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International Harmonization of Nomenclature and Diagnostic Criteria (INHAND): Nonproliferative and Proliferative Lesions of the Rabbit

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The INHAND (International Harmonization of Nomenclature and Diagnostic Criteria for Lesions Project (www.toxpath.org/inhand.asp) is a joint initiative of the Societies of Toxicologic Pathology from Europe (ESTP), Great Britain (BSTP), Japan (JSTP) and North America (STP) to develop an internationally accepted nomenclature for proliferative and non-proliferative lesions in laboratory animals. The purpose of this publication is to provide a standardized nomenclature for classifying microscopic lesions observed in most tissues and organs from the laboratory rabbit used in nonclinical safety studies. Some of the lesions are illustrated by color photomicrographs. The standardized nomenclature presented in this document is also available electronically on the internet (http://www.goreni.org/). Sources of material included histopathology databases from government, academia, and industrial laboratories throughout the world. Content includes spontaneous lesions as well as lesions induced by exposure to test materials. Relevant infectious and parasitic lesions are included as well. A widely accepted and utilized international harmonization of nomenclature for lesions in laboratory animals will provide a common language among regulatory and scientific research organizations in different countries and increase and enrich international exchanges of information among toxicologists and pathologists. (DOI: 10.1293/tox.2021-I001; J Toxicol Pathol 2021; 34: 183S–292S)

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Section 1: Introduction

The INHAND Project (International Harmonization of Nomenclature and Diagnostic Criteria for Lesions) is a joint initiative of the societies of toxicologic pathology from Europe (European Society of Toxicologic Pathology - ESTP), UK (British Society of Toxicological Pathologists - BSTP), Japan (Japanese Society of Toxicologic Pathology - JSTP), and North America (Society of Toxicologic Pathology - STP) to unify, update and complete the existing WHO/IARC and STP/SSNDC nomenclature systems. The INHAND nomenclature and the related diagnostic criteria should represent the future international standard in toxicologic pathology. They represent a consensus of senior toxicologic pathologists and were reviewed by the INHAND-GESC (INHAND-Global Editorial and Steering Committee) for compliance with INHAND principles. The initial series of nomenclature publications were focused on lesions in rats and mice. With the decision of the SEND initiative (Standard for the Exchange of Non-clinical Data) to model the

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controlled terminology (CT) based on the INHAND nomenclature and the decision of the Federal Drug Administration (FDA) to make the use of the SEND CT mandatory for electronic submissions of nonclinical studies, the INHAND project was extended to other laboratory animal species including the monkey, rabbit, mini-pig, dog and fish.

However, the recommendations for diagnostic criteria and preferred terminology may not be applicable in all situations. Purposes of specific experiments or the specific context of a given study may require deviation from this standardized nomenclature and diagnostic criteria. The appropriate diagnoses are ultimately based upon on the discretion of the senior toxicologic Study Pathologist.

The present publication provides a set of standardized terms and diagnostic criteria to be used in toxicologic pathologic studies on the most commonly used strains of laboratory rabbits - New Zealand White (NZW) representative of non-pigmented and Dutch Belted representative of a pigmented rabbit. Throughout this publication, lesions applicable for use in toxicologic-pathology studies in rabbits are tabulated. As rabbits have been most frequently used for tissue specific studies in young animals (e.g. ocular, dermal, and intramuscular), compilation of a broad listing of the incidence of spontaneous or background findings, and a tabulation of the incidence of subacute to chronic responses to chemicals, drugs and biomaterials are limited. The terms and thus, the tabulations, build on the existing rodent nomenclature. In most instances, the description and definition of the rodent lesion applies to the rabbit and is not further described. This publication focuses on lesions that are unique to the rabbit and are not observed in rodents, and lesions in rabbit that share the same terminology with a rodent lesion but display different morphologic features. Lesions that are unique to rats or mice and are not to be used in rabbit are denoted accordingly in the tabulation. The tabulated lesions are categorized according to the following characteristics: “Common”, “Uncommon”, “Not Observed but Potentially Relevant” and “Not Applicable”. The distinction between common and uncommon lesions is based on the occurrence in untreated laboratory rabbits in the authors’ experience and is not based on published references. Also, it should be kept in mind that the rabbit used in toxicologic studies are usually of young age and are only for a relative short time on study, a fraction of the normal life span of a rabbit. In addition, references to lesions seen in older pet and breeding animals are mentioned in the text where relevant. Before entering a study, the health status of individual animals is checked carefully, and the individual rabbits selected for a toxicologic study are in excellent condition. For these reasons, the spectrum and frequency of changes are different from those in diagnostic laboratories, and, therefore, common age-related lesions including neoplasms are rarely seen in these animals. Thus the vast majority of neoplastic lesions have been categorized as “Uncommon”. The category “Not Applicable” refers to rodent specific lesions and terms as the use of these terms in rabbits is considered not appropriate. Examples are chronic progressive nephropathy in the kidney or fibro-osseous lesion of bones. “Not Observed but Potentially Relevant” are changes that have not been described or observed in laboratory rabbits, however, the use of these terms has been considered permissible should a lesion meet the diagnostic criteria.

Like all other INHAND publications, the nomenclature and diagnostic criteria for the rabbit are also available online (www.goreni.org). The online version contains any change controls, additional images and useful links to differential diagnoses characterizing it as a practical tool for diagnostic work.

The recommended nomenclature is generally descriptive rather than diagnostic. The diagnostic criteria used require standard hematoxylin and eosin stained paraffin sections only. Histochemical or immunohistochemical staining characteristics may be addressed in the comments section of the respective lesion. Such special techniques may be required in some situations, but a comprehensive discussion of these methods is outside the scope of this publication. Systemic non-proliferative lesions that occur across organ systems and are not specific to an organ are reviewed in the section on systemic pathology. Although the rodent publications provide “synonyms” for each term, the non-rodent publications have used the notation “Other term(s)”. While these “synonyms” or “other terms” have been used historically, the primary listed term is the preferred term and will link to the controlled terminology in SEND. These “other terms” are listed with some of the entries to aid the pathologist when comparing current study findings with archival material. These other terms are archaic terms and should not be used because they are no longer preferred diagnostic entities.

Lesions included in this nomenclature system may be further specified by modifiers. Criteria are given for modifiers that are considered to be of particular relevance. These modifiers should be consistently applied. It is upon the discretion of the pathologist to use additional modifiers not suggested in this nomenclature system. Such modifiers may describe the location, tissue type, or duration among others. Further principles of the INHAND nomenclature have been published separately[1].

Section 2: Systemic Pathology

There are a number of microscopic findings that may be seen across several organs and/or tissues and are not specific to just one organ system. There are also a number of different findings that are present across several organs and/or tissues that together constitute a syndrome. Those findings that occur in multiple tissues are listed here for convenience, and they are also described under the organ systems in which they occur if they have unique features. Syndromes specific to the rabbit are mentioned in individual chapters, but their definitive descriptions are presented here.

