barrier for absorption of substances through the skin. Any compound absorbing through the skin follows one of three routes: through the intercellular lipid between cells of the stratum corneum; through the keratin bundles within the stratum corneum; or via the skin appendages, such as sweat glands, sebaceous glands, or hair follicles. For this reason, there are considerable interspecies differences in degrees of absorption of substances through the skin due to differences in thickness of the skin, especially the stratum corneum, different intercellular lipid compositions, and differences in the density of hair follicles and other appendages. In general, the skin of domestic swine (or minipig within the context of a species of laboratory animal sometimes used in toxicologic pathology) most closely resembles human skin, with similar thickness of the various layers and hair follicle density. As with other species, both swine and humans have variable skin thickness, hair follicle density, and type and density of skin appendages in different regions of the body (Figure 3).

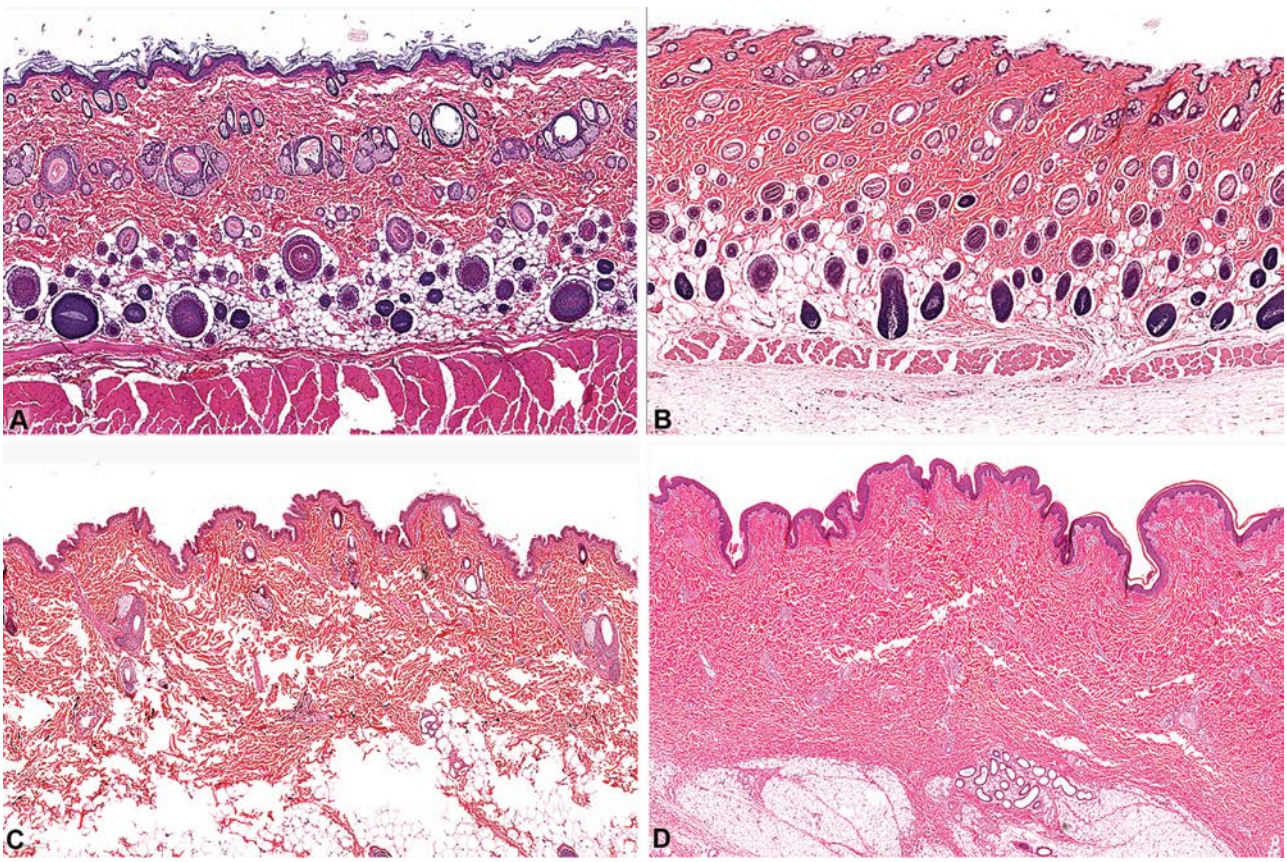


FIGURE 3 Normal rat (A), mouse (B), monkey (C), and pig (D) skin, H&E. Similarities exist between rodent species, but rodent, monkey, and pig skin differ significantly.

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Dermis is a fibrous and elastic layer of skin below the epidermis and above the subcutis, derived from mesoderm. Dermis gives the skin its strength and elasticity through its fibrous extracellular matrix composed primarily of collagen fibers, elastic fibers, and fibrillin. It contains the blood vessels, lymphatics, and nerves that supply the skin, as well as the skin appendages consisting of hair follicles, sweat, and sebaceous glands. The adventitial dermis is a loosely woven layer of thin fibrils just beneath the epidermis surrounding adnexa and contains the majority of type III collagen in the dermis. The reticular dermis is composed of thick, coarse, interwoven fibers, and is primarily composed of type I collagen.

Subcutis (hypodermis) is the deepest layer of the skin, underlying the dermis. It attaches the skin to underlying tissues and contributes to energy storage and thermoregulation with its adipose-rich composition. In addition to fat, this skin layer is comprised of dense connective tissue, vessels, and nerves that provide strength and shock absorption, and aid in elasticity.

Adnexa are skin appendages that consist of hair follicles and hair shafts with their associated arrector pili muscle and sebaceous glands (collectively referred to as the pilosebaceous unit), as well as apocrine and eccrine sweat glands. Other skin appendages such as claws, and their homologues nails, are also commonly included as skin adnexa. All cutaneous adnexa develop embryologically from surface ectoderm.

Hair follicle is comprised of three distinct segments: the outermost infundibulum, which is contiguous with the interfollicular epidermis and lined by stratified squamous epithelium; the isthmus, which extends from the sebaceous gland duct to the arrector pili muscle insertion and is lined by an epithelial sheath that exhibits distinctive tricholemmal keratinization; and the deepest inferior segment, which contains the hair bulb composed of epithelial matrix cells that encircle the dermal papilla. The hair shaft is composed of an inner medulla, a surrounding cortex, and outer cuticle. The arrector pili muscle attaches to the hair follicle and has functions in piloerection as well as in gland secretion under cholinergic control (see figure for detail).

At the base of the follicle is the hair bulb, which is composed of the hair matrix, mitotically active epithelial cells that produce the hair shaft, and the dermal papilla, which is an extension of the dermis encircled by the hair bulb and composed of mesenchymal cells. Hair matrix cells give rise to the inner root sheath, which is characterized by the presence of intracytoplasmic eosinophilic trichohyalin granules and is attached to the hair shaft cuticle. The outer root sheath is a downgrowth of the surface epidermis and contains a slightly expanded region near the insertion of the arrector pili muscle, termed the "bulge," which contains keratinocyte stem cells with a highly proliferative potential that are capable of repopulating both the pilosebaceous unit as well as the epidermis during the process of wound repair. The bulge has been described to date only in humans and mice.

Hair growth cycle consists of three phases: anagen, catagen, and telogen. Anagen is the active growth phase, characterized by elongated hair follicles and hair shafts with active follicular bulbs that make contact with the dermal papilla. Catagen is the transition phase, characterized by follicular atrophy and tricholemmal keratinization. Telogen is the resting phase characterized by marked follicular atrophy, absence of a hair shaft, and complete disengagement of the atrophied follicle bulb from the dermal papilla.



FIGURE 4 A = Actively growing anagen hair with prominent, active hair bulb (HB), with hair matrix (HM) and large dermal papilla (DP). The inner root sheath (IRS), and external root sheath (ERS) are clearly visible. B = Two late catagen/early telogen hair follicles with atrophied dermal papilla (DPa), and inactive hair matrix. Mouse, H&E.

Sebaceous glands develop from the follicular isthmus and are composed of a short duct lined by keratinized squamous epithelium and a glandular component composed of large polyhedral lipid-laden cells that develop from a surrounding peripheral ring of basaloid epithelial cells. The large polyhedral glandular cells undergo holocrine secretion by rupture, and slough their contents (termed sebum) into the short duct and then into the isthmus of the hair follicles where it spreads to the epidermal surface and functions to lubricate the skin surface. Sebum also has antimicrobial properties associated with its free fatty acid content.

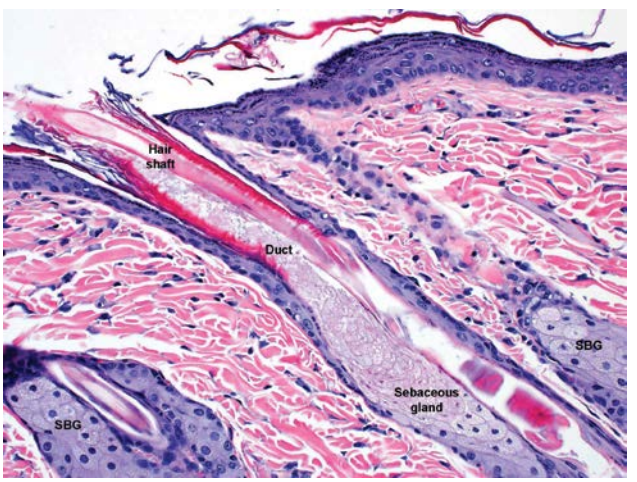


FIGURE 5 Sebaceous gland (SBG), with duct emptying into hair shaft. SBGs associated with adjacent hair follicles are also present. CD Hairless Rat, H&E.

Sweat glands have two types: apocrine and eccrine. Apocrine sweat glands are the most common in animals other than humans. They are widely distributed in most animals, while in humans their distribution is limited to the axillary and inguinal region as well as to the nipples. The apocrine gland duct terminates at the hair follicle at or near the sebaceous gland duct. The apocrine secretion is a watery, proteinaceous material derived from blebs of cytoplasm that arise from the apices of the simple columnar glandular epithelia. Their function is not clear, but they are related to accessory scent glands (e.g., porcine mental organ, eyelid/external ear glands, glands of anal sac in dogs, etc.) that produce attractant odors in some species. Mammary glands are also modified apocrine glands that specialize in producing milk. Eccrine glands are merocrine glands that are composed of a long coiled secretory tubule and a connecting long excretory duct lined by simple columnar epithelium that ends at the epidermal surface. Their function is thermoregulatory and they act by secreting water and salts in response to increased body temperature. They are widespread throughout the body in humans and great apes, but in other animals are limited to areas such as the foot pads in dogs.

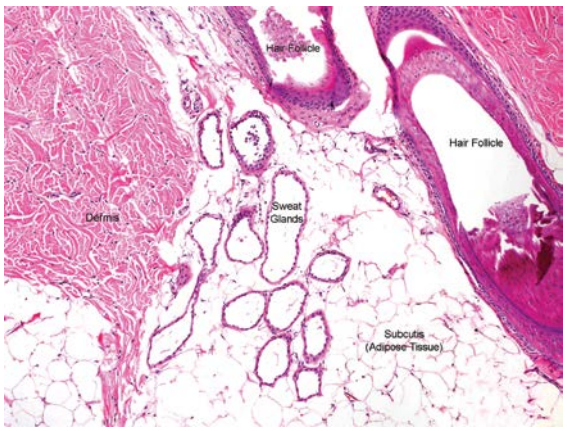


FIGURE 6 Sweat glands from a pig, H&E.

SPECIAL SENSES

The special senses are specialized organs that provide vision (eye), hearing and balance (ear), smell (nasal cavity), and taste (tongue). These organs are supported by the brain (visual, auditory and gustatory cortices, and olfactory bulb), eye (for balance), and specialized structures on the tongue (taste buds) and in the nasal cavity (olfactory epithelium, vomeronasal organ, septal organ of Masera, and Grueneberg ganglion). For toxicologic pathologists, examination of the special senses is usually restricted to the eye and optic nerve, along with the examination of the nervous system. The tongue may be examined as part of the upper gastrointestinal tract, the outer ear as part of the integument, but examination of the extraocular and periaural glandular tissues, the middle and inner ear, nasal cavity and specific olfactory or nasal chemosensory structures is needs-based or as required for risk assessment of therapeutics targeting these areas. Microanatomy of the eye and ear will be emphasized in this section, noting that microanatomy of the nervous system, and upper respiratory and gastrointestinal tracts should also be consulted.

ANATOMY OF THE EYE AND EXTRAOCULAR TISSUES

Vision occurs via the complex microanatomy of the cornea which provides a clear light-gathering and refractive membrane, a lens for refining the focus of light onto the intraocular neural retina, and transfer of neural signals for processing by the brain via the optic nerve (CN II). The eye is derived as an evagination of the embryonic forebrain with contributions from neural crest and ectodermal and mesodermal tissues. Anomalous development results in lack of or reduced size of the globe, missing or malformed structures along the ocular fissure, dystrophy of individual components, and retained or deficient embryonic vasculature. Maturity of the eye continues postnatally, but altricial species, such as rodents and carnivores born with fused eyelids that do not open until 10–14 days postnatally, will have histologically immature retinas during this postnatal period.

The exposed front of the eye is lubricated and protected mechanically and immunologically by the eyelids (palpebrum), conjunctiva, periocular secretory glands, and the tear film. Meibomian (also called tarsal gland) sebaceous gland secretions at the eyelid margin and the outer haired skin protect the ocular surface from exposure and trauma. Specialized hair follicles along the upper and lower lid margins produce a protective mesh of long cilia (eyelashes), except in the cat and only from the upper eyelid in the dog. The conjunctiva is a thin, transparent mucous membrane in 3 joined sections. The bulbar conjunctiva folds back from the limbus at the edge of the cornea back to the fornix conjunctiva, which folds forward to join to the palpebral conjunctiva which covers the inner surface of the eyelids. The fornix forms a loose pocket, the conjunctival cul-de-sac that permits independent movement of the eye and eyelids. Conjunctiva consists of stratified nonkeratinizing epithelium with goblet cells and melanocytes (in pigmented strains) resting on fibrovascular connective tissue (substantia propria). Conjunctival epithelium is stratified polyhedral to columnar with randomly distributed goblet cells in the nonhuman primate, dog, rabbit, and mouse, and stratified squamous with clusters of goblet cells in the rat. The highest density of goblet cells is found in the fornix and bulbar regions. Closer to the cornea, goblet cells disappear and dendritic Langerhans cells predominate. **Conjunctiva-associated lymphoid tissue**, is most frequently found in the palpebral conjunctiva, is an acquired part of the mucosal immune system. The nictitating membrane or third eyelid is a transparent or translucent epithelial fold that can extend from the medial canthus across the cornea to moisten and protect the eye while allowing vision. This membrane contains hyaline (dog) and elastic (pig and cat) cartilage, and small serous (cat), seromucoid (dog and rabbit), and mucous (pig) glands. The nictitating membrane is vestigial in rodents, nonhuman primates, and humans (semi-lunar fold).

