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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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Edited by
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Robert H. Spaet
Philip Bentley
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* Indicates Lead Contributor.

** Deepa B. Rao (Nervous System chapter) 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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** Contributions to the section Drug Development Overview coauthored by Deepa B. Rao reflects her own views and should not be construed as representing views or policies of her employer, The US Food and Drug Administration.

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,

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.

Pritam S. Sahota
Robert H. Spaet
Philip Bentley
Zbigniew W. Wojcinski

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

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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* Contributions to Appendix 1 (Drug Development Overview) and Nervous System, both co-authored by Deepa B. Rao, reflect 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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Advisory Group

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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A

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.

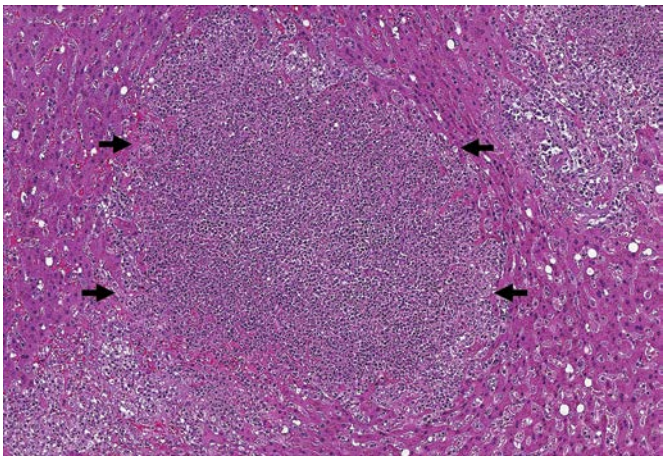
ABC-binding cassette transporters are a family of active transporters that have an ATP binding site (ATP-binding cassette) and are responsible for the transport of drugs both into and out of cells. Effects of the latter on transporters are studied to understand the factors affecting the distribution 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.

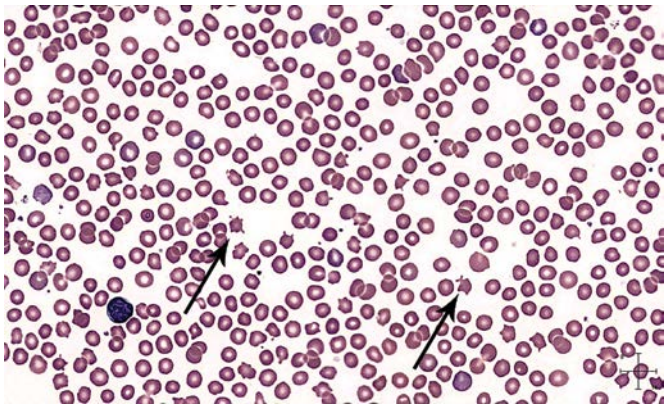
Absolute bioavailability is the amount of a nonintravenously administered drug (e.g., oral, inhaled, intramuscular, subcutaneous, etc.) which reaches the systemic circulation as active drug compared to the amount of active drug in the circulation following intravenous administration of the same dose. 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

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.

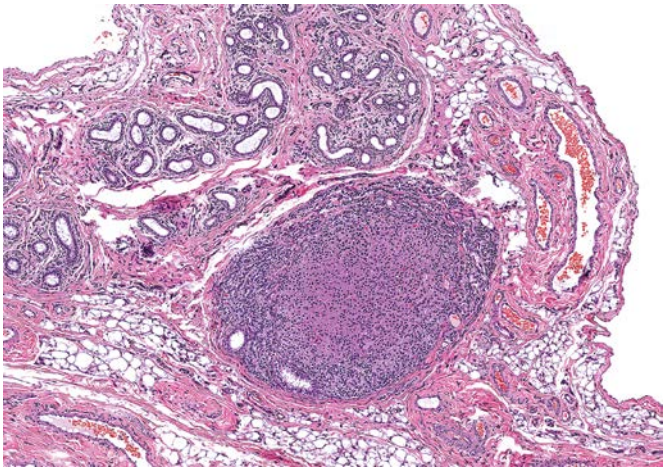
Acanthoma, infundibular, keratinizing, see the preferred term **Keratoacanthoma**.

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.

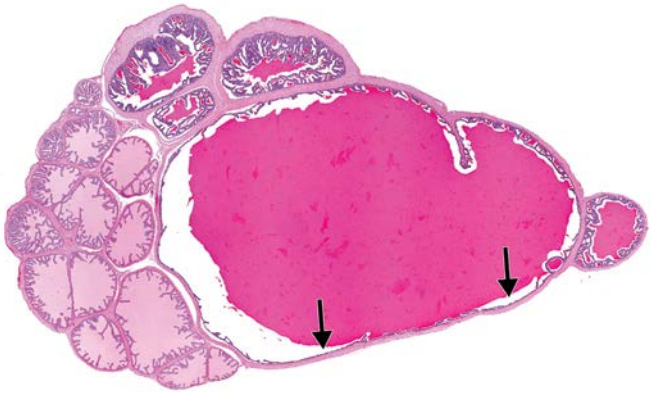
Accessory male sex organ acinar cystic dilation, see the preferred term **Accessory male sex organs, acinar/vesicle dilation**.

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

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**.

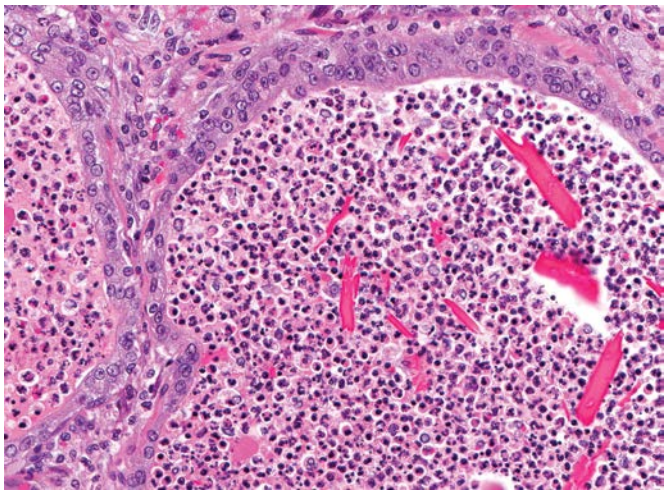
Accessory male sex organ hypoplasia (prostate, seminal vesicle, coagulating gland, and/or bulbourethral gland) is a rare congenital abnormality consisting of the underdevelopment of organ(s). It has been observed in transgenic rodent strains such as the 5alpha-reductase type 2 knockout mouse (prostatic 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

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.**

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-l0 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.

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.