Rabbits used in general toxicology studies are bred under barrier conditions, which are microbiologically defined, and are kept in strictly controlled/biosecure facilities when on study, so infectious disease (parasitism, bacterial, fungal and viral diseases) is unlikely. *Pasteurella, Encephalitozoon* and *Eimeria* spp. have been reported in the past but are rarely observed today[2, 3].

The tables below give an indication of how frequently the changes may be observed in the laboratory rabbit, associated diseases/conditions, etiologies or inducing agents, and a list of tissues where they may be found. Where further explanation is deemed useful, selected lesions are discussed in more detail below the table (Table 1).

Apoptosis

Comments: For a full discussion see Elmore, S. (2007). Apoptosis: A Review of Programmed Cell Death. *Toxicologic Pathology*, *35*(4), 495–516

Infiltrate, Inflammatory Cell

Comments: NZW rabbits on surgical studies may develop granulomas if orthopedic sutures are implanted into dorsal fascia[5]. NZW Rabbits are commonly used to test biocompatibility by implantation of novel medical materials into intramuscular and other tissue locations. Tissue reaction is scored using ISO 10993-6:2016[6] by characterizing inflammatory cells, necrosis, granulation tissue and fibrosis. Injured and regenerating skeletal muscle may also stimulate adipogenesis resulting in fatty infiltration[7]. Fatty metaplasia needs to be differentiated from the normal fat pads containing blood vessels and nerves that occur between muscle bundles when implants are incorrectly implanted or medical materials migrate into intermuscular sites.

Metaplasia, Osseous or Cartilaginous

Comments: Cartilage and bone formation, with or without intraosseous bone marrow is a common finding with intramuscular but not subcutaneous implantation tests of bone substitution biomaterials. Osseous metaplasia is readily induced in dogs and baboons, and to a lesser extent in rabbits and mice with calcium phosphates (CP) or hydroxyapatite/calcium phosphate (HCP). Rabbits form bone and bone marrow with HCP[8-10]. Rarely, cartilage, bone and bone marrow may form as a sequela of intramuscular implantation of novel polymers and other biomaterials.

Mineralization

Comments: Rabbits do not require Vitamin D to regulate calcium absorption from the gut. Excess calcium in the diet is therefore more likely to cause metastatic calcification than in other species[11].

Vacuolation, Macrophages

Other term(s): Phospholipidosis

Pathogenesis/cell of origin: Macrophage

Differential diagnoses: accumulation adipocyte, phagocytic vesicle, lysosome.

Comments: Phospholipid vacuoles may be positive for LAMP2. Similar to the other laboratory species. Tissues affected by phospholipidosis vary by drug.

Table 1. Microscopic Findings of Systemic Pathology (Generally Used Preferred Terms): Rabbit

Finding	Common	Uncommon	Associated Diseases/ Conditions	Tissues commonly reported in:
Non-proliferative				
Congenital				
Agenesis/hypoplasia		X		
Malformation syn. congenital malformation		X		Gall bladder (bifurcation)
Multisystemic				
Abscess		X		
Accumulation, adipocytes	X			
Amyloid		X		
Apoptosis *ǂ		X		
Atrophy		X		
Basophilic granules		X		
Congestion		X		Nasal cavity, lung, liver, vagina
Edema		X		
Extramedullary hematopoiesis		X		Spleen, liver, adrenal
Fracture		X		Lumbar spine, usually associated with handling
Hemorrhage	X			Larynx, trachea, thyroid, thymus, bronchi, bronchioles
Infiltrate, inflammatory cell * [insert appropriate cell type]		X	Mononuclear, lymphocyte, plasma cell, macrophage/ monocyte, neutrophil, eosinophil, heterophil, mixed	Multiple tissues; differentiate form MALT
Inflammation		X	Acute, chronic, chronic active, granulomatous, granuloma	Multiple tissues; may be due to bacterial, viral or parasitic diseases e.g. *Pasteurella* sp. in the lungs; foreign body inflammatory reactions with multinucleated giant cells are common with implantation of biomaterials and medical devices
Metaplasia		X		
Metaplasia, Osseous/cartilaginous *		X		Lung, eye and skeletal muscle (implant associated)
Mineralization *	X			Ovary, kidney, cerebral & cerebellar leptomeninges, blood vessels, lung, skeletal muscle
Necrosis		X		
Parasite		X	Coccidiosis (*Eimeria spp*); Microsporidiosis (*Encephalitozoon cuniculi)*	Adrenal gland, brain, eye, intestine, kidney, liver
Pigment		X	Hemosiderin	Spleen, liver, bone marrow, adrenal, glomeruli, lymph node sinuses
Pigment		X	Melanin, hemosiderin, lipofuscin	Skin, leptomeninges of pigmented strains
Pigment, macrophage	X		Tattoo ink, inhaled particulate matter	(cervical) lymph node (from ear tattoos), lung
Serous atrophy of fat		X		
Single cell necrosis ǂ		X		
Tissue, ectopic	X			Accessory adrenal cortical tissue, accessory spleen, bifurcate gall bladder; ectopic thyroid, ectopic thymus
Vacuolation		X		Spleen, lymph node, lungs, choroid plexus
Vacuolation, macrophages *#		X		
Proliferative Neoplastic				
Lymphoma		X		Liver, small intestine, multiple tissues

* Terminology with diagnostic criteria or comments described in the text. # Inducible lesion. ǂ Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

Section 3: Cardiovascular System

A. Anatomy of the Heart

Detailed anatomy and physiology of the rabbit heart has been described by various authors[12, 13] and is not within the scope of this text. However, one difference to note is that the right atrioventricular valve of the heart is bicuspid instead of tricuspid as occurs in the rodent.

Histopathology of the heart should include all relevant compartments and structures of the heart, including the ventricular, atrial and interventricular septal wall, the valves and the coronary vessels.

Xenobiotics may cause myocardial changes due to exaggerated pharmacodynamic activity or as a result of a direct toxic effect on cardiomyocytes. Severe acute toxic insults can cause acute cardiomyocyte death, and the regenerative potential of cardiomyocytes is generally insufficient to replace significant myocardial loss. Biochemical changes such as alterations in calcium homeostasis can occur if the insult is of mild severity, and these generally result in reversible cardiac arrhythmia. Cardiomyocytes are generally replaced by fibroblasts, with collagenous deposits leading to loss of cardiac contractility. Changes in the heart are known to be induced by "stress" i.e. catecholamine (CA) induced cardiomyopathy. Study-related procedures can elevate serum stress biomarkers and exacerbate the frequency and severity of myocardial inflammatory cell infiltrates[14].