The lacrimal gland system provides apocrine gland secretions that keep the ocular surface moist. This system includes a single dorsal lateral lacrimal gland in nonhuman primates, an extraocular lacrimal gland and gland of the nictitating

membrane (third eyelid) in carnivores, and an extraorbital (or exorbital) lacrimal gland near the ear and intraorbital (infraorbital) gland near the Harderian gland in rabbits and rodents. The Harderian gland is located behind the globe on the nasal side. Glandular tissue in the nictitating membrane (third eyelid) is robust in carnivores but minimal in rabbits. In the absence of a nictitating member in nonhuman primates and rodents, glandular tissue in the conjunctival sac also provides secretions. Lacrimal secretions are distributed to the conjunctiva by multiple ducts, with the small conjunctival glands providing continual supply to the tear film and the larger glands providing excess during irritation. In rodents, the Harderian gland contributes lipid to tears which reduces the need for blinking, and secreted porphyrin imparts a red-brown staining to fur (chromodacryorrhea). Meibomian gland secretions from the eyelid margin contribute lipid in other species. The composition of the precorneal tear film varies between species but in addition to water, includes lipids, mucins, enzymes, cytokines, chemokines, immunoglobulins, and antimicrobial peptides and proteins. Tears drain from the upper and lower puncta at the inner corner of the eyelids. The puncta fuse at the lacrimal sac which drains into the nasolacrimal ducts, which carry lacrimal secretions into the nasal cavity. The paired nasolacrimal ducts are lined by epithelium that may be cuboidal, columnar to stratified squamous epithelium depending on the section level sampled in the nasal cavity.

Anatomically, the eye is often divided into the anterior and posterior segments. The anterior segment consists of the parts in front of the lens including the outer adnexa and fibrous tunic (cornea and sclera) and internally the iris, ciliary body, and lens with the anterior (in front of the iris) and posterior chambers (between the posterior lens and iris) both containing aqueous humor. The posterior segment consists of the components behind the lens including the vitreous chamber with vitreous, the retina, and choroid. The eye can also be thought of as 3 layers with contributions from the anterior and posterior segments consisting of the outer corneoscleral coat (cornea+sclera), the middle uveal or vascular tract including the stroma of the iris and ciliary body and choroid, and the inner retina including the retinal pigment epithelium, the neural retina and epithelium of the ciliary body and iris.

Cornea is the avascular transparent anterior portion of the exterior eye that covers the iris, pupil, and anterior chamber. Relative to the volume of the globe, the cornea is larger in rodents and rabbits compared to dogs and nonhuman primates. Anterior to posterior, a precorneal tear film, an outer, nonkeratinized stratified squamous epithelium, basement membrane with or without a Bowman's layer, stroma, Descemet's membrane, and endothelium form the protective layers of the cornea. The nutrient supply for the cornea consists of the precorneal tear film, limbal scleral vessels, and aqueous humor. Anteriorly, the cornea is a hydrophobic structure of nonkeratinized stratified squamous epithelium, polyhedral wing cells, and basal cells on a basement membrane, with an abrupt change to bulbar conjunctiva at the corneoscleral junction (limbus). Bowman's layer is a subepithelial anterior limiting layer of collagen fibers that is present in humans and nonhuman primates, but is microscopically absent in the stroma of most other mammals. The majority of the cornea is stroma which consists of small diameter collagen fibers (a mixture of type I and V collagens) arranged as flat lamella in a lattice pattern in a proteoglycan matrix with interspersed modified fibroblasts (keratocytes). Ordered turnover of the stromal cells and the complex organization of the lamellae ensure transparency of the cornea. Descemet's membrane is a thin, uniform layer produced by corneal endothelial cells which terminates peripherally at the pectinate ligament. The innermost corneal layer is a monolayer of polarized endothelial cells. Endothelial cells maintain stromal deturgescence (relative dehydration) critical to clarity. Endothelial cell density is variable among species, within the cornea (less dense in the superior than in inferior cornea) and decreases with age. Humans, nonhuman primates, and cats have little or no regenerative capacity and undergo repair by cell sliding (migration) and individual cell enlargement. Dogs have some regenerative capacity, but repair is mostly due to cell sliding. The endothelial cells of rodents can divide throughout life and endothelial cells may form multinucleated cells in rabbits.

The anterior chamber is the space between the cornea and the iris. The posterior chamber is the space between the posterior surface of the iris and the anterior surface of the lens.

Aqueous humor, produced by the ciliary processes, passes from the posterior chamber into the anterior chamber between the iris and the lens. It is drained by the trabecular meshwork in the angle of the eye to an aqueous plexus or the canal of Schlemm (nonhuman primates). The uvea or uveal tract consists of the iris, ciliary body, and choroid. The iris contains blood vessels, muscles, and pigment (melanocytes) in pigmented species. The anterior side of the iris is an incomplete layer of fibroblasts and the posterior side is a double layer of epithelial cells. At the base of the iris, the muscular ciliary body extends from the limbus (transition from cornea to sclera) to the ora serrata (the anterior limit of the retina and choroid). The filtration angle of the eye is a triangular space between the end of Descemet's membrane of the cornea and base of the iris. Aqueous humor, produced by the ciliary processes forms in the posterior chamber, flows through the pupil and enters the anterior chamber to drain via the trabecular meshwork into the angular aqueous plexus (rodents, dogs, and rabbits) or canal of Schlemm (humans and nonhuman primates). The choroid is the posterior portion of the uveal tract that supplies much of the blood to the eye and nutrients to the outer retina. This connective tissue and heavily pigmented vascular layer is between the retina and the sclera. Bruch's membrane is a pentilaminar molecular sieve containing abundant collagen and elastin fibers that also provides physical support between the choroid and the retinal pigment epithelium (RPE). The tapetum lucidum, mostly in the superior half of the fundus, is a specialized layer of the inner choroid of many vertebrates, particularly dogs, but not found in pigs, rodents, rabbits, and nonhuman primates. Its specialized epithelium with intracytoplasmic, reflective crystalline rods rich in zinc reflects light to aid vision in low ambient light. The RPE overlying the tapetum is nonpigmented. The posterior sclera is a dense connective

tissue and grossly white outer coat of the eye where periocular eye muscles attach and which transitions to the anterior cornea. Ocular barriers are involved in immune privilege in the eye, but these epithelial gates allow selective trafficking of leukocytes and antigens across what would otherwise be an absolute barrier. In the anterior segment, the blood-aqueous barrier is a physical blood-ocular barrier composed of tight junctions between endothelial cells of the iridal vessels, and tight junctions between nonpigmented epithelial cells of the ciliary body, which contains fenestrated capillaries.

The lens is an avascular round (rodents) or biconvex (other species) epithelial tissue suspended in aqueous humor of the posterior chamber by modified elastin fibers of the zonular ligament, which are attached to the ciliary body and lens capsule at the equator and provide changes to focal length by altering lens curvature. Proportionally, the round lens of rodents occupies nearly the entire ocular space compared to the smaller space occupied by the biconvex lens in most species. The lens is nourished by the aqueous humor of the posterior chamber and anterior portion of the vitreous. Simple cuboidal epithelial cells that secrete protein to form the capsule are only present on the more flattened anterior lens between the capsule and fibers. The outer lens capsule is a hypertrophied basal laminal. The actively dividing columnar epithelial cells found at the bow region above the lens equator regulate fluid and are progenitors of the new elongated lens fibers progressively laid down from the nucleus to the outer cortex throughout life. The majority of the lens is composed of concentric layers of lens fibers.

Behind the lens is the posterior segment starting with the vitreal cavity containing vitreous. The gel-like vitreous is a loose connective tissue composed of thin, mostly randomly oriented, type II collagen filaments anchored into the basal lamina of the retina, the ciliary body, and the lens. There are no blood vessels or nerves in the vitreous, but a monolayer of scattered tissue-resident phagocytic cells (hyalocytes) is usually embedded in the outer margin near the retina and ciliary body.

The retina is the innermost light-sensitive layer of the eye, and starting adjacent to the vitreous there are 10 layers in mammals:

1. Inner limiting membrane – basement membrane elaborated by Müller glia (neurotransmitter cells that span the entire retina and transmit light to rods and cones).
2. Nerve fiber layer – axons of the ganglion cell nuclei.
3. Ganglion cell layer – nuclei of ganglion cells with axons that become the optic nerve fibers.
4. Inner plexiform layer – contains the synapse between the bipolar cell axons and the dendrites of the ganglion (neuron) and amacrine cells (inhibitory neuron).
5. Inner nuclear layer – contains the nuclei and surrounding cell bodies (perikarya) of the amacrine, horizontal cells (interneurons), and bipolar cells (connection between photoreceptors and ganglion cells).
6. Outer plexiform layer – processes of rods and cones, dendrites of bipolar cells and interneurons.
7. Outer nuclear layer – cell bodies and nuclei of rods and cone photoreceptor cells (outer segment absorbs light and transduces the signal and the metabolically active inner segment with photopigments).
8. External limiting membrane – layer that separates the inner segment portions of the photoreceptors from their cell nucleus.
9. Photoreceptors – layer of rod (low light vision) and cone (color vision and bright light) photoreceptor cells.
10. Retinal pigment epithelium (RPE) – is attached to photoreceptors and Bruch's membrane at the basal surface and consists of outer pigmented cells of the retina which absorb light, phagocytose membranes shed by the photoreceptor cells, provide metabolic balance, secret signaling molecules and provide immune privilege.

Similar to the blood-aqueous barrier of the anterior segment, the blood-retinal barrier is a physical blood-ocular barrier of the posterior segment that provides selective macromolecular occlusion and immune privilege due to tight junctions (zonula occludens) of the retinal endothelium and the RPE, by a discontinuous layer of pericytes and by basement membrane of Müller cells and astrocytes. Specialized regions of the retina include the macula, a central region with a high density of photoreceptor cells and other retinal neurons, the fovea, and optic disc. In nonhuman primates, but not other laboratory animals, the center of the macula is the fovea, an area of densely packed cone photoreceptors and with a pit lacking the inner layers of the retina, which provides high visual acuity. Dogs have a fovea-like area with cone-enrichment without a pit. Abundant ganglion cells around the fovea provide maximal resolution connections to the foveal cones. The optic disc is the area where all the ganglion cell axons exit the retina to the optic nerve and is a visual blind spot. The main blood vessels of the retina enter and leave at the optic disc. The majority of laboratory rodents and non-rodents have a holangiotic (dispersed over retina) retinal vasculature, but the vasculature is merangiotic (horizontal band over myelinated nerve fibers) in rabbits and paurangiotic (restricted around optic disc) in the guinea pig. Normally, the embryonic vasculature atrophies before or shortly after birth, but persistent fetal vasculature of the hyaloidal system around the lens (tunica vasculosa lentis), the vascular connection from the lens through the vitreous to the optic nerve (hyaloid artery and vasa hyaloidea propria) or remnants of other vessels may be encountered.

Toxicologic pathologists should be familiar with the Latin designations for laterality of eyes as these abbreviations are still used in ophthalmology studies for eye observations and sampling: Oculus dexter (OD) for right eye, Oculus sinister (OS) for left eye, and Oculi uterque (OU) for both eyes. Multiple unique routes of ocular drug delivery for the eye are also based on anatomical compartments. Intraocular injection is a nonspecific term for administration of a substance into the eye with a hypodermic needle, but the anatomical compartment-specific terms are preferred: 1) intravitreal (injection into

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the vitreous body, 2) intracameral (injection into the anterior or posterior chamber), 3) sub-Tenon's (injection into the lymphatic space between Tenon's capsule and sclera), 4) subretinal (between the retina and retinal pigment epithelium), 5) suprachoroidal (space between choroid and sclera), 6) retrobulbar (beside or behind the globe), 7) subconjunctival (below the conjunctival epithelium), and 8) topical (into conjunctival sac or onto cornea and tear film). Systemic delivery is also applicable to ocular therapeutics.

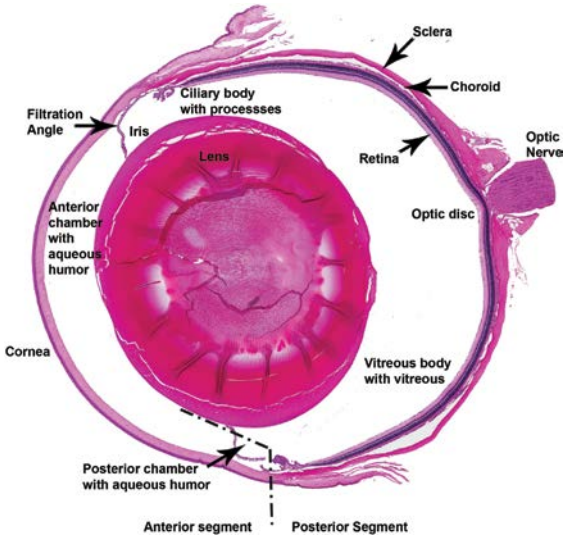


FIGURE 1 Compartments and major structures of the eye, Sprague Dawley rat, H&E.

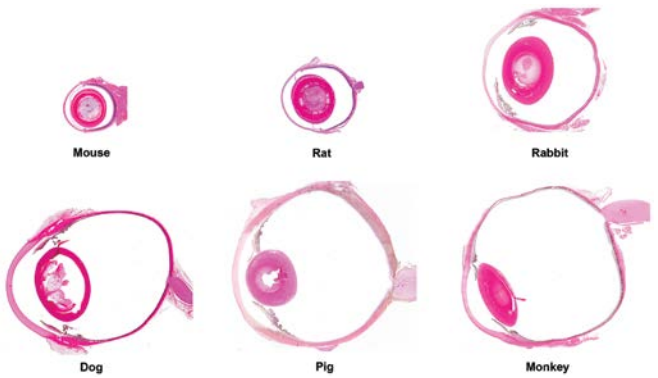


FIGURE 2 Comparative ocular anatomy: the lens shape is round in rodents and biconvex in other species, and the ratio of lens to ocular space is large in mouse and rat, moderate in rabbit, and small in dog, pig, and monkey. Lack of fixation in the center of the lens and sectioning loss and fragmentation of the lens are frequent artefacts, particularly in large eyes. H&E (mouse, rat, rabbit, dog, and monkey) and hematoxylin phloxine and saffron (pig).

Anatomy of the Ear and Associated Glands

Damage to, and inflammation within the delicate cells of the inner ear, fluid imbalances, and neural damage are most frequently responsible for otic pathology and toxicity. Numerous drugs, chemicals, heavy metals, and noise may damage auditory function with tinnitus and loss of hearing at one or more frequencies, or effects on balance causing dizziness, ataxia, and vertigo. Age (young and the old), genetics, trans-tympanic injections, and pre-existing aural or ocular abnormalities may enhance auditory and vestibular dysfunction. The ear is derived from an invagination of the embryonic surface ectoderm with contributions from the mesoderm. Anomalous development results in missing or malformed structures and dystrophy of entire regions or individual components in the external, middle, and inner ear.

The external ear in animals consists of the pinna or auricle (nonhuman primates) on the upper lateral skull and the air-filled auditory or ear canal (external acoustic meatus), which collects and amplifies sound transmitted to the middle ear. The pinnae are lined by typical skin (epidermis on a thin dermis) which is haired (hair follicles and sebaceous and apocrine glands) on the convex side and sparsely haired to hairless on the concave side, and supported on an internal auricular cartilage core. The ear canal in most animals bends from rostroventral to horizontal prior to tunneling into the temporal bone as the internal auditory canal (internal acoustic meatus). The canal is lined by pseudostratified, ciliated columnar squamous epithelium with scattered goblet cells. Except for rodents, circumferential sebaceous (ceruminous) glands are found near the acute angle where the canal turns into the temporal bone. Rather, rodents have a compound sebaceous gland, Zymbal's gland found rostral and ventral to the ear, which is responsible for producing cerumen (ear wax) to mechanically trap foreign bodies. Muscles surround the ears and attach them to the skull to allow movement of the pinna toward sound. In many nonhuman primates, the auricles are vestigial, placed more laterally on the sides of the skull and are immobile or of limited mobility as in humans. The tympanic membrane (eardrum) is the innermost margin between the ear canal and middle ear. Squamous epithelium lines the membrane on both sides, but the lamina propria varies from a thin fibrous section whereas the peripheral sections are vascularized. The outer epithelium of the membrane is lined by a continuation of squamous epithelium from the ear canal and sits on a connective tissue lamina propria lined on the inner side with cuboidal epithelium. Defects in the membrane (usually in the lower pars tensa rather than the upper pars flaccid) heal by epithelial migration.

The middle ear, within the temporal bone, consists of the tympanic cavity, the auditory ossicles and the Eustachian tube. This cavity is lined by a mucous membrane composed of tall columnar cells with goblet cells mostly in the ventral areas and near the Eustachian tube or lined by simple squamous epithelium, including over the ossicles. The dorsal part of the tympanic cavity contains two ossicles, the malleus ("hammer"), and incus ("anvil") attached by ligaments and muscles to the cavity, and with the malleus partially embedded in the tympanic membrane. The middle portion with the tympanic membrane contains the third ossicle or stapes ("stirrup") which is attached by a muscle and ligament to the tympanic cavity and has its footplate within the oval window. The oval window is the boundary between the middle and inner ear. Sound is transmitted from the tympanic membrane into the tympanic cavity by the malleus and incus and then into the stapes and through the oval window into the inner ear. Muscles associated with these ossicles control amplification of sound

such that contraction of the tensor tympani muscle between the tympanic cavity and malleus increases tension and sound transmission across the tympanic membrane. Conversely, contraction of the stapedius muscle attached between the tympanic cavity and the stapes pulls the stapes away from the oval window to reduce sound transmission. Except in old world monkeys and apes, the ventral tympanic cavity contains a thin-walled enlargement of the temporal bone, the tympanic bulla. Nerves including the facial and vagus nerve and several arteries are found in association with the lower tympanic cavity and bulla. The Eustachian (auditory) tube opening is also within this middle portion of the cavity and connects the tympanic cavity to the nasopharynx and clears fluid from the middle ear to the nasopharynx. This connection provides ventilation and allows pressure to be equalized within the tympanic cavity by swallowing or yawning. The Eustachian tube is lined by a columnar ciliated respiratory epithelium with cilia and goblet cells, particularly concentrated at the tympanic cavity end. Mucosa-associated lymphoid tissue may also be identified in the Eustachian tube, particularly after middle ear infections or with aging. The secretions of the Eustachian tube have a surfactant-like quality that decrease surface tension and keep the tube from collapsing. As the Eustachian tube approaches the nasopharynx behind the soft palate, the epithelium has fewer to no goblet cells or cilia, and it leaves the bony support of the tympanic cavity to enter a cartilaginous matrix.

The oval window (connected to the stapes) and the round window sealed by the round window membrane (secondary tympanic membrane) are the two openings connecting the middle and inner ear. These windows are on the lateral wall of the vestibule, a chamber that communicates with the cochlea (otic capsule) which is the sensory organ for hearing (auditory system) and the vestibular apparatus which is the sensory organ for balance (vestibular system) of the inner ear. The cochlea is mostly embedded in the temporal bone (petrous portion) and consists of a supporting osseous labyrinth which surrounds the membranous labyrinth. The cochlea forms a spiral-shaped structure that has 2.5–3.5 turns, depending on the mammalian species. Humans and rats have 2.5 turns, while chinchillas and guinea pigs have 3.5 turns. Apical, middle, and basal levels are defined, each with a thin lining of epithelial cells. Sound waves are differentially detected with the basal turns of the cochlea detecting high-frequency sounds and the apical turns detecting low-frequency sounds. Normally, histologic sections are obtained longitudinally through the modiolus, the conical central axis of spongy bone supporting the cochlea and the cochlear and vestibular branches of the vestibulocochlear nerve (CN VIII). The cochlea is split into three fluid-filled chambers called the scala vestibuli, scala media (cochlear duct), and scala tympani. The scala tympani and scala vestibuli contain perilymph and are continuous chambers that meet at the apical turn (helicotrema). The scala media, containing endolymph, is a separate chamber bounded by the organ of Corti (adjacent to the scala tympani) and Reissner's membrane (adjacent to the scala vestibuli). Non-regenerative hair cells, the mechanosensory epithelium in the organ of Corti are critical to hearing and consist of a single row of inner and a triple row of outer hair cells which have apical stereocilia that contact the endolymph in the scala media. The tectorial membrane, a gelatinous structure of protein and fibrils, floating in the endolymph contacts these stereocilia. A fibrous connective tissue cushion called the spiral ligament forms the outer wall of the scala media. The stria vascularis along the upper portion of spiral ligament produces the endolymph and is a highly vascular structure formed by marginal and basal epithelial cells, and intermediate melanocyte-like cells. The inner ear is protected by immune privilege via the blood labyrinth barrier formed by tight junctions in the stria vascularis which would limit, but not completely exclude exposure to antigens, antibodies, immune cell secretions, and immune cells. Tissue resident macrophages in the spiral ligament and the perivascular macrophage-like melanocytes in the stria vascularis appear to be involved in inflammatory responses in this region. The auditory system is initiated when sound vibrations are transferred to the inner ear by the footplate of the stapes in the middle ear causing displacement of the oval window. This causes movement of perilymph within the scala vestibuli and the scala tympani and this transmitted movement causes the round window membrane to move in the opposite direction to the oval window leading to fluid wave propagation. Perilymph movement also causes movement of structures on the basilar membrane of the organ of Corti, which transfers fluid movement to the endolymph within the scala media. Perilymph is high in sodium and low in potassium (similar to other bodily fluids), but endolymph is high in potassium and low in sodium, forming a critical endocochlear potential across the hair cells. Fluid pressure placed on the tectorial membrane causes the outer hair cells to depolarize which causes an influx of potassium ions. Excitation of the contracting outer hair cells amplifies the initial sound vibration transferred into the fluid wave. Deflection of the inner hair cells by movement of the tectorial membrane induces calcium and potassium channel fluxes and a neurotransmitter potential which activates a synaptic connection with the spiral ganglion. The axons of the spiral ganglion form part of the cochlear branch of the vestibulocochlear nerve which transmits the neural signal to the brain.

The chinchilla is an uncommon laboratory animal, but this species is commonly used in otic research. The chinchilla ear shares an audiogram range and anatomy similar to that in humans. This species has a wide tympanic membrane, surgically accessible middle ear through a very large and thin tympanic bulla, surgically accessible cochlea which projects into the tympanic cavity, and a long lifespan which reduces the dramatic aging of the auditory system seen in short-lived rodents. Unlike most species, the tympanic bullae in chinchillas are exceptionally large and bony struts partially subdivide this structure. The round window is also thinner than in humans, so chinchillas tend to be very sensitive to ototoxicity within the cochlea. Chinchillas also have a permanently semipatulous (semi-patent or open) Eustachian tube, making them a model for pediatric otitis media. Guinea pigs have a similarly prominent and accessible tympanic bulla, middle ear, and cochlea and will also be encountered as a favored species. However, background data for histopathology of other tissues typically

sampled for preclinical safety studies are limited in both the chinchilla and guinea pig.

The vestibular labyrinth or system, responsible for balance, consists of the semicircular ducts within the semicircular canals, the utricle, and saccule which are entirely within the temporal bone. The utricle is close to and communicates with the semicircular canals. The saccule is close to the cochlea and connected to the cochlear duct by the ductus reuniens and to the utricle by the utriculosaccular duct. Uptake and removal of endolymph occurs by the endolymphatic duct and sac which is a termination of the utriculosaccular duct which also connects to the dura mater. The bony semicircular canals are membrane-lined, contain endolymph and have an expanded area at the base, the ampulla, containing a single crista ampullaris, a neuroepithelium that protrudes into the lumen. The three canals are generally orientated in different (X,Y,Z) planes which allow detection of rotation in three dimensions. The cristae ampullaris consists of a loose connective tissue with overlying hair cells and supporting cells. On the luminal surface of the cristae, stereocilia of the hair cells are embedded in a gelatinous mass, the cupula. The semicircular canals detect rotational motion by the inertia of the endolymph which causes the stereocilia to flex and detect angular acceleration of the head. The vestibular branch of the vestibulocochlear nerve (CN VIII) innervating the connective tissue of the cristae synapses with the basilar cytoplasm of the hair cells to transmit the rotational motion to the brain. The saccule and utricle are the otolith organs lined by simple squamous epithelium over the loose connective tissue which detects linear motion and each have a sensing membrane called the macula (otolith membrane), lined by hair cells and supporting epithelial cells. Similar to those of the cristae, the hair cells of the macula are innervated by the vestibular branch of the vestibulocochlear nerve (CN VIII). The hair cells of the macula are embedded in a viscous gel which contains otoliths (microliths, statoliths, statoconia or otoconia). The calcareous otolith crystals are denser than the surrounding gel and fluid and detect gravity and linear acceleration by deflection of the stereocilia on the hair cells and detection of vertical (saccule) or horizontal (utricle) motion.

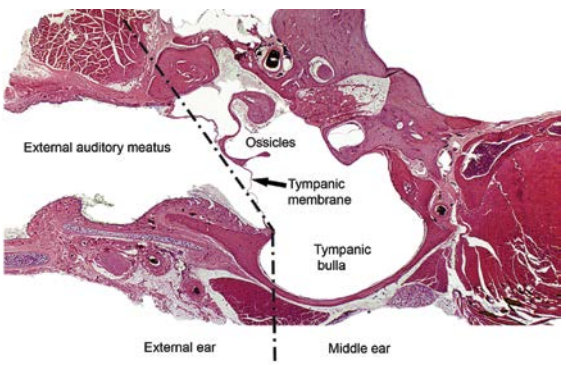


FIGURE 3 Major components of the outer ear and middle ear (tympanic membrane, ossicles, and tympanic bulla), rat, H&E. (Image courtesy of the U.S. National Toxicology Program; National Institutes of Health.)

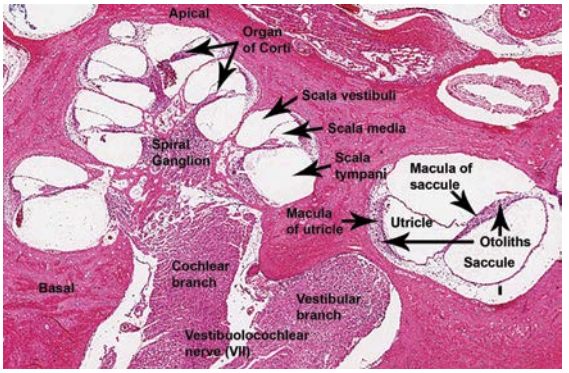


FIGURE 4 Inner ear auditory system (cochlea) and semicircular canals of the vestibular system (utricle and saccule), rhesus monkey, H&E.

URINARY SYSTEM

Normal Anatomy

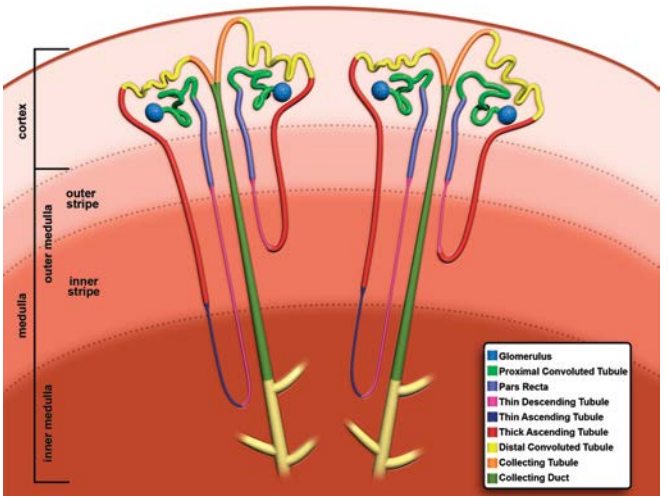


FIGURE 1 Schematic of the normal nephron. (Image provided courtesy of the National Toxicology Program.)

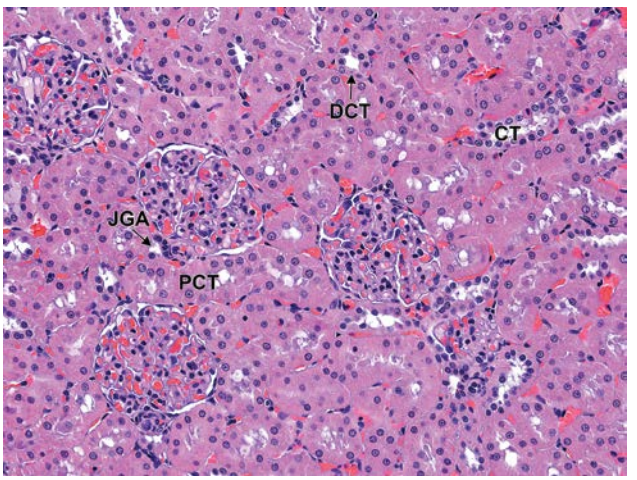


FIGURE 2 Normal microanatomy of rat kidney, H&E. Four glomeruli surrounded by proximal convoluted tubules (PCT), distal convoluted tubules (DCT), juxtaglomerular apparatus (JGA), and collecting tubules (CT). (Image courtesy of the U.S. National Toxicology Program, National Institutes of Health.)

For Further Reading by Organ System

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Figure Acknowledgments

A–Z DICTIONARY

Bone, Muscle, and Tooth: Nonproliferative

Bone decreased (trabecular or cortical)

Bone decreased in the tibia of a rat, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Degenerative joint disease (DJD)

Osteophyte with degenerative joint disease (DJD), femorotibial joint, medial meniscal tear model of osteoarthritis (OA), rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Fossey et al. 2016. *J Toxicol Pathol* 29:49S–103S. https://www.ncbi.nlm.nih.gov/pubmed/27621538.)

Lipogranulomatous inflammation

Mesenteric fat from a C67B1 mouse fed a high fat diet, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Greaves et al. 2013. *J Toxicol Pathol* 26:1S–26S. https://www.ncbi.nlm.nih.gov/pubmed/25035576.)

Cardiovascular System

Angiectasis, valve, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Berridge, B.R. et al. 2016. *J Toxicol Pathol* 29(3 Suppl):1S–47S.)

Arterial intimal thickening, subcutis of rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Berridge, B.R. et al. 2016. *J Toxicol Pathol* 29(3 Suppl):1S–47S.)

Arterial intramural plaque, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Berridge, B.R. et al. 2016. *J Toxicol Pathol* 29(3 Suppl):1S–47S.)