Rabbit models of heart disease have been comprehensively reviewed[15] (Table 2).

Malformation

Other terms: Congenital malformation

Comments: Congenital lesions of the heart and blood vessels are rare and are reported infrequently in rabbits. Consequently, the lesions are usually only seen in Developmental and Reproduction Toxicity (DART) studies, in which fetuses are carefully dissected. Ventricular septal defect has been reported in a 10-month-old female NZW rabbit[16]. Other conditions occasionally seen in rabbits are: right sided aortic arch and patent ductus arteriosus.

Fibrosis, Myocardium (Figure 1)

Comments: Myocardial fibrosis may be induced in rabbits after anesthesia with the α2-agonist detomidine, alone and in combination with ketamine or diazepam[17, 18]. The presence of myocardial fibrosis does not always result in clinical signs and adversity should be judged on a case by case basis. There is also an age-related increased fibrosis in the ventricles and interventricular septum. Ventricular stiffness and wall thickness increase in the aging rabbit heart[19].

Infiltrate, Inflammatory Cell, Myocardium (Figure 2)

Comments: Mononuclear inflammatory cell infiltrates are recorded infrequently in the myocardium. The foci are usually at the base of the interventricular septum but have been reported in the atrial and ventricular free walls. There is no accompanying myocardial necrosis or fibrosis associated with this lesion.

Inflammation, Myocardium

Comments: Inflammatory cells may be associated with cardiomyocyte necrosis, interstitial edema and early fibrosis (see Necrosis). This finding can be induced by catecholamines secondary to stress[14, 20]. Severity and incidence are increased in rabbits subjected to more handling and procedures. Increase in circulating catecholamines act on adrenergic receptors expressed in the heart and stimulate contractility. Heart lesions are primarily in the left ventricle and papillary muscle[20, 21]. In severe cases, the inflammatory cell foci may resolve as focal fibrosis. This tends to be an idiosyncratic reaction and may affect one or two animals in a study, suggesting a subset of animals may be more vulnerable to stress responses and/or do not habituate to stressors[14].

Mineralization, Cardiomyocyte/Myocardium (Figure 3)

Comments: Generally a background lesion but may be exacerbated by some xenobiotics; common in left atrial appendage. Mineralization may be seen at necropsy in older animals, e.g. ex-breeding colony animals.

Necrosis, Cardiomyocyte (Figure 4)

Other terms: Degeneration/necrosis, cardiomyocyte

Comments: Myocardial inflammation with/without minimal necrosis and/or fibrosis may be seen as a stress-induced finding in occasional animals on toxicity studies. These foci are minimal to moderate in severity grade and most affect one part of the myocardium, usually papillary muscles, left ventricular free wall, or may be multifocal throughout intraventricular septum, right ventricular free wall and atria. They are more commonly seen in animals subject to multiple procedures or handling events and thought to be catecholamine induced necrosis. Animals may be found *in extremis* or dead without previously showing any clinical signs. Although only an occasional occurrence in young rabbits used in toxicology studies, this sudden death syndrome is recognized as a stress induced event, caused by handling/invasive procedures (injections, blood sampling) in pet rabbits (Bradley, unpublished data). A recent study showed that the incidence, composition and severity of these foci may be exacerbated by handling and procedures that occur in toxicology studies, mediated by a stress response[14].

Myocardial necrosis and fibrosis can be induced in rabbits after anesthesia with the α2-agonist detomidine, alone and in combination with ketamine or diazepam[17, 18]. There is reduction in coronary flow reserve as a consequence of the hypoxemia associated with ketamine/xylazine administration due to xylazine interaction with α2-receptors in coronary vessels. Impairment of coronary blood flow causes myocardial ischemia with subsequent necrosis. The rabbit is a species with limited collat-

Table 2. Microscopic Findings of the Heart: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Congenital				
Malformation *		X		
Non-proliferative				
Accumulation, adipocyte, myocardium	X			
Amyloid		X		
Apoptosis ǂ		X		
Atrophy		X		
Cardiomegaly			X	
Degeneration		X		
Degeneration/necrosis		X		
Edema			X	
Fibrosis, myocardium *		X		
Fibrosis			X	
Hypertrophy		X		
Infarct		X		
Infiltrate, inflammatory cell, [insert appropriate cell type] myocardium *	X			
Inflammation, myocardium *		X		
Karyomegaly/Karyocytomegaly			X	
Mineralization *	X			
Necrosis, cardiomyocyte *		X		
Necrosis/infiltrate		X		
Parasite		X		
Pigment		X		
Single cell necrosis ǂ		X		
Thrombus, atrium			X	
Tissue, ectopic, thyroid		X		
Vacuolation, cardiomyocyte		X		
Proliferative Non-neoplastic				
Hyperplasia, subendocardium			X	
Hyperplasia, mesothelium			X	
Proliferative Neoplastic Lesions				
Schwannoma, endocardium			X	
Schwannoma, intramural			X	
Mesothelioma, pericardium			X	
Mesothelioma, atriocaval			X	

* Terminology with diagnostic criteria or comments described in the text. ǂ Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

eral circulation in the myocardium and is therefore predisposed to ischemia induced by coronary vasoconstriction[22, 23].

B. Anatomy of the Blood Vessels

Rabbit blood vessels are generally thin-walled and prone to collapse and may form hematomata on puncture – a feature important for studies where test items are given by intravenous administration. The exception to this is the pulmonary arteries which are enveloped in a prominent smooth muscle layer, which may be misinterpreted as hypertrophy[24, 25].

Specific large vessels may be required on safety assessment studies in which animals have been dosed via intravascular catheter through bolus injection or slow infusion. Large vessels that can be easily sampled in rabbits include the thoracic and abdominal aorta/vena cava, carotid arteries, femoral arteries/veins and iliac arteries/veins. Some lesions occur in vessel-specific progression (e.g. atherosclerosis) (Table 3).

Malformation

Other terms: Congenital malformation

Comments: Congenital lesions of the blood vessels are rare and are reported infrequently in rabbits. Consequently, the lesions are usually only seen macroscopically in Developmental and Reproduction Toxicity (DART) studies, in which fetuses are carefully dissected. Conditions occasionally seen in rabbits are right sided aortic arch and patent ductus arteriosus.

Table 3. Microscopic Findings of the Vessels and Valves: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Congenital				
Malformation *		X		
Non-proliferative				
Abscess		X		
Amyloid		X		
Aneurysm, artery or aortic			X	
Angiectasis			X	
Apoptosis ǂ		X		
Degeneration/necrosis, media or wall		X		
Dilatation		X		
Embolus		X		
Fibrosis, perivascular		X		
Hemorrhage, media or wall		X		
Hypertrophy, endothelium/media or wall, artery		X		
Infiltrate, inflammatory cell [insert appropriate cell type]		X		
Inflammation, media or wall, artery		X		
Intimal thickening, acellular *#		X		
Intramural plaque, artery			X	
Metaplasia			X	
Mineralization *	X			
Necrosis		X		
Necrosis/inflammation, media or wall, artery		X		
Single cell necrosis ǂ		X		
Thrombus			X	
Vacuolation, media or adventitia, artery			X	
Proliferative Non-Neoplastic Lesions				
Hyperplasia, intima		X		
Proliferative Neoplastic Lesions				
Hemangioma			X	
Hemangiosarcoma			X	

* Terminology with diagnostic criteria or comments described in the text. # Inducible lesion. ǂ Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

Intimal Thickening, Acellular

Other terms: Atherosclerosis

Diagnostic Features: Atherosclerotic plaques primarily composed of macrophage-derived foam cells.

Comments: In rabbits, the presence of atherosclerosis-like lesions was first described in 1913[26]. High plasma cholesterol concentrations, especially of low-density lipoprotein (LDL) cholesterol, result in atherosclerotic lesion formation. The accumulation of foam cells results in the formation of fatty streaks, the earliest observable abnormality of the vessel wall. The rabbit exhibits hypercholesterolemia within a few days of an administration of a high cholesterol diet, and so can be used as an animal model in efficacy studies to see if drugs affect inducement of atheromatous lesions. The basal release of nitric oxide (NO), is greater with endothelium-intact aortic rings from female rabbits than from male rabbits, and so this protective effect of circulating estradiol means female animals are less prone to diet-induced atherosclerotic lesions than male animals. Cholesterol-rich diets have been used to induce widespread atheromatous lesions within a short time period (3 months). Genetically altered strains of the NZW rabbit are also used extensively. The Watanabe rabbit (Watanabe heritable hyperlipidaemia rabbit, WHHL) is used to study the pathology of type IIa human familial hypercholesterolemia. The WHHL rabbit has a genetic deprivation of functional LDL receptors. In these animals, the atherosclerotic process begins *in utero*, and the lesions progress with age[27]. Rinke and Hartmann characterized atherosclerosis in NZW and WHHL rabbits[28]. The lesions were extremely pronounced in the vessels of the cardiac atria, including the valves and extended with degenerative changes into the myocardium. Some nearly occlusive arteries, without surrounding myocardial change, were also seen. Inflammatory response and areas of regeneration, occasionally accompanied by dystrophic mineralization, were

frequently observed. Rabbit models for the study of human atherosclerosis have been reviewed previously[29].

Mineralization, Aorta/Medial or Mural Artery (Figure 5)

Comments: Generally, a background lesion but may be exacerbated by some xenobiotics. Occasionally evidence of the closure of the ductus arteriosus may be seen as foci of mineralization in the media of major blood vessels of young rabbits, depending on plane of section. Calcification of the aorta, pulmonary artery, and femoral artery may be seen microscopically in young animals as an incidental finding. These lesions can be exacerbated by an increased calcium supply or vitamin D overdosage[11] or where fresh pellets are given (freshly opened packets of standard rabbit chow contain more degradable vitamins as the declaration of ingredient contents are corrected to be those present at the expiry date of the food). Mineralization may be seen at necropsy in older animals, e.g. ex-breeding colony animals.

Section 4: Digestive System (Oral Cavity, Salivary Glands, Esophagus, Stomach, Intestines, and Exocrine Pancreas)

A. Anatomy of the Oral Cavity and Esophagus

The mouth opening of rabbits is small so that a thorough examination of the buccal cavity is difficult or in some animals almost impossible. The oral cavity is long and curved. Erosions of the mucosa may occur due to irregular growth or sharp edges of broken teeth.

Teeth

The dental formula of the rabbit is 26 or 28 teeth. The maxilla contains 4 incisors, no canines, six premolars, and 4–6 molars. The second set of maxillary incisors are small, caudal to the main incisors, and are known as the peg teeth. The mandible contains 2 incisors, no canines, 4 premolars, and 6 molars. Rabbits are hypsodonts and have a long crown without a true tooth root[30]. Rabbits chew their food using their tongue elaborately, moving their jaw more than 120 times per minute.

Tongue

The tongue is relatively large in comparison to the overall body size of rabbits and has the standard 4 papillae types, namely vallate, foliate, fungiform, filiform[30].

Esophagus

The esophagus comprises three layers of semi-involuntary striated muscle; the rabbit esophagus lacks mucus glands[30] (Table 4).

Cleft Palate

Comments: Cleft Palate is a common finding in rabbit teratogenicity studies. Congenital alveolar cleft is a malformation occurring as a result of non-fusion of primary palate during weeks 4–12 of gestation and may be induced by glucocorticoids[31].

Hyperplasia

Comments: Gingival hyperplasia has been recorded in NZW rabbits administered cyclosporine A chronically (L. Himmel, personal communication).

Papilloma, Squamous Cell

Comments: Caused by oral papilloma virus (papovavirus). Small grayish nodules present on the ventral buccal cavity and/or the underside of the tongue. Lesions are seen in animals 2–18 months old. The infection is self-limiting and uncommon in young animals but may occur in older breeding stock.

B. Anatomy of the Salivary Glands

Salivary Glands

There are 4 pairs of salivary glands in the rabbit: parotid, submaxillary (also called mandibular), sublingual, and zygomatic. The parotid gland is the largest and runs from below the ear base to the front of the ear base and is bounded by the skin and masseter muscle. The parotid gland duct runs rostrally along the lateral surface of the masseter muscle and is adjacent to the branches of the facial nerve. The parotid gland duct empties into the oral cavity opposite the last upper molar. The submaxillary gland is oval-shaped and located at the angle of the mandible. The sublingual gland is small in the rabbit. The zygomatic salivary gland rests just ventral to the lacrimal gland adjacent to the anteroventral angle of the orbit (see also Lacrimal Glands subsection in Special Senses section). Rabbit saliva contains amylase but has only trace amounts of lipase and urea. The rabbit submaxillary gland has continuous secretion of saliva[30] (Table 5).

Accumulation

Comments: This diagnosis should be used to describe the microscopic correlates with a macroscopic sialocele.

Depletion, Secretory, Acinar Cell

Comments: This is seen as a generalized process secondary to reduced food intake in rabbits as in many other species, and also in animals suffering from mucoid enteropathy. There may be diffuse depletion of parotid salivary gland zymogen, with associated vacuolar degeneration of exocrine cell cytoplasm[32].

Necrosis, Glandular

Other terms: Infarct; Metaplasia, Squamous Cell

Unilateral minimal focal/multifocal mandibular salivary gland necrosis with acute inflammation has been reported in rabbits after auricular artery catheterization. Although thrombi were not identified microscopically, necrosis/acute inflammation was consistent with recent infarction[33]. Extensive coagulative necrosis and associated squamous metaplasia (so-called "necrotizing sialometaplasia") have been reported in the mandibular salivary as sequelae of mandibular fracture[34] and photodynamic therapy (di-sulfonated phthalaocyanine and laser irradiation)[35] and were likewise attributed to infarction[35].