Arterial medial degeneration, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Berridge, B.R. et al. 2016. *J Toxicol Pathol* 29(3 Suppl):1S–47S.)

Arterial medial hemorrhage, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Berridge, B.R. et al. 2016. *J Toxicol Pathol* 29(3 Suppl):1S–47S.)

Arterial medial mineralization, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Berridge, B.R. et al. 2016. *J Toxicol Pathol* 29(3 Suppl):1S–47S.)

Cardiomegaly, rat heart, from a rat treated with a compound that induced symmetrical heart enlargement and increased heart weight, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Berridge, B.R. et al. 2016. *J Toxicol Pathol* 29(3 Suppl):1S–47S.)

Age matched control heart, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Berridge, B.R. et al. 2016. *J Toxicol Pathol* 29(3 Suppl):1S–47S.)

Cardiomyocyte apoptosis, rat, H&E. (Image courtesy of the National Toxicology Program. Reproduced with permission of the Japanese Society of Toxicologic Pathology from Berridge, B.R. et al. 2016. *J Toxicol Pathol* 29(3 Suppl):1S–47S.)

Cardiomyocyte degeneration; hypereosinophilia of peracute injury, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Berridge, B.R. et al. 2016. *J Toxicol Pathol* 29(3 Suppl):1S–47S.)

Focal cardiomyocyte hypertrophy with minimal accompanying hypercellularity, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Berridge, B.R. et al. 2016. *J Toxicol Pathol* 29(3 Suppl):1S–47S.)

Cardiomyocyte necrosis, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Berridge, B.R. et al. 2016. *J Toxicol Pathol* 29(3 Suppl):1S–47S.)

Embolus, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Berridge, B.R. et al. 2016. *J Toxicol Pathol* 29(3 Suppl):1S–47S.)

Myocardial fibrosis, rat, H & E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Berridge, B.R. et al. 2016. *J Toxicol Pathol* 29(3 Suppl):1S–47S.)

Myocardial mineralization, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Berridge, B.R. et al. 2016. *J Toxicol Pathol* 29(3 Suppl):1S–47S.)

Myocardial pigment, rat, Perl's Prussian blue stain. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Berridge, B.R. et al. 2016. *J Toxicol Pathol* 29(3 Suppl):1S–47S.)

Perivascular fibrosis, rat, H&E. (Image courtesy of the National Toxicology Program. Reproduced with permission of the Japanese Society of Toxicologic Pathology from Berridge, B.R. et al. 2016. *J Toxicol Pathol* 29(3 Suppl):1S–47S.)

Endocrine Glands: Nonproliferative

Adrenal cortical atrophy

Adrenal gland, cortex, Sprague Dawley rat, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Adrenal gland cystic degeneration

Adrenal gland, cortex, cystic degeneration, F344/N rat, H&E. (Images provided courtesy of National the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Spontaneously hypertensive rat

Spontaneously hypertensive rat. (Images courtesy of Charles River Preclinical Services, Reno, NV.)

Thyroglossal duct persistence

Thyroglossal duct cyst, B6C3F1 mouse, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Thyroid gland atrophy

Thyroid, glandular atrophy, Harlan Sprague Dawley rat, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Thyroid gland inflammation

Thyroid gland, inflammation, Sprague Dawley rat, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Ultimobranchial cyst

Ultimobranchial cyst, F344/N rat, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Zucker diabetic fatty (ZDF) rat

Zucker diabetic fatty (ZDF) rat. (Image provided courtesy of Charles River Preclinical Services, Reno, NV.)

Gastrointestinal Tract: Nonproliferative

Brunner′ gland atrophy

Duodenum, rat. H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Nolte, T. et al. 2016. *J Toxicol Pathol* 29(1 Supplement Winter):93S.)

Esophageal dilatation/diverticulum

Esophagus, mouse. H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Esophagus erosion/ulcers

Tongue, rat. H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Glandular stomach diverticulum

Glandular stomach, mouse. H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Nolte, T. et al. 2016. *J Toxicol Pathol* 29(1 Supplement Winter):89S.)

Mineralization of glandular stomach

Glandular stomach, rat. H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Nolte, T. et al. 2016. *J Toxicol Pathol* 29(1 Supplement Winter):86S.)

Rectal prolapse

Rectum, Mouse (Bouin's fixed). H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Nolte, T. et al. 2016. *J Toxicol Pathol* 29(1 Supplement Winter):97S.)

Stomach glandular cysts

Stomach, male B6C3F1 mouse. H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

General Pathology

Amyloid

Amyloid in the renal glomeruli of a mouse, H&E. (Reproduced with the permission of Germann, P. and Morawietz, G. (eds.) 2004. Toxicopathology Case Collection CD-ROM. European Society of Toxicologic Pathology. ISBN: 3-9522681-1-9. https://www.eurotoxpath.org/publications/form_cdrom.php?id=casecoll.)

Amyloid in the brain of a transgenic mouse, Congo red stain. (Reproduced with the permission of Germann, P. and Morawietz, G. (eds.) 2004. Toxicopathology Case Collection CD-ROM. European Society of Toxicologic Pathology. ISBN: 3-9522681-1-9. https://www.eurotoxpath.org/publications/form_cdrom.php?id=casecoll.)

Ballooning degeneration

Ballooning degeneration of renal tubular epithelial cells in a rabbit administered anthracyclin, H&E. (Reproduced with the permission of Germann, P. and Morawietz, G. (eds.) 2004. Toxicopathology Case Collection CD-ROM. European Society of Toxicologic Pathology. ISBN: 3-9522681-1-9. https://www.eurotoxpath.org/publications/form_cdrom.php?id=casecoll.)

Basophilia

Basophilia of the tubules of the kidney of a rat, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Callus

Callus in the tail of a rat, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Cholesterol clefts

Cholesterol clefts in the brain of a mouse, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Cystadenoma

Cystadenoma in the ovary of a mouse, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Cystadenocarcinoma

Cystadenocarcinoma of the ovary of a mouse, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Cytomegaly

Cytomegaly and karyomegaly of renal tubular epithelial cells in a mouse, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Degeneration

Degeneration of testicular germ cells in the seminiferous tubules of a dog, H&E. (Reproduced with the permission of Germann, P. and Morawietz, G. (eds.) 2004. Toxicopathology Case Collection CD-ROM. European Society of Toxicologic Pathology. ISBN: 3-9522681-1-9. https://www.eurotoxpath.org/publications/form_cdrom.php?id=casecoll.)

Ectasia

Ectasia of glands within the glandular portion of the stomach of a rat, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Ectopic tissue

Ectopic liver tissue in the kidney of a rat, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Edema

Edema in the testis of a rat, H&E. (Reproduced with the permission of Germann, P. and Morawietz, G. (eds.) 2004. Toxicopathology Case Collection CD-ROM. European Society of Toxicologic Pathology. ISBN: 3-9522681-1-9. https://www.eurotoxpath.org/publications/form_cdrom.php?id=casecoll.)

Eosinophilic globules

Eosinophilic globules in the renal tubular epithelium of a rat, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Erosion

Erosion of the stomach of a rat, H&E. (Reproduced with the permission of Germann, P. and Morawietz, G. (eds.) 2004. Toxicopathology Case Collection CD-ROM. European Society of Toxicologic Pathology. ISBN: 3-9522681-1-9. https://www.eurotoxpath.org/publications/form_cdrom.php?id=casecoll.)

Fat necrosis

Fat necrosis in the mesentery of a mouse, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Fatty change

Fatty change in the liver of a rat, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Glycogen accumulation

Glycogen accumulation in the liver of a dog, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Granular cell aggregate

Granular cell aggregate in the brain of a rat, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Hydropic change

Hydropic change in the nonglandular portion of the stomach of a rat, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Hypertrophy

Hypertrophy of centrilobular hepatocytes in a rodent, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Infarct

Infarct in the myocardium of a rat, H&E. (Reproduced with the permission of Germann, P. and Morawietz, G. (eds.) 2004. Toxicopathology Case Collection CD-ROM. European Society of Toxicologic Pathology. ISBN: 3-9522681-1-9. https://www.eurotoxpath.org/publications/form_cdrom.php?id=casecoll.)

Lipid accumulation

Lipid accumulation in the liver of a rat, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

FA

Lipofuscin accumulation

Lipofuscin accumulation in the brain of a rat, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Luminal cell debris

Luminal cell debris in the epididymis of a dog, H&E. (Reproduced with the permission of Germann, P. and Morawietz, G. (eds.) 2004. Toxicopathology Case Collection CD-ROM. European Society of Toxicologic Pathology. ISBN: 3-9522681-1-9. https://www.eurotoxpath.org/publications/form_cdrom.php?id=casecoll.)

Metastasis

Metastasis of tumor cells to the lung of a rat, H&E. (Reproduced with the permission of Germann, P. and Morawietz, G. (eds.) 2004. Toxicopathology Case Collection CD-ROM. European Society of Toxicologic Pathology. ISBN: 3-9522681-1-9. https://www.eurotoxpath.org/publications/form_cdrom.php?id=casecoll.)

Mitotic figure

Mitotic figures (as indicated by arrows) in the epithelial cells of the cornea of a rat, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Mucification

Mucification in the vagina of a rat, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Pigment accumulation

Pigment accumulation in the spleen of a rat, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Pigmented macrophage

Pigmented macrophages in the liver of a rat, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Thrombosis

Thrombosis of a pulmonary vessel in a rat, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Liver, Gallbladder, and Exocrine Pancreas

Pancreas adipocyte accumulation, mouse pancreas, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Nolte, T. et al. 2016. *J Toxicol Pathol* 29(1 Suppl):1S–125S. https://www.ncbi.nlm.nih.gov/pubmed/26973378.)

Biliary cysts, rat liver, H&E. (Reproduced with permission of the Society of Toxicologic Pathology from Thoolen, B. et al. 2010. *Toxicol Pathol* 38(7 Suppl):5S–81S. http://journals.sagepub.com/doi/abs/10.1177/0192623310386499?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed.)

Pancreatic duct ectasia, mouse pancreas, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Nolte, T. et al. 2016. *J Toxicol Pathol* 29(1 Suppl):1S–125S. https://www.ncbi.nlm.nih.gov/pubmed/26973378.)

Pancreatic edema, mouse pancreas, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Nolte, T. et al. 2016. *J Toxicol Pathol* 29(1 Suppl):1S–125S. https://www.ncbi.nlm.nih.gov/pubmed/26973378.)

Pancreatic eosinophilic globules, mouse pancreas, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Nolte, T. et al. 2016. *J Toxicol Pathol* 29(1 Suppl):1S–125S. https://www.ncbi.nlm.nih.gov/pubmed/26973378.)

Hepatocellular glandular metaplasia, rat liver, H&E. (Reproduced with permission of the Society of Toxicologic Pathology from Thoolen, B. et al. 2010. *Toxicol Pathol* 38(7 Suppl):5S–81S. http://journals.sagepub.com/doi/abs/10.1177/0192623310386499?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed.)

Helicobacter, mouse liver, silver stain. (Reproduced with permission of the Society of Toxicologic Pathology from Thoolen, B. et al. 2010. *Toxicol Pathol* 38(7 Suppl):5S–81S. http://journals.sagepub.com/doi/abs/10.1177/0192623310386499?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed.)

Hepatic cholestasis, dog liver, H&E. (Reproduced with permission of Elsevier from Cattley, R.C. and Cullen, J.M. 2013. In: Haschek, W. et al. (eds.) *Haschek and Rousseaux's Handbook of Toxicologic Pathology*, 3rd ed. Academic Press, Elsevier, San Diego, CA, pp. 1509–1566.)

Hepatic cholesterol granuloma, rat liver, H&E. (Reproduced with permission of the Society of Toxicologic Pathology from Thoolen, B. et al. 2010. *Toxicol Pathol* 38(7 Suppl):5S–81S. http://journals.sagepub.com/doi/abs/10.1177/0192623310386499?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed.)

Hepatic ectopic pancreatic acinar tissue, rat liver, H&E. (Reproduced with permission of the Society of Toxicologic Pathology from Thoolen, B. et al. 2010. *Toxicol Pathol* 38(7 Suppl):5S–81S. http://journals.sagepub.com/doi/abs/10.1177/0192623310386499?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed.)

Intrahepatocellular erythrocytes, mouse liver, H&E. (Reproduced with permission of the Society of Toxicologic Pathology from Thoolen, B. et al. 2010. *Toxicol Pathol* 38(7 Suppl):5S–81S. http://journals.sagepub.com/doi/abs/10.1177/0192623310386499?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed.)

Hepatic extramedullary hematopoiesis, mouse liver, H&E. (Reproduced with permission of Elsevier from Cattley, R.C. and Cullen, J.M. 2013. In: Haschek, W. et al. (eds.) *Haschek and Rousseaux's Handbook of Toxicologic Pathology*, 3rd ed. Academic Press, Elsevier, San Diego, CA. pp. 1509–1566.)

Hepatic peroxisome proliferation, rat liver, H&E. (Reproduced with permission of CRC Press from Cattley, R.C. et al. 2013. In: Sahota, P. et al. (eds.) *Toxicologic Pathology: Nonclinical Safety Assessment*. CRC Press, Taylor & Francis Group, Boca Raton, FL. pp. 313–366.)

Hepatic pigment deposition (lipofuscin), dog liver, Schmorl's stain. (Reproduced with permission of Elsevier from Cattley, R.C. and Cullen, J.M. 2013. In: Haschek, W. et al. (eds.) *Haschek and Rousseaux's Handbook of Toxicologic Pathology*, 3rd ed. Academic Press, Elsevier, San Diego, CA. pp. 1509–1566.)

Mouse hepatitis virus, necrosis and multinucleated cells, mouse liver, H&E. (Reproduced with permission of the Society of Toxicologic Pathology from Thoolen, B. et al. 2010. *Toxicol Pathol* 38(7 Suppl):5S–81S. http://journals.sagepub.com/doi/abs/10.1177/0192623310386499?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed.)

Hepatic inflammation, rat liver, H&E. (Reproduced with permission of CRC Press from Cattley, R.C. et al. 2013. In: Sahota, P. et al. (eds.) *Toxicologic Pathology: Nonclinical Safety Assessment*. CRC Press, Taylor & Francis Group, Boca Raton, FL. pp. 313–366.

Hepatocellular atrophy, rat liver, H&E. (Reproduced with permission of the Society of Toxicologic Pathology from Thoolen, B. et al. 2010. *Toxicol Pathol* 38(7 Suppl):5S–81S. http://journals.sagepub.com/doi/abs/10.1177/0192623310386499?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed.)

Hepatocellular focal/multifocal necrosis, rat liver, H&E. (Reproduced with permission of the Society of Toxicologic Pathology from Thoolen, B. et al. 2010. *Toxicol Pathol* 38(7 Suppl):5S–81S. http://journals.sagepub.com/doi/abs/10.1177/0192623310386499?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed.)

Hepatocellular glycogen accumulation, dog liver, H&E. (Reproduced with permission of Elsevier from Cattley, R.C. and Cullen, J.M. 2013. In: Haschek, W. et al. (eds.) *Haschek and Rousseaux's Handbook of Toxicologic Pathology*, 3rd ed. Academic Press, Elsevier, San Diego, CA. pp. 1509–1566.)