C. Anatomy of the Stomach

Stomach

The stomach of a healthy rabbit is never empty, due to the practice of coprophagy, and like the rat and horse, a rabbit cannot vomit[36]. In new-born rabbits, an empty stomach indicates agalactia of the mother. The stomach is large, thin walled, and unlike rodents, there is no non-glandular region

Table 4. Microscopic Findings of the Oral Cavity, Pharynx, Tongue and Esophagus: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Non-proliferative				
Congenital				
Cleft palate *	X			
Malformation			X	
Non-proliferative				
Amyloid		X		
Apoptosis ǂ		X		
Cyst	X			
Degeneration/necrosis, muscle		X		
Edema		X		
Erosion/ulcer	X			
Hemorrhage		X		
Hyperkeratosis		X		
Infarct		X		
Infiltrate, inflammatory cell [insert appropriate cell type]	X			
Inflammation, foreign body		X		
Inflammation, mixed cell	X			
Inflammation, mononuclear cell	X			
Inflammation, vessel		X		
Metaplasia			X	
Mineralization (+ locator)	X			
Necrosis (+ locator)	X			
Pigment		X		
Single cell necrosis ǂ		X		
Syncytia, epithelium	X			
Tissue, ectopic		X		
Tissue, ectopic, sebaceous gland		X		
Yeast		X		
Proliferative Non-Neoplastic				
Hyperplasia *#		X		
Proliferative Neoplastic				
Adenoma			X	
Adenocarcinoma			X	
Carcinoma, squamous cell			X	
Leiomyoma			X	
Leiomyosarcoma			X	
Papilloma, squamous cell *		X		
Tumor, granular cell, benign			X	
Tumor, neuroendocrine cell			X	

* Terminology with diagnostic criteria or comments described in the text. # Inducible lesion. ǂ Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

in the rabbit stomach (Figures 6, 7). Occasionally, a bezoar may be found acting as a foreign body and eventually obstructing the pyloric region. Free ingesta in the abdominal cavity may mimic rupture of the gastric wall. *Helicobacter* spp. have been identified in the stomach of rabbits but not associated with inflammation or ulceration[37]. The stomach is prone to very fast autolysis and in premature decedent toxicologic study animals it should be sampled as soon as possible (Table 6).

Parasite

Comments: Parasites of the gastrointestinal system include nematodes, cestodes and protozoans, but are rarely a problem in well-managed barriered facilities. Protozoal parasites cause the most common and significant disease. Numerous species of *Eimeria* are capable of infecting rabbits: *Eimeria stiedai* (frequently referred to as *E. stiedae), E. magna, E irresidua* and *E. intestinalis.*

Table 5. Microscopic Findings of the Salivary Glands: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Congenital				
Ectopic tissue	X			
Non-proliferative				
Abscess		X		
Accumulation *		X		
Accumulation, adipocytes		X		
Amyloid		X		
Angiectasis		X		
Apoptosis ǂ		X		
Atrophy	X			
Calculus, duct		X		
Cyst	X			
Degeneration/necrosis		X		
Degranulation, (+ locator)		X		
Depletion, secretory *		X		
Dilatation, duct		X		
Ectasia, duct		X		
Edema		X		
Focus, basophilic		X		
Fibrosis		X		
Granules increased		X		
Hemorrhage		X		
Hypertrophy		X		
Infarct		X		
Infiltrate, inflammatory cell [insert appropriate cell type]	X			
Inflammation, mixed cell	X			
Inflammation, mononuclear cell	X			
Inflammation, vessel		X		
Metaplasia, acinar cell		X		
Metaplasia, osseous		X		
Metaplasia, squamous cell	X			
Mineralization (+ locator)	X			
Multinucleated giant cells		X		
Necrosis, glandular *	X			
Pigment		X		
Secretion, deceased, acinar cell		X		
Single cell necrosis ǂ		X		
Tissue, ectopic		X		
Vacuoles, autophagic, acinar cell		X		
Vacuolation		X		
Yeast	X			
Proliferative Non-neoplastic				
Hyperplasia #		X		
Proliferative Neoplastic				
Adenoma			X	
Adenocarcinoma			X	
Myoepithelioma, malignant			X	
Tumor, mixed, benign			X	
Tumor, mixed, malignant			X	

* Terminology with diagnostic criteria or comments described in the text. # Inducible lesion. ǂ Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

Table 6. Microscopic Findings of the Stomach: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Congenital				
Ectopic tissue	X			
Malformation			X	
Non-proliferative				
Amyloid		X		
Apoptosis ǂ		X		
Atrophy	X			
Cyst	X			
Degeneration/necrosis		X		
Dilatation, glands	X			
Diverticulum	X			
Edema		X		
Erosion/ulcer	X			
Globules, eosinophilic		X		
Helicobacter sp.		X		
Hemorrhage		X		
Infarct		X		
Infiltrate, inflammatory cell [insert appropriate cell type]	X			
Inflammation (+ cell type)		X		
Metaplasia		X		
Mineralization (+ locator)	X			
Necrosis, mucosa	X			
Parasite *		X		
Pigment		X		
Single cell necrosis ǂ		X		
Syncytia, epithelium	X			
Yeast	X			
Proliferative Non-neoplastic				
Hyperplasia #		X		
Proliferative Neoplastic				
Adenoma			X	
Adenocarcinoma			X	
Gastrointestinal stromal tumor (GIST), benign			X	
Gastrointestinal stromal tumor (GIST), malignant			X	
Leiomyoma			X	
Leiomyosarcoma			X	
Tumor, basal cell, benign			X	
Tumor, neuroendocrine cell, benign			X	

* Terminology with diagnostic criteria or comments described in the text. # Inducible lesion. ǂ Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

D. Anatomy of the Small and Large Intestines

Intestine

The intestinal tract of the rabbit is anatomically distinct from that of the other laboratory species. Locations from which samples for histopathological examinations should be ideally taken are illustrated.

Duodenum

The length of the duodenum is relatively great in rabbits and the proximal part of the duodenum is characterized by a wide layer composed of Brunner's glands. The sample for histology therefore should be taken close to the pyloric region. In the rabbit two distinct cell types are present within the glands. Serous cells, which occur in small groups in the blind endings to the tubules, contain a concentration of rough endoplasmic reticulum in the basal cytoplasm, and the apical cytoplasm is occupied principally by discrete secretory droplets. Intercellular secretory canaliculi occur between opposed serous cells and between serous and

mucous cells. The latter cells possess little rough endoplasmic reticulum but exhibit an extensive development of the Golgi apparatus in the supranuclear region. Secretory droplets are pale and show a tendency to fuse into complexes. No intercellular canaliculi occur between mucous cells[38]. In contrast to other species, Paneth cells are visible in the duodenum at the base of the duodenal crypts and are easily recognized by the large eosinophilic granules that occupy most of the cytoplasm.

Jejunum

The jejunum is located along the left side of the cecum. It is very long and its junction with the ileum is indicated by the ileocecal fold, which attaches to the apex of the vermiform appendix of the rabbit. The jejunum should be sampled distal to the junction with the pancreatic ducts. The villi of the jejunum are thin and longer than in the duodenum and display a tall columnar epithelium with a low number of intermingled goblet cells. Paneth cells are easily to detect at the base of the crypts. Peyer's patches can be found only in the distal region of the jejunum.

Ileum

The ileum is also located along the left side of the cecum. The terminal part of the ileum is enlarged to form the round, expanded muscular sac – the sacculus rotundus. The sacculus rotundus is a common site for foreign body impaction. Both the sacculus rotundus and vermiform appendix appear pale coloured at necropsy due to the large amount of lymphoid tissue in their walls. These two lymphoid organs contain more than 50% of the total lymphoid tissue of the rabbit, accounting for the relatively small size of the spleen. The surface of the sacculus rotundus is covered by short villi, and the lamina propria is similar to that of the vermiform appendix. The thickness of the lymphoid tissue is variable. The tunica muscularis of the sacculus rotundus is thicker than that seen in the vermiform appendix.

Cecum

The cecum occupies the major portion of the middle to lower abdomen ventrally, being coiled around itself into three major turns or gyri and is freely movable in the peritoneal cavity. The cecal wall consists of epithelium-lined lamina propria, with short indented crypts giving an irregular contour to the surface. Both tunica muscularis and submucosa are thin. Scattered goblet cells are located between tall columnar cells[39]. The haustrated cecum is tightly coiled and tapers to form the light-colored vermiform appendix. The rabbit is a hindgut fermenter, and so the cecum is much larger than the stomach (about 10 times the size). There is a small area of lymphoid tissue approximately 2 mm in diameter on the inner wall of the cecum adjacent to the ileocecal orifice. The lymphoid follicles at this site have direct contact with the lumen of the cecum (unlike the follicles in the vermiform appendix and sacculus rotundus). The lymphoid tissue in this ileocecal plaque is more loosely arranged and more diffuse in character than that of the other two intestinal lymphoid structures. A tall columnar epithelium covers the surface of the follicle and goblet cells are rare. The tunica submucosa and muscularis are thin[39].

The vermiform appendix consists of a thick continuous layer of lymph follicles, the apical portions of which extend as protrusions above the lymph follicle proper. These protrusions are covered by columnar epithelium which is strongly infiltrated with lymphoid cells. At the base of the protruding portion of the follicle a thin column of lamina propria, emerging from the reticular connective tissue surrounding the lymph follicles, extends between the protruding portions of neighbouring follicles. This column of lamina propria is covered by a high columnar epithelium which contains numerous goblet cells and is continuous with the epithelium overlying the lymph follicle at the base of the apical protrusion. Above the bulging portion of the follicle the columns of lamina propria combine to form a covering over the follicle with a slightly lower columnar epithelium. Oval and slit like openings indicate areas which are not covered by the lamina propria. Occasional goblet cells are present in this columnar epithelium; the lamina muscularis mucosae is dispersed and difficult to define. The lymph follicles constitute 70% of the entire thickness of the intestinal wall. The epithelium adjacent to the lymphoid follicles is of a higher columnar cell type. The nuclei are more elongated, microvilli are short and sparse, and vesicles and mitochondria are abundant on the apical portions when examined by SEM. Goblet cells are numerous within this epithelium[39].

Colon

The proximal part of the ascending colon is closely associated with the cecum but can be identified by its characteristic tight haustrations and prominent teniae. The transverse colon is divided into proximal and distal portions and is separated by the fusi coli - a muscular spindle-shaped organ with a greatly thickened mucosa. The fusi coli is heavily supplied with ganglion cell aggregates and is under the influence of prostaglandins. The fusi coli, along with the muscular contractions of the sacculations and haustra, is responsible for directing the separation of fiber from non-fiber components of feeds. This speeds the fiber components through the colon where it is excreted as hard feces. Antiperistaltic action moves fluids and small particles in a retrograde manner through the colon to the cecum, where it is retained for fermentation[40]. Cecal contents are selectively passed as cecotrophs, also referred to as "soft feces", to be consumed directly from the rectum. Cecotrophs are covered with mucus to protect them from the acid pH of the stomach (pH 1.2–1.5) and composed of water, nitrogen, electrolytes and vitamins. The arrival of cecotrophs at the anus triggers a neural response, resulting in licking the anal area and consumption of the cecotrophs. This is usually 4–8 hours after feeding, generally in the evenings, therefore cecotrophs are also known as "night feces". These soft pellets contain twice the protein and half the fibre of the

daytime fecal pellets. Coprophagy improves the utilisation of nitrogen, provides an abundance of certain B vitamins and conserves water. The excretion of hard daytime feces is related to feeding. Daytime fecal pellets are firm and dry, are excreted during the first four hours after feeding and are not ingested.

The most proximal part of the colon, adjacent to the sacculus rotundus, is expanded to form the bulb like structure – the ampulla cecalis coli, which is the most muscular portion. It consists of epithelial lined lamina propria (tunica mucosa) possessing wide open crypts. The walls of the crypts often show irregular contours, especially near the lumen, and give the impression of villi. The tunica muscularis is thicker than in other parts. Goblet cells are scarce[39]. The ampulla coli is entirely free of mesenteric connections. Distal to the ampulla, the ascending colon spirals around the cecum producing several flexures before joining the transverse colon. The distal ascending colon, and transverse colon are small in diameter, and are not haustrated.

Peri-rectal tissue

There are focal apocrine-type glands in the submucosa near the anorectal junction, often called "anal glands" (further discussed in the Integument section). Their relationship to the "inguinal" (apocrine/sebaceous) gland complex (Integument section) is not clear (Table 7).

Degeneration, Neuron, Myenteric Plexus

Diagnostic features: Chromatolytic degeneration of pre- and postganglionic sympathetic and parasympathetic neurons (enteric neurons in the myenteric and submucosal plexus in the small intestine), as well as chromatolysis of somatic and autonomic lower motor neurons in the brain stem and spinal cord.

Comments: This is part of a "syndrome" or constellation of findings that includes both plexus and brain stem. The dysautonomia has been compared to similar lesions in horses, cats and hares. It is assumed that the causative toxin is present in hay and grass, causing the same lesion in horses, rabbits and hares. Animals affected also show impaction of the large intestine with dry food material.