Hepatocellular hypertrophy, with increased endoplasmic reticulum, rat liver, H&E. (Reproduced with permission of CRC Press from Cattley, R.C. et al. 2013. In: Sahota, P. et al. (eds.) *Toxicologic Pathology: Nonclinical Safety Assessment*. CRC Press, Taylor & Francis Group, Boca Raton, FL. pp. 313–366.)

Hepatocellular hypertrophy, with mitochondrial proliferation, rat liver, H&E. (Reproduced with permission of the Society of Toxicologic Pathology from Thoolen, B. et al. 2010. *Toxicol Pathol* 38(7 Suppl):5S–81S. http://journals.sagepub.com/doi/abs/10.1177/0192623310386499?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed.)

Hepatocellular lipidosis, macrovesicular, rat liver, H&E. (Reproduced with permission of CRC Press from Cattley, R.C. et al. 2013. In: Sahota, P. et al. (eds.) *Toxicologic Pathology: Nonclinical Safety Assessment*. CRC Press, Taylor & Francis Group, Boca Raton, FL. pp. 313–366.)

Hepatocellular lipidosis, microvesicular, rat liver, H&E. (Reproduced with permission of Elsevier from Cattley, R.C. and Cullen, J.M. 2013. In: Haschek, W. et al. (eds.) *Haschek and Rousseaux's Handbook of Toxicologic Pathology*, 3rd ed. Academic Press, Elsevier, San Diego, CA. pp. 1509–1566.)

Hepatocellular zonal necrosis, central, rat liver, H&E. (Reproduced with permission of CRC Press from Cattley, R.C. et al. 2013. In: Sahota, P. et al. (eds.) *Toxicologic Pathology: Nonclinical Safety Assessment*. CRC Press, Taylor & Francis Group, Boca Raton, FL. pp. 313–366.)

Hepatocellular zonal necrosis, portal, rat liver, H&E. (Reproduced with permission of Elsevier from Cattley, R.C. and Cullen, J.M. 2013. In: Haschek, W. et al. (eds.) *Haschek and Rousseaux's Handbook of Toxicologic Pathology*, 3rd ed. Academic Press, Elsevier, San Diego, CA. pp. 1509–1566.)

Hepatocellular zonal necrosis, midzonal, mouse liver, H&E. (Reproduced with permission of Elsevier from Cattley, R.C. and Cullen, J.M. 2013. In: Haschek, W. et al. (eds.) *Haschek and Rousseaux's Handbook of Toxicologic Pathology*, 3rd ed. Academic Press, Elsevier, San Diego, CA. pp. 1509–1566.)

Hepatocytic metaplasia, rat pancreas, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Nolte, T. et al. 2016. *J Toxicol Pathol* 29(1 Suppl):1S–125S. https://www.ncbi.nlm.nih.gov/pubmed/26973378.)

Hepatodiaphragmatic nodule, rat liver, H&E. (Reproduced with permission of the Society of Toxicologic Pathology from Thoolen, B. et al. 2010. *Toxicol Pathol* 38(7 Suppl):5S–81S. http://journals.sagepub.com/doi/abs/10.1177/0192623310386499?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed.)

Intranuclear inclusions, mouse liver, H&E. (Reproduced with permission of Elsevier from Cattley, R.C. and Cullen, J.M. 2013. In: Haschek, W. et al. (eds.) *Haschek and Rousseaux's Handbook of Toxicologic Pathology*, 3rd ed. Academic Press, Elsevier, San Diego, CA. pp. 1509–1566.)

Hepatocellular hydropic degeneration, dog liver, H&E. (Reproduced with permission of Elsevier from Cattley, R.C.

and Cullen, J.M. 2013. In: Haschek, W. et al. (eds.) *Haschek and Rousseaux's Handbook of Toxicologic Pathology*, 3rd ed. Academic Press, Elsevier, San Diego, CA. pp. 1509–1566.)

Pancreatic increased peri-insular halos, mouse pancreas, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Nolte, T. et al. 2016. *J Toxicol Pathol* 29(1 Suppl):1S–125S. https://www.ncbi.nlm.nih.gov/pubmed/26973378.)

Pancreatic inflammation, mononuclear cells, rat pancreas, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Nolte, T. et al. 2016. *J Toxicol Pathol* 29(1 Suppl):1S–125S. https://www.ncbi.nlm.nih.gov/pubmed/26973378.)

Pancreatic inflammation, neutrophils, mouse pancreas, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Nolte, T. et al. 2016. *J Toxicol Pathol* 29(1 Suppl):1S–125S. https://www.ncbi.nlm.nih.gov/pubmed/26973378.)

Hepatocellular intracytoplasmic inclusions, rat liver, H&E. (Reproduced with permission of Elsevier from Cattley, R.C. and Cullen, J.M. 2013. In: Haschek, W. et al. (eds.) *Haschek and Rousseaux's Handbook of Toxicologic Pathology*, 3rd ed. Academic Press, Elsevier, San Diego, CA. pp. 1509–1566.)

Intravascular hepatocytes, mouse liver, H&E. (Reproduced with permission of the Society of Toxicologic Pathology from Thoolen, B. et al. 2010. *Toxicol Pathol* 38(7 Suppl):5S–81S. http://journals.sagepub.com/doi/abs/10.1177/0192623310386499?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed.)

Pancreatic acinar cell atrophy, mouse pancreas, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Nolte, T. et al. 2016. *J Toxicol Pathol* 29(1 Suppl):1S–125S. https://www.ncbi.nlm.nih.gov/pubmed/26973378.)

Pancreatic acinar cell atrophy, rat pancreas, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Nolte, T. et al. 2016. *J Toxicol Pathol* 29(1 Suppl):1S–125S. https://www.ncbi.nlm.nih.gov/pubmed/26973378.)

Pancreatic acinar cell secretory depletion, rat pancreas H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Nolte, T. et al. 2016. *J Toxicol Pathol* 29(1 Suppl):1S–125S. https://www.ncbi.nlm.nih.gov/pubmed/26973378.)

Pancreatic acinar cell vacuolation, rat pancreas, H&E. (Reproduced with permission of CRC Press from Cattley, R.C. et al. 2013. In: Sahota, P. et al. (eds.) *Toxicologic Pathology: Nonclinical Safety Assessment*. CRC Press, Taylor & Francis Group, Boca Raton, FL. pp. 313–366.)

Pancreatic autophagy, mouse pancreas, H&E. (Reproduced with permission of CRC Press from Cattley, R.C. et al. 2013. In: Sahota, P. et al. (eds.) *Toxicologic Pathology: Nonclinical Safety Assessment*. CRC Press, Taylor & Francis Group, Boca Raton, FL. pp. 313–366.)

Peribiliary (intrahepatic) infiltration, mouse liver, H&E. (Reproduced with permission of the Society of Toxicologic Pathology from Thoolen, B. et al. 2010. *Toxicol Pathol* 38(7 Suppl):5S–81S. http://journals.sagepub.com/doi/abs/10.1177/0192623310386499?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed.)

Hepatic inflammatory cell infiltration, mouse liver, H&E. (Reproduced with permission of the Society of Toxicologic Pathology from Thoolen, B. et al. 2010. *Toxicol Pathol* 38(7 Suppl):5S–81S. http://journals.sagepub.com/doi/abs/10.1177/0192623310386499?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed.)

Hepatic single cell necrosis (apoptosis), rat liver, H&E. (Reproduced with permission of Elsevier from Cattley, R.C. and Cullen, J.M. 2013. In: Haschek, W. et al. (eds.) *Haschek and Rousseaux's Handbook of Toxicologic Pathology*, 3rd ed. Academic Press, Elsevier, San Diego, CA. pp. 1509–1566.)

Cystic degeneration, rat liver, H&E. (Reproduced with permission of CRC Press from Cattley, R.C. et al. 2013. In: Sahota, P. et al. (eds.) *Toxicologic Pathology: Nonclinical Safety Assessment*. CRC Press, Taylor & Francis Group, Boca Raton, FL. pp. 313–366.)

Pancreatic zonal necrosis, mouse pancreas, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Nolte, T. et al. 2016. *J Toxicol Pathol* 29(1 Suppl):1S–125S. https://www.ncbi.nlm.nih.gov/pubmed/26973378.)

Pancreatic acinar cell hypertrophy, rat pancreas, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Nolte, T. et al. 2016. *J Toxicol Pathol* 29(1 Suppl):1S–125S. https://www.ncbi.nlm.nih.gov/pubmed/26973378.)

Pancreatic basophilic focus of cellular alteration, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Nolte, T. et al. 2016. *J Toxicol Pathol* 29(1 Suppl):1S–125S. https://www.ncbi.nlm.nih.gov/pubmed/26973378.)

Lymphoid System: Nonproliferative

Splenic decreased cellularity of the lymphoid follicle marginal zone

Splenic lymphoid follicles from cynomolgus monkey that demonstrate a decrease in marginal zone cellularity, H&E. (Reproduced with minor modifications with permission from the American Society of Investigative Pathology from Vugmeyster, Y. et al. 2006. *Am J Pathol* 168:476–489.)

Nervous System: Nonproliferative

Chromatolysis, dorsal root ganglion in a mouse, Cresyl violet. (Copyright 2018 Georg Krinke, AnaPath GmbH, Switzerland. Used with permission.)

Intramyelinic edema, cerebellum in a rat Luxol fast blue/Cresyl violet. (Copyright 2018 Georg Krinke, AnaPath GmbH, Switzerland. Used with permission.)

Neuronal apoptosis, spinal cord in a mouse, H&E. (Image courtesy Dr. Jerry Ward. Used with permission.)

Reproductive System and Mammary Gland: Female

Paraovarian cyst

Paraovarian cyst, ovary, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Dixon, D. et al. 2014. *J Toxicol Pathol* 26(3 Suppl):1S–107S. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/.)

Corpora lutea (CL) decreased number/absent

Numerical decreases in corpora lutea, ovary, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Dixon, D. et al. 2014. *J Toxicol Pathol* 26(3 Suppl):1S–107S. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/.)

Corpora lutea (CL) vacuolation

Corpora lutea vacuolation, ovary, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Dixon, D. et al. 2014. *J Toxicol Pathol* 26(3 Suppl):1S–107S. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/.)

Corpora lutea (CL) hypertrophy

Hypertrophic corpora lutea, rat, ovary, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Dixon, D. et al. 2014. *J Toxicol Pathol* 26(3 Suppl):1S–107S. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/.)

Corpora lutea (CL) increased

Numerical increases in corpora lutea, ovary, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Dixon, D. et al. 2014. *J Toxicol Pathol* 26(3 Suppl):1S–107S. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/.)

Follicular cyst

Follicular cyst, ovary, B6C3F1/N mouse, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Decidual reaction

Decidual reaction, uterus, F344/N rat, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Decidualization

Decidualization, uterus, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Dixon, D. et al. 2014. *J Toxicol Pathol* 26 (3 Suppl):1S–107S. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/.)

Endometrial necrosis

Necrosis, inflammation, and mineralization, uterus, F344/N rat, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Female sex hormones

Female hypothalamic-pituitary-ovarian hormonal axis. (Reproduced with permission of Academic Press from Rudmann, D.G. and Foley, G.L. 2013. In: Haschek, W.M. et al. (eds.) *Haschek and Rousseaux's Handbook of Toxicologic Pathology*, 3rd ed. Elsevier, Academic Press, pp. 2599–2660.)

Cystic luteinized follicle

Cystic luteinized follicle, ovary, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Dixon, D. et al. 2014. *J Toxicol Pathol* 26(3 Suppl):1S–107S. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/.)

Mammary gland, duct/alveolus, dilation

Marked dilation (ectasia) of mammary gland duct, H&E. (Reproduced with permission of the Society of Toxicologic Pathology from Rudmann, D. et al. 2012. *Toxicol Pathol* 40:7S–39S. https://www.ncbi.nlm.nih.gov/pubmed/22949413.)

Mesonephritic duct remnants

Cystic remnants of mesonephric duct, ovary, Wistar rat, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Vaginal mucification increased

Increased mucin in vaginal epithelium, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Dixon, D. et al. 2014. *J Toxicol Pathol* 26(3 Suppl):1S–107S. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/.)

Age-related ovarian atrophy

Atrophy characterized by decreased follicles, no corpora lutea, ovary, F344/N rat, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Ovarian atrophy

Atrophy characterized by lack of follicles and corpora lutea, ovary, F344/N rat, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Oviduct inflammation

Neutrophils in oviduct lumen, oviduct, B6C3F1/N mouse, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Sexual immaturity, female

Histology of immature ovary and uterus, dog and cynomolgus monkey, H&E. (Reproduced with permission of Academic Press from Rudmann, D.G. and Foley, G.L. 2013. In: Haschek, W.M. et al. (eds.) *Haschek and Rousseaux's Handbook of Toxicologic Pathology*, 3rd ed. Elsevier, Academic Press, pp. 2599–2660.)

Vaginal stromal hypertrophy

Thickened stroma, vagina, F344/N rat, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Pseudopregnancy

Prominent ovarian CL (A), increased vaginal mucification (B), diffuse endometrial hyperplasia (C), and mammary lobuloalveolar hyperplasia (D), rat, H&E. (Reproduced with permission of the Academic Press from Rudmann, D.G. and Foley, G.L. 2013. In: Haschek, W.M. et al. (eds.) *Haschekand Rousseaux's Handbook of Toxicologic Pathology*, 3rd ed. Elsevier, Academic Press, pp. 2599–2660.)

Pyometra

Accumulation of uterine luminal neutrophils, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Dixon, D. et al. 2014. *J Toxicol Pathol* 26(3 Suppl):1S–107S. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/.)

Selective estrogen receptor modulators (SERM)

Hypertrophy/hyperplasia of ducts/alveoli of female mammary gland in rat given a SERM, H&E. (Reproduced with permission of Academic Press from Rudmann, D.G. and Foley, G.L. 2013. In: Haschek, W.M. et al. (eds.) *Haschek and Rousseaux's Handbook of Toxicologic Pathology*, 3rd ed. Elsevier, Academic Press, pp. 2599–2660.)

Uterine stromal fibrosis

Thickened, fibrotic endometrial stroma, uterus, F344/N rat, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Endometrial subnuclear vacuoles

Subnuclear vacuoles, endometrial gland, cynomolgus monkey, H&E. (Reproduced with permission of Academic Press from Rudmann, D.G. and Foley, G.L. 2013. In: Haschek, W.M. et al. (eds.) *Haschek and Rousseaux's Handbook of Toxicologic Pathology*, 3rd ed. Elsevier, Academic Press, pp. 2599–2660.)

Theca cell vacuolation

Theca cell vacuolation, ovary, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Dixon, D. et al. 2014. *J Toxicol Pathol* 26(3 Suppl):1S–107S. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/.)

Interstitial cell vacuolation

Interstitial cell vacuolation, ovary, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Dixon, D. et al. 2014. *J Toxicol Pathol* 26(3 Suppl):1S–107S. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/.)

Interstitial cell hypertrophy

Interstitial cell hypertrophy, ovary, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Dixon, D. et al. 2014. *J Toxicol Pathol* 26(3 Suppl):1S–107S. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/.)

Uterine atrophy

Bilateral atrophy, uterus, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Dixon, D. et al. 2014. *J Toxicol Pathol* 26(3 Suppl):1S–107S. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4253081/.)

Reproductive System and Mammary Gland: Male

Accessory male sex organs, acinar/vesicle dilation

Dilated (cystic) acinus, seminal vesicle, F344/N rat, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Epididymal adenosis

Adenosis, mouse epididymis, H&E. (Reproduced with permission of the Society of Toxicologic Pathology from Creasy, D. et al. 2012. *Toxicol Pathol* 40:40S–121S. https://www.ncbi.nlm.nih.gov/pubmed/22949412.)

Epididymal aspermia

Aspermia, epididymis, F344/N rat, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Testicular germ cell degeneration

Degeneration, spermatocytes, Stage XIII, rat, H&E. (Reproduced with permission of the Society of Toxicologic Pathology from Creasy, D. et al. 2012. *Toxicol Pathol* 40:40S–121S. https://www.ncbi.nlm.nih.gov/pubmed/22949412.)

Preputial gland ductal dilation

Dilated preputial gland ducts with inflammation, F344/N rat, H&E. (Image provided courtesy of the National Toxicology

Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Testis, efferent ducts, and epididymis inflammation

Neutrophilic inflammation, epididymis, B6C3F1 mouse, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Accessory male sex organs inflammation

Neutrophilic inflammation, prostate, F344/N rat. H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Epididymis and efferent duct luminal cell debris

Luminal germ cell debris, epididymis, rat, H&E. (Reproduced with permission of the Society of Toxicologic Pathology from Creasy, D. et al. 2012. *Toxicol Pathol* 40: 40S–121S. https://www.ncbi.nlm.nih.gov/pubmed/22949412.)

Testicular multinucleated giant cells

Multinucleated giant cells, testis, F344/N rat, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Epididymis and efferent duct single cell epithelial necrosis

Single cell necrosis (arrows), epididymal epithelial cells, rat, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Testes, efferent ducts and epididymis tubular necrosis

Extensive coagulative necrosis, testis, rat, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Prostate atrophy

Atrophic prostatic acinae, F344/N rat, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Testis, efferent ducts and epididymis sperm granuloma

Sperm granuloma, epididymis, rat, H&E. (Reproduced with permission of the Society of Toxicologic Pathology from Creasy, D. et al. 2012. *Toxicol Pathol* 40:40S–121S. https://www.ncbi.nlm.nih.gov/pubmed/22949412.)

Testis, efferent ducts and epididymis sperm stasis

Sperm stasis adjacent to empty ducts, epididymis, B6C3F1 mouse, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Spermatid retention

Retained spermatids adjacent to spermatocytes, testis, rat, H&E. (Reproduced with permission of the Society of Toxicologic Pathology from Creasy, D. et al. 2012. *Toxicol Pathol* 40:40S–121S. https://www.ncbi.nlm.nih.gov/pubmed/22949412.)

Spermatocele

Duct filled with sperm, testis, B6C3F1 mouse, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Testicular tubular atrophy

Tubular atrophy, rat, H&E. (Reproduced with permission of the Society of Toxicologic Pathology from Creasy, D. et al. 2012. *Toxicol Pathol* 40:40S–121S. https://www.ncbi.nlm.nih.gov/pubmed/22949412.)

Testicular tubular degeneration

Tubular degeneration, testis, rat, H&E. (Reproduced with permission of the Society of Toxicologic Pathology from Creasy, D. et al. 2012. *Toxicol Pathol* 40:40S–121S. https://www.ncbi.nlm.nih.gov/pubmed/22949412.)

Testicular tubular dilation

Tubular dilation, testis, rat, H&E. (Reproduced with permission of the Society of Toxicologic Pathology from Creasy, D. et al. 2012. *Toxicol Pathol* 40:40S–121S. https://www.ncbi.nlm.nih.gov/pubmed/22949412.)

Epididymis and efferent duct epithelial vacuolation

Epididymal epithelial vacuolation, rat, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Respiratory System: Nonproliferative

Pulmonary alveolar phospholipidosis

Pulmonary alveolar phospholipidosis, alveolar macrophage, lung rat, transmission electron micrograph. (Image courtesy of Paul McGill and Ian Francis, Ex-vivo Bioimaging, GSK, Ware, UK.)

Skin: Nonproliferative

Adnexal inflammation

CD45RBHi SCID mouse immune transfer model of psoriasis illustrating peri- and intrafollicular infiltration of inflammatory cells with a predominance of lymphocytes. (Reproduced with permission from Mecklenburg, L. et al. 2013. *J Toxicol Pathol* 26(Suppl 1):27S–57S.)

Adnexal necrosis

A hair follicle from a Lewis rat given a kinase inhibitor with multifocal single cell necrosis as illustrated by the arrows,

H&E. (Reproduced with permission from Diegel, K.L. et al. 2013. In: Haschek-Hock, W.M. et al. (eds.) *Integument in Handbook of Toxicologic Pathology,* 3rd ed. Elsevier Press.)

Special Senses: Eye

Conjunctival inflammation

Conjunctival inflammation with edema, bulbar conjunctiva, BALB/c mouse, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Corneal inflammation

Corneal inflammation with corneal neovascularization, corneal stroma, rabbit, H&E. (Image provided courtesy of L. Teixeira, Department of Pathobiological Sciences, School of Veterinary Medicine, University of Wisconsin, Madison, WI.)

Corneal keratinization

Corneal keratinization, B6C3F1 mouse, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Corneal stromal fibrosis

Corneal stromal fibrosis, corneal inflammation and mineralization, Hans Wistar rat, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Filtration angle narrowed

Filtration angle narrowed with destruction of the trabecular cell meshwork and iris inflammation, rabbit, H&E. (Image provided courtesy of L. Teixeira, Department of Pathobiological Sciences, School of Veterinary Medicine, University of Wisconsin, Madison, WI.)

Harderian gland alteration

Harderian gland alteration, lacrimal gland, B6C3F1 mouse, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Iris inflammation

Iris inflammation with corneal inflammation and ulcer, B6C3F1 mouse, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Lens capsule hypertrophy

Lens capsule hypertrophy with capsule rupture, and iris adhesion, vitreal fibroplasia and retinal atrophy, F344/N rat, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Lens epithelial fibroplasia

Lens epithelial hypertrophy with lens fiber degeneration, F344/N rat, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Lens epithelial hyperplasia

Lens epithelial hypertrophy with lens fiber degeneration, F344/N rat, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Lens fiber degeneration

Lens fiber degeneration with vacuolation, rat, H&E. (Image provided courtesy of L. Teixeira, Department of Pathobiological Sciences, School of Veterinary Medicine, University of Wisconsin, Madison, WI.)

Nasolacrimal duct inflammation

Nasolacrimal duct inflammation, mouse, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Optic nerve head necrosis

Optic nerve head necrosis with collapse into the optic nerve (optic disc cupping), rhesus monkey, H&E. (Image provided courtesy of L. Teixeira, Department of Pathobiological Sciences, School of Veterinary Medicine, University of Wisconsin, Madison, WI.)

Retina light-induced atrophy

Retina light-induced atrophy, rat, toluidine blue stain on epoxy. (Image provided courtesy of L. Teixeira, Department of Pathobiological Sciences, School of Veterinary Medicine, University of Wisconsin, Madison, WI.)

Retinal atrophy—Inner retinal atrophy

Retinal atrophy—Inner retinal atrophy with early outer retinal atrophy, F344/N rat, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Retinal detachment

Retinal detachment (rhegmatogenous due to hemorrhage) with retinal pigment epithelial hypertrophy, F344/N rat, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Retinal folds

Retinal fold, B6C3F1 mouse, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Scleral bone or cartilage metaplasia

Scleral bone metaplasia, F344/N rat, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Special Senses: Ear

External ear canal inflammation

External ear canal inflammation with cellular debris, hemorrhage, and epithelial hyperplasia, bony canal of the external ear, rabbit, H&E. (Image provided courtesy of K. Schafer, Vet Path Services, Mason, Ohio.)

Hair cell necrosis

Hair cell necrosis with hair cell numbers decreased and disorganized, organ of Corti, inner ear, chinchilla, H&E. (Image provided courtesy of K. Schafer, Vet Path Services, Mason, Ohio.)

Hair cell numbers decreased

Hair cell numbers decreased with hair cell degeneration and vacuolation due to macrolide antibiotic, vestibular organ crista ampullaris, vestibular system, chinchilla, H&E. (Image provided courtesy of K. Schafer, Vet Path Services, Mason, Ohio.)

Inner ear edema

Inner ear edema with inflammation and hemorrhage, spiral ligament, chinchilla, H&E. (Image provided courtesy of K. Schafer, Vet Path Services, Mason, Ohio.)

Inner ear hemorrhage

Inner ear hemorrhage associated with inflammation, cochlea, chinchilla, H&E. (Image provided courtesy of K. Schafer, Vet Path Services, Mason, Ohio.)

Inner ear inflammation

Inner ear inflammation with cellular debris, cochlea, chinchilla, H&E. (Image provided courtesy of K. Schafer, Vet Path Services, Mason, Ohio.)

Inner ear cartilage necrosis

Inner ear cartilage necrosis, oval window footplates, chinchilla, H&E. (Image provided courtesy of K. Schafer, Vet Path Services, Mason, Ohio.)

Inner ear neuronal necrosis

Inner ear neuronal necrosis and spiral ganglion decreased cellularity, cochlea, chinchilla, H&E. (Image provided courtesy of K. Schafer, Vet Path Services, Mason, Ohio.)

Middle ear granulomatous inflammation

Middle ear granulomatous inflammation with multinucleated giant cells due to a foreign body (glue), Guinea pig, H&E. (Image provided courtesy of K. Schafer, Vet Path Services, Mason, Ohio.)

Otolith loss, disorganization, and disruption

Otolith loss, disorganization, and disruption, inner ear, chinchilla, H&E. (Image provided courtesy of K. Schafer, Vet Path Services, Mason, Ohio.)

Spiral ganglion decreased cellularity

See **Inner ear neuronal necrosis** for illustration. (Image provided courtesy of K. Schafer, Vet Path Services, Mason, Ohio.)

Stria vascularis vacuolation

Stria vascularis vacuolation, cochlea, chinchilla, H&E. (Image provided courtesy of K. Schafer, Vet Path Services, Mason, Ohio.)

Tympanic bulla new bone formation

Tympanic bulla new bone formation, auditory bulla, rat, H&E. (Image provided courtesy of K. Schafer, Vet Path Services, Mason, Ohio.)

Tympanic bulla squamous cell metaplasia

Tympanic bulla squamous cell metaplasia, rat, H&E. (Image provided courtesy of K. Schafer, Vet Path Services, Mason, Ohio.)

Tympanic membrane cyst

Tympanic membrane cyst, rabbit, H&E. (Image provided courtesy of K. Schafer, Vet Path Services, Mason, Ohio.)

Tympanic membrane perforation

Tympanic membrane perforation, rat, H&E. (Image provided courtesy of K. Schafer, Vet Path Services, Mason, Ohio.)

Urinary System

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Urinary System: Nonproliferative

Alpha 2u-globulin nephropathy

Rat kidney, Mallory-Heidenhain. (Reproduced with permission of Society of Toxicology from Frazier, K. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse urinary system. *J Toxicol Pathol* 40:14S–86S. https://www.ncbi.nlm.nih.gov/pubmed/22637735.)

FA

CPN

Rat, H&E. (Reproduced with permission of Society of Toxicology from Frazier, K. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse urinary system. *J Toxicol Pathol* 40:14S–86S. https://www.ncbi.nlm.nih.gov/pubmed/22637735.)

Glomerulosclerosis

As part of CPN, rat kidney, H&E. (Reproduced with permission of Society of Toxicology from Frazier, K. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse urinary system. *J Toxicol Pathol* 40:14S–86S. https://www.ncbi.nlm.nih.gov/pubmed/22637735.)

End-stage renal disease

Rat kidney, H&E. (Reproduced with permission of Society of Toxicology from Frazier, K. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse urinary system. *J Toxicol Pathol* 40:14S–86S. https://www.ncbi.nlm.nih.gov/pubmed/22637735.)

Proximal tubular necrosis

Acute, mouse kidney, H&E. (Reproduced with permission of Society of Toxicology from Frazier, K. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse urinary system. *J Toxicol Pathol* 40:14S–86S. https://www.ncbi.nlm.nih.gov/pubmed/22637735.)

Tubule cell regeneration

Rat kidney, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

APPENDIX 2

Bone, Muscle, and Tooth: Proliferative

Ameloblastoma

Figure 1 Ameloblastoma, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Fossey et al. 2016. Nonproliferative and proliferative lesions of the rat and mouse skeletal tissues (bones, joints, and teeth). *J Toxicol Pathol* 29:49S–103S. https://www.ncbi.nlm.nih.gov/pubmed/27621538.)

Chondrosarcoma

Figure 3 Chondrosarcoma in a rat, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Fibroma

Figure 5 Fibroma in the subcutaneous tissues of a rat, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Fibrosarcoma

Figure 6 Fibrosarcoma in the subcutaneous tissues of a mouse, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Hibernoma

Figure 7 Hibernoma in the subcutaneous tissues of a rat, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Odontoma, complex

Figure 11 Odontoma, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Fossey et al. 2016. Nonproliferative and proliferative lesions of the rat and mouse skeletal tissues (bones, joints, and teeth). *J Toxicol Pathol* 29:49S–103S. https://www.ncbi.nlm.nih.gov/pubmed/27621538.)

Osteochondroma

Figure 12 Osteochondroma, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Fossey et al. 2016. Nonproliferative and proliferative lesions of the rat and mouse skeletal tissues (bones, joints, and teeth). *J Toxicol Pathol* 29:49S–103S. https://www.ncbi.nlm.nih.gov/pubmed/27621538.)

Osteoma

Figure 13 Osteoma, mouse, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Fossey et al. 2016. Nonproliferative and proliferative lesions of the rat and mouse skeletal tissues (bones, joints, and teeth). *J Toxicol Pathol* 29:49S–103S. https://www.ncbi.nlm.nih.gov/pubmed/27621538.)

Osteosarcoma

Figure 14 Osteosarcoma, mouse, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Fossey et al. 2016. Nonproliferative and proliferative lesions of the rat and mouse skeletal tissues (bones, joints, and teeth). *J Toxicol Pathol* 29:49S–103S. https://www.ncbi.nlm.nih.gov/pubmed/27621538.)

Cardiovascular System: Proliferative

Figure 1 Atriocaval mesothelioma, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Berridge, B.R. et al. 2016. Non-proliferative and proliferative lesions of the cardiovascular system of the rat and mouse. *J Toxicol Pathol* 29(3 Suppl):1S–47S.)

Figure 3 Hyperplasia, hemangioendothelial. 1,3-butadiene, mouse, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Berridge, B.R. et al. 2016. Non-proliferative and proliferative lesions of the cardiovascular system of the rat and mouse. *J Toxicol Pathol* 29(3 Suppl):1S–47S.)