Dilatation, Duct

Comments: In animals suffering from mucoid enteropathy, the ducts of the Brunner's glands in the duodenum become dilated, with cuboidal to low columnar acinar epithelium, rather than tall mucus-filled epithelial cells[32].

Hyperplasia, Goblet Cell

Comments: Mucoid enteropathy is usually seen in young animals, 2–3 months old, but can be seen in adults. In animals suffering from mucoid enteropathy there is an increase in the size and number of goblet cells in the intestinal epithelium, affecting duodenum, jejunum and ileum, but most apparent in sections of the ileum. Colonic crypts may be irregularly dilated due to mucous plugs. Goblet cell hyperplasia may also occur in the cecum due to cecal stasis and impaction, and in the hepatic bile ducts. Staining with Alcian blue-Periodic Acid Schiff indicates depletion of richly stained acidic colonic mucus and replacement with weakly staining light green-blue foamy mucus. Mucoid "enteritis" is a misnomer, for there is no hyperemia, congestion, local leukocytic response, necrosis, or fever, with goblet cell hyperplasia and a mucus hypersecretory state instead being the pathognomonic finding. Mucoid "enteropathy" is the correct term for this condition[32]. The etiology is unknown, but an enterotoxin-induced secretory diarrhea caused by *Escherichia coli* or *Clostridium spiriforme* is suspected. Antibiotic induced enterotoxemia can also be a factor, especially with lincomycin, clindamycin or erythromycin. The finding may be induced in toxicology studies assessing antibiotics.

Parasite (Figures 8, 9)

Comments: Parasites of the gastrointestinal system include nematodes, cestodes and protozoans, but are rarely a problem in well-managed barriered facilities. Protozoal parasites cause the most common and significant disease. Numerous species of *Eimeria* are capable of infecting rabbits: *Eimeria stiedai* (frequently referred to as *E. stiedae), E. magna, E irresidua* and *E. intestinalis.*

E. Anatomy of the Exocrine Pancreas

The pancreas of the rabbit is small and diffuse and located in a pocket formed by the transverse colon, the stomach and the duodenum. It may be difficult to locate in the abundant adipose tissue of the omentum, and retains only the accessory pancreatic duct, which enters the ascending duodenum distal to the entrance of the biliary duct. The right lobe of the pancreas is situated in the mesoduodenum of the duodenal loop. The left lobe lies between the stomach and transverse colon. There is a single pancreatic duct that opens at the junction of the transverse and ascending loops of the duodenum. The duct drains both pancreatic lobes. Technically, this is the accessory pancreatic duct as the main pancreatic duct connection to the duodenum disappears during embryonic development (Table 8).

Tissue, Ectopic

Comments: Ectopic spleen has been recorded in the pancreas of a NZW[41].

Table 7. Microscopic Findings of the Small and Large Intestines: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Congenital				
Ectopic tissue	X			
Malformation			X	
Non-proliferative				
Abscess		X		
Amyloid		X		
Apoptosis ǂ		X		
Atrophy	X			
Cyst	X			
Degeneration		X		
Degeneration/necrosis		X		
Degeneration, neuron, myenteric plexus *	X			
Dilatation, (+ locator) *	X			
Edema		X		
Erosion/ulcer	X			
Hemorrhage		X		
Hypertrophy, Paneth cell	X			
Infarct		X		
Infiltrate, inflammatory cell [insert appropriate cell type]	X			
Inflammation, mixed cell	X			
Inflammation, mononuclear cell	X			
Inflammation, vessel		X		
Intussusception	X			
Lymphangiectasis		X		
Metaplasia, squamous cell/Paneth cell/osseous	X			
Mineralization (+ locator)	X			
Necrosis, mucosa	X			
Paneth cell, decreased		X		
Parasite *		X		
Pigment		X		
Prolapse		X		
Single cell necrosis ǂ		X		
Syncytia, epithelium	X			
Vacuolation, mucosa	X			
Yeast	X			
Proliferative Non-neoplastic				
Hyperplasia *		X		
Hyperplasia, goblet cell *#		X		
Proliferative Neoplastic				
Adenoma			X	
Adenocarcinoma			X	
Carcinoma, Brunner's glands			X	
Gastrointestinal stromal tumor (GIST), benign			X	
Gastrointestinal stromal tumor (GIST), malignant			X	
Leiomyoma			X	
Leiomyosarcoma			X	
Tumor, neuroendocrine cell, benign			X	

* Terminology with diagnostic criteria or comments described in the text. # Inducible lesion. ǂ Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

Table 8. Microscopic Findings of the Exocrine Pancreas: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Congenital				
Ectopic tissue *		X		
Non-proliferative				
Abscess		X		
Accumulation, adipocytes	X			
Amyloid		X		
Apoptosis ǂ		X		
Atrophy	X			
Autophagic vacuoles, acinar cell		X		
Cyst	X			
Degeneration/necrosis		X		
Degranulation, (+ locator)		X		
Dilatation, duct		X		
Ectasia, duct		X		
Edema		X		
Focus, basophilic		X		
Fibrosis		X		
Halos, peri-insular, decreased		X		
Halos, peri-insular, increased		X		
Hemorrhage		X		
Infarct		X		
Infiltrate, inflammatory cell [insert appropriate cell type]	X			
Inflammation, mixed cell	X			
Inflammation, mononuclear cell	X			
Inflammation, vessel		X		
Metaplasia, ductular		X		
Metaplasia, hepatocyte	X			
Mineralization (+ locator)	X			
Necrosis		X		
Pigment		X		
Secretion, decreased		X		
Single cell necrosis ǂ		X		
Tissue, ectopic		X		
Proliferative Non-neoplastic				
Hyperplasia #		X		
Proliferative Neoplastic				
Adenoma, acinar cell			X	
Adenoma, ductal cell			X	
Adenocarcinoma, acinar cell			X	
Adenocarcinoma, ductal cell			X	

* Terminology with diagnostic criteria or comments described in the text. # Inducible lesion. ǂ Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

Section 5: Endocrine System: (Pituitary, Pineal, Thyroid, Parathyroid, Adrenal Glands and Endocrine Pancreas)

For detailed general considerations on the endocrine system, please refer to the rodent INHAND publication[42].

The endocrine system of the rabbit is made up of the pituitary, pineal, thyroid, parathyroid, adrenal, and islets of Langerhans of the pancreas as well as parts of the male and female gonads and the epithelial lining of the duodenum[43].