Figure 4 Hemangioma. 1,3-butadiene, mouse, subcutaneous, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Berridge, B.R. et al. 2016. Non-proliferative and proliferative lesions of the cardiovascular system of the rat and mouse. *J Toxicol Pathol* 29(3 Suppl):1S–47S.)

Figure 5 Hemangiosarcoma. 1,3-Butadiene, mouse, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Berridge, B.R. et al. 2016. Non-proliferative and proliferative lesions of the cardiovascular system of the rat and mouse. *J Toxicol Pathol* 29(3 Suppl):1S–47S.)

Figure 8 Endocardial Schwann cell hyperplasia, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Berridge, B.R. et al. 2016. Non-proliferative and proliferative lesions of the cardiovascular system of the rat and mouse. *J Toxicol Pathol* 29(3 Suppl):1S–47S.)

Endocrine Glands: Proliferative

Acinar-islet cell tumor, benign

Figure 1 Pancreas, acinar-islet cell tumor, benign, F344/N rat, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Acinar-islet cell tumor, malignant

Figure 2 Acinar-islet cell tumor, malignant, F344 rat, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Adrenal cortical adenoma, benign

Figure 3 Adrenal gland, cortical adenoma, benign, Sprague Dawley rat, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Adrenal cortical carcinoma, malignant

Figure 4 Adrenal gland cortical carcinoma, malignant, Sprague Dawley rat, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Adrenal gland subcapsular cell hyperplasia

Figure 7 Adrenal gland, cortex, subcapsular cell hyperplasia, B6C3F1 mouse, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Adrenal gland subcapsular cell tumor, benign

Figure 8 Adrenal gland, subcapsular cell adenoma, B6C3F1/N mouse, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Adrenal gland subcapsular cell tumor, malignant

Figure 9 Adrenal gland, cortex, subcapsular cell tumor, malignant, B6C3F1/N mouse, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Adrenal medullary ganglioneuroma

Figure 10 Adrenal gland, medulla, ganglioneuroma, F344/N rat, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Adrenal medullary neuroblastoma

Figure 11 Adrenal gland, medulla, neuroblastoma, F344/N rat, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Endocrine pancreas cell hyperplasia

Figure 12 Endocrine pancreas cell hyperplasia, B6C3F1 mouse, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Islet cell adenoma, benign

Figure 13 Islet cell adenoma, benign, Sprague Dawley rat, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Islet cell carcinoma, malignant

Figure 14 Islet cell carcinoma, malignant, Sprague Dawley rat, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Neuroendocrine cell tumor, benign

Figure 15 Neuroendocrine cell, tumor, benign, F344/N rat, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Oncocytoma

Figure 16 Oncocytoma (kidney), benign, F344/N rat, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Pars distalis adenoma, benign

Figure 17 Pituitary, pars distalis adenoma, benign, Sprague Dawley rat, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Pars distalis carcinoma, malignant

Figure 18 Pituitary, pars distalis carcinoma, malignant, Sprague Dawley rat, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Pars distalis, pituitary hyperplasia

Figure 19 Pituitary, pars distalis, hyperplasia, Sprague Dawley rat, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Pars distalis, pituitary hypertrophy

Figure 20 Pituitary gland, pars distalis hypertrophy, F344/N rat, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Pars intermedia, pituitary hyperplasia

Figure 21 Pituitary gland, pars intermedia hyperplasia, B6C3F1 mouse, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Pheochromocytoma, benign

Figure 22 Adrenal gland, medulla, pheochromocytoma, benign, F344/N rat, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Pheochromocytoma, malignant

Figure 23 Adrenal gland, medulla, pheochromocytoma, malignant, F344/N rat, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Pineoblastoma, malignant

Figure 24 Pineoblastoma, malignant, Sprague Dawley rat, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Pituicytoma

Figure 25 Pituitary, pituicytoma, B6C3F1 mouse, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Thyroid C cell adenoma, benign

Figure 26 Thyroid gland, C cell adenoma, benign F344/N rat, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Thyroid C cell carcinoma, malignant

Figure 27 Thyroid gland, C cell carcinoma, malignant F344/N rat, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Thyroid C cell hyperplasia

Figure 28 Thyroid gland, C cells, hyperplasia, Sprague Dawley rat, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Thyroid follicular hyperplasia

Figure 31 Thyroid gland, follicular hyperplasia, F344/N rat, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Gastrointestinal Tract: Proliferative

Leiomyoma

Figure 3 Glandular stomach, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Nolte, T. et al. 2016. Nonproliferative and proliferative lesions of the gastrointestinal tract, pancreas and salivary glands of the rat and mouse. *J Toxicol Pathol* 29(1 Supplement Winter):92S.)

Leiomyosarcoma

Figure 4 Nonglandular stomach, rat, H&E. Leiomyosarcoma. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Nolte, T. et al. 2016. Nonproliferative and proliferative lesions of the gastrointestinal tract, pancreas and salivary glands of the rat and mouse. *J Toxicol Pathol* 29(1 Supplement Winter):93S.)

Squamous cell hyperplasia of nonglandular stomach

Figure 8 Nonglandular stomach, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Nolte, T. et al. 2016. Nonproliferative and proliferative lesions of the gastrointestinal tract, pancreas and salivary glands of the rat and mouse. *J Toxicol Pathol* 29(1 Supplement Winter):87S.)

Tumor, neuroendocrine cell, benign

Figure 9 Glandular stomach, rat, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Nolte, T. et al. 2016. Nonproliferative and proliferative lesions of the gastrointestinal tract, pancreas and salivary glands of the rat and mouse. *J Toxicol Pathol* 29(1 Supplement Winter):92S.)

Hematopoietic System

Figure 2 Erythroid leukemia, liver, mouse (H&E). (Image provided courtesy of Jerry Ward, Global Vet Pathology, Montgomery Village, MD.)

Figure 4 Lymphoma, immunoblastic, mouse (H&E). (Image provided courtesy of Jerry Ward, Global Vet Pathology, Montgomery Village, MD.)

Liver, Gallbladder, and Exocrine Pancreas

Figure 1 Basophilic focus of cellular alteration, rat liver, H&E. (Reproduced with permission of Elsevier from Cattley, R.C. and Cullen, J.M. 2013. In: Haschek, W. et al. (eds.) *Haschek and Rousseaux's Handbook of Toxicologic Pathology*, 3rd ed. Academic Press, Elsevier, San Diego, CA. pp. 1509–1566.)

Figure 3 Bile duct hyperplasia, rat liver, H&E. (Reproduced with permission of CRC Press from Cattley, R.C. et al. 2013. In: Sahota, P. et al. (eds.) *Toxicologic Pathology: Nonclinical Safety Assessment*. CRC Press, Taylor & Francis Group, Boca Raton, FL. pp. 313–366.)

Figure 4 Cholangiocarcinoma, rat liver, H&E. (Reproduced with permission of Elsevier from Cattley, R.C. and Cullen, J.M. 2013. In: Haschek, W. et al. (eds.) *Haschek and Rousseaux's Handbook of Toxicologic Pathology*, 3rd ed. Academic Press, Elsevier, San Diego, CA. pp. 1509–1566.)

Figure 5 Cholangiofibrosis, rat liver, H&E. (Reproduced with permission of the Society of Toxicologic Pathology from Thoolen, B. et al. 2010. Proliferative and nonproliferative lesions of the rat and mouse hepatobiliary system. *Toxicol Pathol* 38(7 Suppl):5S–81S. http://journals.sagepub.com/doi/abs/10.1177/0192623310386499?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed.)

Figure 6 Cholangioma, rat liver, H&E. (Reproduced with permission of CRC Press from Cattley, R.C. et al. 2013. In: Sahota, P. et al. (eds.) *Toxicologic Pathology: Nonclinical Safety Assessment*. CRC Press, Taylor & Francis Group, Boca Raton, FL. pp. 313–366.)

Figure 7 Clear cell focus of cellular alteration, rat liver, H&E. (Reproduced with permission of Elsevier from Cattley, R.C. and Cullen, J.M. 2013. In: Haschek, W. et al. (eds.) *Haschek and Rousseaux's Handbook of Toxicologic Pathology*, 3rd ed. Academic Press, Elsevier, San Diego, CA. pp. 1509–1566.)

Figure 8 Eosinophilic focus of cellular alteration, rat liver, H&E. (Reproduced with permission of CRC Press from Cattley, R.C. et al. 2013. In: Sahota, P. et al. (eds.) *Toxicologic Pathology: Nonclinical Safety Assessment*. CRC Press, Taylor & Francis Group, Boca Raton, FL. pp. 313–366.)

Figure 9 Gallbladder adenoma, mouse liver, H&E. (Reproduced with permission of CRC Press from Cattley, R.C. et al. 2013. In: Sahota, P. et al. (eds.) *Toxicologic Pathology: Nonclinical Safety Assessment*. CRC Press, Taylor & Francis Group, Boca Raton, FL. pp. 313–366.)

Figure 10 Hepatic hemangiosarcoma, mouse liver, H&E. (Reproduced with permission of CRC Press from Cattley, R.C. et al. 2013. In: Sahota, P. et al. (eds.) *Toxicologic Pathology: Nonclinical Safety Assessment*. CRC Press, Taylor & Francis Group, Boca Raton, FL. pp. 313–366.)

Figure 11 Hepatic histiocytic sarcoma, mouse liver, H&E. (Reproduced with permission of the Society of Toxicologic Pathology from Thoolen, B. et al. 2010. Proliferative and nonproliferative lesions of the rat and mouse hepatobiliary system. *Toxicol Pathol* 38(7 Suppl):5S–81S. http://journals.sagepub.com/doiabs/10.1177/0192623310386499?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed.)

Figure 12 Hepatoblastoma, mouse liver, H&E. (Reproduced with permission of CRC Press from Cattley, R.C. et al. 2013. In: Sahota, P. et al. (eds.) *Toxicologic Pathology: Nonclinical Safety Assessment*. CRC Press, Taylor & Francis Group, Boca Raton, FL. pp. 313–366.)

Figure 14 Hepatocellular carcinoma, rat liver, H&E. (Reproduced with permission of CRC Press from Cattley, R.C. et al. 2013. In: Sahota, P. et al. (eds.) *Toxicologic Pathology: Nonclinical Safety Assessment*. CRC Press, Taylor & Francis Group, Boca Raton, FL. pp. 313–366.)

Figure 15 Hepatocellular hyperplasia, non-regenerative, rat liver, H&E. (Reproduced with permission of the Society of Toxicologic Pathology from Thoolen, B. et al. 2010. Proliferative and nonproliferative lesions of the rat and mouse hepatobiliary system. *Toxicol Pathol* 38(7 Suppl):5S–81S. http://journals.sagepub.com/doi/abs/10.1177/0192623310386499?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed.)

Figure 16 Hepatocellular hyperplasia, regenerative, rat liver, H&E. Reproduced with permission of the Society of Toxicologic Pathology from Thoolen, B. et al. 2010. Proliferative and nonproliferative lesions of the rat and mouse hepatobiliary system. *Toxicol Pathol* 38(7 Suppl):5S–81S. http://journals.sagepub.com/doi/abs/10.1177/0192623310386499?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed.)

Figure 17 Hepatocholangiocellular carcinoma, rat liver, H&E. (Reproduced with permission of the Society of Toxicologic Pathology from Thoolen, B. et al. 2010. Proliferative and nonproliferative lesions of the rat and mouse hepatobiliary system. *Toxicol Pathol* 38(7 Suppl):5S–81S. http://journals.sagepub.com/doi/abs/10.1177/0192623310386499?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed.)

Figure 18 Ito cell hyperplasia, mouse liver, H&E. Reproduced with permission of the Society of Toxicologic Pathology from Thoolen, B. et al. 2010. Proliferative and nonproliferative lesions of the rat and mouse hepatobiliary system. *Toxicol Pathol* 38(7 Suppl):5S–81S. http://journals.sagepub.com/doi/abs/10.1177/0192623310386499?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed.)

Figure 19 Ito cell tumor, mouse liver, H&E. (Reproduced with permission of Elsevier from Cattley, R.C. and Cullen, J.M. 2013. In: Haschek, W. et al. (eds.) *Haschek and Rousseaux's Handbook of Toxicologic Pathology*, 3rd ed. Academic Press, Elsevier, San Diego, CA. pp. 1509–1566.)

Figure 20 Kupffer cell hypertrophy/hyperplasia, mouse liver, H&E. (Reproduced with permission of the Society of Toxicologic Pathology from Thoolen, B. et al. 2010. Proliferative and nonproliferative lesions of the rat and mouse hepatobiliary system. *Toxicol Pathol* 38(7 Suppl):5S–81S. http://journals.sagepub.com/doi/abs/10.1177/0192623310386499?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed.)

Figure 21 Oval cell hyperplasia, mouse liver, H&E. (Reproduced with permission of CRC Press from Cattley, R.C. et al. 2013. In: Sahota, P. et al. (eds.) *Toxicologic Pathology: Nonclinical Safety Assessment*. CRC Press, Taylor & Francis Group, Boca Raton, FL. pp. 313–366.)

Figure 22 Pancreatic acinar cell adenocarcinoma, rat pancreas, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Nolte, T. et al. 2016. Nonproliferative and proliferative lesions of the gastrointestinal tract, pancreas and salivary glands of the rat and mouse. *J Toxicol Pathol* 29(1 Suppl):1S–125S. https://www.ncbi.nlm.nih.gov/pubmed/26973378.)

Figure 23 Pancreatic acinar cell adenoma, rat pancreas, H&E; arrows depict fibrous capsule. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Nolte, T. et al. 2016. Nonproliferative and proliferative lesions of the gastrointestinal tract, pancreas and salivary glands of the rat and mouse. *J Toxicol Pathol* 29(1 Suppl):1S–125S. https://www.ncbi.nlm.nih.gov/pubmed/26973378.)

Figure 24 Pancreatic acinar cell hyperplasia, rat pancreas, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Nolte. T. et al. 2016. Nonproliferative and proliferative lesions of the gastrointestinal tract, pancreas and salivary glands of the rat and mouse. *J Toxicol Pathol* 29(1 Suppl):1S–125S. https://www.ncbi.nlm.nih.gov/pubmed/26973378.)

Figure 25 Pancreatic ductal cell adenocarcinoma, rat pancreas, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Nolte, T. et al. 2016. Nonproliferative and proliferative lesions of the gastrointestinal tract, pancreas and salivary glands of the rat and mouse. *J Toxicol Pathol* 29(1 Suppl):1S–125S. https://www.ncbi.nlm.nih.gov/pubmed/26973378.)

Figure 26 Pancreatic ductal cell adenoma, mouse pancreas, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Nolte, T. et al. 2016. Nonproliferative and proliferative lesions of the gastrointestinal tract, pancreas and salivary glands of the rat and mouse. *J Toxicol Pathol* 29(1 Suppl):1S–125S. https://www.ncbi.nlm.nih.gov/pubmed/26973378.)

Figure 27 Pancreatic ductal cell hyperplasia, mouse pancreas, H&E. (Reproduced with permission of the Japanese Society of Toxicologic Pathology from Nolte, T. et al. 2016. Nonproliferative and proliferative lesions of the gastrointestinal tract, pancreas and salivary glands of the rat and mouse. *J Toxicol Pathol* 29(1 Suppl):1S–125S. https://www.ncbi.nlm.nih.gov/pubmed/26973378.)

Lymphoid System: Proliferative

Lymphoma, follicular center cell

Figure 2 Follicular center cell lymphoma with a multinodular presentation in the spleen of an aged mouse, H&E. (Image courtesy of Jerold Rehg, St. Jude Children's Research Hospital, Memphis TN.)

Nervous System: Proliferative

Figure 1 Astrocytoma in the brain of a rat, H&E. (Copyright 2018 Klaus Weber, AnaPath GmbH, Switzerland. Used with permission.)

Figure 3 Ependymoma in the brain of a rat, H&E. (Copyright 2018 Klaus Weber, AnaPath GmbH, Switzerland. Used with permission.)

Figure 4 Glioma, mixed, in the brain of a rat, H&E. (Copyright 2018 Klaus Weber, AnaPath GmbH, Switzerland. Used with permission.)

Figure 5 Granular cell tumor, benign, in the brain of a rat, H&E. (Copyright 2018 Klaus Weber, AnaPath GmbH, Switzerland. Used with permission.)

Figure 6 Medulloblastoma in the brain of a rat, H&E. (Copyright 2018 Klaus Weber, AnaPath GmbH, Switzerland. Used with permission.)

Figure 7 Meningioma, malignant, in the brain of a rat, H&E. (Copyright 2018 Klaus Weber, AnaPath GmbH, Switzerland. Used with permission.)

Figure 9 Oligodendroglioma, malignant, high grade, in the brain of a rat, H&E. (Copyright 2018 Klaus Weber, AnaPath GmbH, Switzerland. Used with permission.)

Figure 10 Oligodendroglioma, malignant, low grade, in the brain of a rat, H&E. (Copyright 2018 Klaus Weber, AnaPath GmbH, Switzerland. Used with permission.)

Figure 11 Paraganglioma in the heart of a rat, H&E. (Copyright 2018 Klaus Weber, AnaPath GmbH, Switzerland. Used with permission.)

Figure 13 Schwannoma in the heart of a rat, H&E. (Copyright 2018 Klaus Weber, AnaPath GmbH, Switzerland. Used with permission.)

Figure 14 Malignant schwannoma in the heart of a rat, H&E. (Copyright 2018 Klaus Weber, AnaPath GmbH, Switzerland. Used with permission.)

Respiratory System: Proliferative

Laryngeal, tracheal, bronchial, and bronchiolar neuroendocrine cell hyperplasia

Figure 6 Neuroendocrine cell hyperplasia, bronchus, rat, H&E. (Reproduced with permission of the Society of Toxicologic Pathology from Renne, R. et al. 2009. Proliferative and nonproliferative lesions of the rat and mouse respiratory tract.

Toxicol Pathol 37(7 suppl):5S–73S. https://www.ncbi.nlm.nih.gov/pubmed/20032296.)

Laryngeal, tracheal, bronchial, and bronchiolar papilloma

Figure 7 Papilloma, bronchus, mouse, H&E. (Reproduced with permission of the Society of Toxicologic Pathology from Renne, R. et al. 2009. Proliferative and nonproliferative lesions of the rat and mouse respiratory tract. *Toxicol Pathol* 37(7 suppl):5S–73S. https://www.ncbi.nlm.nih.gov/pubmed/20032296.)

Nasal cavity adenosquamous carcinoma

Figure 8 Adenosquamous carcinoma, nasal cavity, rat, H&E. (Reproduced with permission of the Society of Toxicologic Pathology from Renne, R. et al. 2009. Proliferative and nonproliferative lesions of the rat and mouse respiratory tract. *Toxicol Pathol* 37(7 suppl):5S–73S. https://www.ncbi.nlm.nih.gov/pubmed/20032296.)

Nasal cavity neuroepithelial carcinoma

Figure 10 Neuroepithelial cell carcinoma, nasal cavity, rat, H&E. (Reproduced with permission of the Society of Toxicologic Pathology from Renne, R. et al. 2009. Proliferative and nonproliferative lesions of the rat and mouse respiratory tract. *Toxicol Pathol* 37(7 suppl):5S–73S. https://www.ncbi.nlm.nih.gov/pubmed/20032296.)

Skin: Proliferative

Adnexal hyperplasia

Figure 1 Adnexal hyperplasia in a mouse, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Basal cell carcinoma

Figure 2 Basal cell carcinoma in a mouse at low (top) and high (bottom) power magnifications, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Basal cell tumor

Figure 3 An early benign cutaneous basal cell tumor arising from the epidermal surface of a patched 1(PTCH1) heterozygous null C57BL/6 mouse, H&E. (Figure used by permission from Diegel, K.L. et al. 2013. In: Wanda, M. et al. (eds.) *Handbook of Toxicologic Pathology*, 3rd ed. Elsevier Press.)

Figure 4 Another example of a benign basal cell tumor in a mouse, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Epidermal hyperplasia

Figure 5 Epidermal hyperplasia in skin from a minipig, H&E. (Image used by permission from Danilenko, D.M. et al. 2016. In vitro skin models and their predictability in defining normal and disease biology, pharmacology and toxicity. *Toxicol Pathol* 44:555–563.)

Hair follicle tumor, benign

Figure 6 Benign hair follicle tumor (tricholemmoma) in the skin of a rat, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Mast cell tumor

Figure 9 Mast cell tumor in a mouse, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Melanoma/melanocytic tumor

Figure 10 Benign melanocytic tumor in a mouse, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Figure 11 Malignant melanoma in the dermis of a mouse, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Sebaceous cell adenoma

Figure 12 Sebaceous cell adenoma in a mouse at low (top) and high (bottom) magnifications, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Squamous cell carcinoma

Figure 13 Squamous cell carcinoma in the skin of a rat, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Figure 14 Squamous cell carcinoma in the skin of a mouse, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Squamous cell papilloma

Figure 15 Squamous cell papilloma in the skin of a mouse, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Special Senses Proliferative: Eye

Harderian gland adenocarcinoma

Figure 1 Harderian gland adenocarcinoma (squamous cell subtype) with invasion that has destroyed the eye (phthisis bulbi), B6C3F1 mouse, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Harderian gland adenoma

Figure 2 Harderian gland adenoma, B6C3F1 mouse, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Intraocular schwannoma

Figure 3 Intraocular schwannoma, malignant, uvea, H&E. (Image provided courtesy of L. Teixeira, Department of Pathobiological Sciences, School of Veterinary Medicine, University of Wisconsin, Madison, WI.)

Lacrimal gland adenocarcinoma

Figure 4 Lacrimal gland adenocarcinoma, B6C3F1 mouse, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Lens epithelial hyperplasia

Figure 5 Lens epithelial hyperplasia with lens capsule hypertrophy, posterior iris adhesion, and degeneration lens fibers (cataract), F344 rat, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Ocular squamous cell carcinoma

Figure 6 Ocular squamous carcinoma, invasion of cornea, dog, H&E. (Image provided courtesy of L. Teixeira, Department of Pathobiological Sciences, School of Veterinary Medicine, University of Wisconsin, Madison, WI.)

Retinal pigment epithelium (RPE) hyperplasia

Figure 7 Retinal pigment epithelium (RPE) hyperplasia with retinal atrophy and retinal detachment, F344 rat, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Uveal melanoma

Figure 8 Uveal melanoma, dog, H&E. (Image provided courtesy of L. Teixeira, Department of Pathobiological Sciences, School of Veterinary Medicine, University of Wisconsin, Madison, WI.)

Special Senses Proliferative: Ear

Zymbal's gland carcinoma

Figure 1 Zymbal's gland carcinoma (squamous cell subtype), invasion of middle ear, F344 rat, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Urinary System: Proliferative

A-V adenoma

Figure 1 Rat kidney, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

A-V Carcinoma

Figure 2 Rat kidney, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Atypical renal tubule cell hyperplasia

Figure 3 Rat kidney, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Nephroblastoma

Figure 5 Rat kidney, H&E. (Reproduced with permission of Society of Toxicology from Frazier, K. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse urinary system. *J Toxicol Pathol* 40:14S–86S. https://www.ncbi.nlm.nih.gov/pubmed/22637735.)

Oncocytic hyperplasia

Figure 6 Rat kidney, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Oncocytoma

Figure 7 Rat kidney, H&E. (Reproduced with permission of Society of Toxicology from Frazier, K. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse urinary system. *J Toxicol Pathol* 40:14S–86S. https://www.ncbi.nlm.nih.gov/pubmed/22637735.)

Renal mesenchymal tumor

Figure 8 Rat kidney, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Renal sarcoma

Figure 9 Rat kidney, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Renal tubular adenoma

Figure 10 Rat kidney, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Renal carcinoma

Figure 11 Rat kidney, H&E. (Reproduced with permission of Society of Toxicology from Frazier, K. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse urinary system. *J Toxicol Pathol* 40:14S–86S. https://www.ncbi.nlm.nih.gov/pubmed/22637735.)

Papilloma

Figure 12 Rat urinary bladder, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Squamous cell carcinoma

Figure 13 Rat urinary bladder, H&E. (Images provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Urothelial cell carcinoma

Figure 14 Rat urinary bladder, H&E. (Reproduced with permission of Society of Toxicology from Frazier, K. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse urinary system. *J Toxicol Pathol* 40:14S–86S. https://www.ncbi.nlm.nih.gov/pubmed/22637735.)

Urothelium hyperplasia

Figure 16 Rat urinary bladder, H&E. (Reproduced with permission of Society of Toxicology from Frazier, K. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse urinary system. *J Toxicol Pathol* 40:14S–86S. https://www.ncbi.nlm.nih.gov/pubmed/22637735.)

APPENDIX 3

Gastrointestinal Tract

Figure 2 Gastrointestinal tract, rat. (Photograph courtesy of Kenard Lee Jr. Novartis. East Hanover, New Jersey.)

Figure 3 Oral cavity, rat, disarticulated at temporomandibular joint. (Photograph courtesy of Kenard Lee Jr. Novartis. East Hanover, New Jersey.)

Figure 4 Stomach, rat. (Photograph courtesy of Kenard Lee Jr. Novartis. East Hanover, New Jersey.)

Liver, Gallbladder, and Exocrine Pancreas

Figure 1 Liver lobule schematic; P, portal triad; CV, central vein. (Liver acinus zones shown for comparison.) (Reproduced with permission of Elsevier from Cattley, R.C. and Cullen, J.M. 2013. In: Haschek, W. et al. (eds.) *Haschek and Rousseaux's Handbook of Toxicologic Pathology*, 3rd ed. Academic Press, Elsevier, San Diego, CA. pp. 1509–1566.)

Lymphoid System

Lymphoid follicle, splenic marginal zone (cynomolgus monkey)

Figure 1 Splenic lymphoid follicle from cynomolgus monkey stained for the B-cell marker CD20 (blue) and α-smooth muscle actin (SMA/brown) (panel A), CD20 (blue) and the T lymphocyte marker, CD3 (brown) (panel B), and IgD (green) and F-actin (red) (panel C). (Reproduced with permission from the American Society of Investigative Pathology from Vugmeyster, Y. et al. 2006. A soluble BAFF antagonist, BR3-Fc, decreases peripheral blood B cells and lymphoid tissue marginal zone and follicular B cells in cynomolgus monkeys. *Am J Pathol* 168:476–489.)

Splenic decreased cellularity of the lymphoid follicle marginal zone

Figure 2 Splenic lymphoid follicles from cynomolgus monkey that demonstrate a decrease in marginal zone cellularity. Panels A and B are stained for the B-cell marker CD20 (blue) and smooth muscle actin SMA (brown) illustrating how the band of SMA+ myofibroblasts (MF) divides the follicle and the inner marginal zone from the outer marginal zone. (Reproduced with minor modifications with permission from the American Society of Investigative Pathology from Vugmeyster, Y. et al. 2006. A soluble BAFF antagonist, BR3-Fc, decreases peripheral blood B cells and lymphoid tissue marginal zone and follicular B cells in cynomolgus monkeys. *Am J Pathol* 168:476–489.)

Nervous System

Normal anatomy

Figure 5 Cerebrospinal fluid circulation in brain of a cynomolgus macaque and showing various barriers in the CNS and PNS. (Copyright 2018 Caroline Frank. Used with permission.)

Reproductive System and Mammary Gland

Figure 1 Estrous cycle−dependent changes in the vaginal epithelium; SD rat, H&E. (Reproduced with permission of Academic Press from Rudmann, D.G. and Foley, G.L. 2013. In: Haschek, W.M. et al. (eds.) *Haschek and Rousseaux's Handbook of Toxicologic Pathology*, 3rd ed. Elsevier, Academic Press, pp. 2599–2660.)

Figure 2 Estrous cycle−dependent changes in the vagina and uterus in the dog, H&E. (Reproduced with permission of Academic Press from Rudmann, D.G. and Foley, G.L. 2013. In: Haschek, W.M. et al. (eds.) *Haschek and Rousseaux's Handbook of Toxicologic Pathology*, 3rd ed. Elsevier, Academic Press, pp. 2599–2660.)

Figure 3 Estrous cycle dependent changes in the uterus in the monkey, H&E. (Reproduced with permission of Academic Press from Rudmann, D.G. and Foley, G.L. 2013. In: Haschek, W.M. et al. (eds.) *Haschek and Rousseaux's Handbook of Toxicologic Pathology*, 3rd ed. Elsevier, Academic Press, pp. 2599–2660.)

Figure 4 Mammary gland, female F344/N rat, H&E. (Reproduced with permission of the Society of Toxicologic Pathology from Rudmann, D. et al. 2012. Proliferative and nonproliferative lesions of the rat and mouse mammary, Zymbal's, preputial, and clitoral glands. *Toxicol Pathol* 40: 7S–39S. https://www.ncbi.nlm.nih.gov/pubmed/22949413.)

Figure 5 Seminal vesicle, F344/N rat, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Figure 6 Preputial gland, F344/N rat, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Respiratory System

Figure 4 Alveolar structure, TEM, 1500×. Note thin epithelial barrier of type I pneumocytes (blue arrows), facilitating gas exchange, and type II pneumocytes found at intersections of alveolar walls (black arrows). (Image courtesy of Ian Francis, Ex-vivo Bioimaging, GSK, Ware, UK.)

Figure 5 Type II pneumocyte (TII cell), TEM, 8000×. Note typical cytoplasmic lamellar bodies (arrows), capillary lumen with erythrocyte (C), and adjacent to capillary endothelium, the epithelial barrier formed by a type I pneumocyte (TI cell). (Image courtesy of Paul McGill, Ex-vivo Bioimaging, GSK, Ware, UK.)

Figure 6 Surfactant, Type II pneumocyte (TII cell), TEM, 20,000×. Secretion of surfactant material (arrow), with typical appearance of secreted tubular myelin (TM) in bottom right of image. (Image courtesy of Paul McGill, Ex-vivo Bioimaging, GSK, Ware, UK.)

Special Senses: Eye

All photomicrographs were provided by the contributing authors.

Special Senses: EAR

Figure 1 Major components of the outer ear and middle ear (tympanic membrane, ossicles, and tympanic bulla), rat, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Urinary System

Figure 1 Schematic of the normal nephron. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

Figure 2 Normal microanatomy of rat kidney, H&E. (Image provided courtesy of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.)

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