A. Anatomy of the Pituitary Gland

In the rabbit the pituitary has three major divisions: lobus glandularis (adenohypophysis), lobus nervosus (neurohypophysis) and the infundibular stalk which attaches the pituitary to the median eminence of the hypothalamus[43, 44]. Strong muscarinic receptor protein-like (mAChRp-L) immunoreactivity is associated with the blood vessels of the anterior and intermediate lobes of the rabbit pituitary[45]. Sensitive and specific autoregulatory control systems for thyrotropin (TSH), luteinizing hormone (LH) and follicle stimulating hormone (FSH) exist in the rabbit pituitary[46] (Table 9).

B. Anatomy of the Pineal Gland

Pineal Gland

Calcareous concretions are common, which increase with age and apparently do not affect function of the gland. The rabbit pineal gland has an inhibitory effect on gonadotropin release[47] (Table 10).

Table 9. Microscopic Findings of the Pituitary Gland: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Congenital				
Aberrant craniopharyngeal structures		X		
Aplasia/hypoplasia		X		
Persistent Rathke's pouch			X	
Non-proliferative				
Angiectasis		X		
Apoptosis ǂ		X		
Atrophy			X	
Cyst		X		
Fibrosis		X		
Gliosis, pars nervosa			X	
Hemorrhage		X		
Hypertrophy, pars distalis		X		
Hypertrophy, pars intermedia		X		
Infarct		X		
Infiltrate, inflammatory cell [insert appropriate cell type]		X		
Inflammation		X		
Metaplasia, osseous		X		
Necrosis		X		
Pigment		X		
Pseudocyst		X		
Single cell necrosis ǂ		X		
Thrombus		X		
Vacuolation		X		
Proliferative Non-neoplastic				
Hyperplasia, pars distalis/intermedia			X	
Proliferative Neoplastic				
Adenoma, pars distalis/intermedia			X	
Carcinoma, pars distalis/intermedia			X	
Craniopharyngioma, benign			X	
Pituicytoma, benign			X	
Craniopharyngioma, malignant			X	
Pituicytoma, malignant			X	

ǂ Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

Table 10. Microscopic Findings of the Pineal Gland: Rabbit

Finding	Common	Uncommon	Not Observed but potentially Relevant	Not Applicable
Congenital				
Aplasia/hypoplasia			X	
Non-proliferative				
Amyloid		X		
Angiectasis		X		
Apoptosis ǂ		X		
Cyst		X		
Fibrosis		X		
Fibers, striated muscle				X
Hemorrhage		X		
Infarct		X		
Infiltrate, inflammatory cell [insert appropriate cell type]		X		
Inflammation		X		
Mineralization		X		
Necrosis		X		
Pigment		X		
Single cell necrosis ǂ		X		
Striated muscle fibers		X		
Thrombus		X		
Vacuolation		X		
Proliferative Non-neoplastic				
Hyperplasia		X		
Proliferative Neoplastic				
Pinealoma, benign			X	
Pinealoma, malignant			X	

Since the pineal gland is not routinely evaluated there is limited experience in incidences of these lesions in the rabbit. ǂ Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

C. Anatomy of the Thyroid Gland

The two lobes of the thyroid gland in the rabbit are less clearly circumscribed compared to other laboratory species and are flattened, with the isthmus barely visible (Table 11).

D. Anatomy of the Parathyroid Gland

The paired parathyroid glands are usually located on the anterior and lateral aspect of the thyroid lobes, located in or immediately outside of the thyroid gland in the rabbit, and are separated from the thyroid by a thin capsule of fibrous connective tissue. The rabbit possesses two parathyroid glands within the thyroid and two located in the fascial plan between the sternohyoid and sternothyroid muscles and the carotid artery[48] (Table 12).

Tissue, Ectopic

Comments: Ectopic parathyroid tissue can occur in the thymus or dorsolateral to the esophagus near the larynx.

E. Anatomy of the Adrenal Gland

Adrenal Cortex and Medulla

In the rabbit, each of the pair of suprarenal adrenal glands is composed of an inner medulla and outer cortex. The adrenal cortex is voluminous in the rabbit and is derived from the interrenal gland associated with the mesonephros in lower vertebrates, which is involved in the maintenance of normal functioning kidneys[43]. The ultrastructure of the capsule of the rabbit adrenal gland is made up of three layers with the outermost layer consisting of collagen and elastic fibrillae with cytoplasmic processes of fibroblasts in between[49]. Myofibroblasts are present in the middle layer as well as unmyelinated nerves, indicating a contractile function. The basal laminae of the fenestrated capillaries in the inner vascular layer is occasionally fused with that of the outer zona glomerulosa, suggesting a probable route for blood supply and secretion[49]. The cortex is made up of three layers: the zona glomerulosa, zona fasciculata, zona reticularis[44]. Fazekas and Sandor have demonstrated that there is an unusual pathway of aldosterone biosynthesis in the rabbit adrenal whereby aldosterone is formed mainly from corticosterone via 18-hydroxy-corticosterone[50]. The adrenal medulla contains chromaffin cells and ganglion cells

Table 11. Microscopic Findings of the Thyroid Gland: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Congenital				
Aplasia/hypoplasia		X		
Cyst, ultimobranchial		X		
Duct, thyroglossal, persistent		X		
Thyroid dysplasia			X	
Non-proliferative				
Alteration, colloid		X		
Amyloid		X		
Angiectasis		X		
Apoptosis ǂ				
Atrophy		X		
Cyst		X		
Fibrosis		X		
Follicle, cystic		X		
Hemorrhage		X		
Hypertrophy, follicular cell		X		
Infarct		X		
Infiltrate, inflammatory cell [insert appropriate cell type]		X		
Inflammation		X		
Mineralization		X		
Necrosis		X		
Pigment		X		
Single cell necrosis ǂ		X		
Tissue, ectopic	X			
Thrombus		X		
Vacuolation		X		
Proliferative Non-neoplastic				
Hyperplasia, C-cell			X	
Hyperplasia, follicular cell			X	
Proliferative Neoplastic				
Adenoma, C-cell			X	
Adenoma, follicular cell			X	
Carcinoma, C-cell			X	
Carcinoma, follicular cell			X	

ǂ Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

arranged into trabeculae[44]. The adrenal glands are the most commonly affected endocrine organs secondary to chemical exposure[51]. In the adrenal glands, chemically induced lesions are found most frequently in the zona fasciculata and reticularis and to a lesser extent in either the zona glomerulosa or the medulla.

Paraganglia

The paraganglia including the carotid and aortic bodies (made up of neuroendocrine cells) are also considered to be endocrine tissues of the rabbit[43] (Table 13).

F. Anatomy of the Endocrine Pancreas (Islets of Langerhans)

Extensive deep connections between the capillary beds of the islets and the exocrine tissue form a highly developed portal system in the rabbit which allows the islet hormones of insulin, glucagon and somatostatin to influence exocrine pancreatic cells[52]. Nearly all of the efferent islet blood flow goes to the acinar capillaries before leaving the pancreas. Thus, the flow to the islets is large enough to permit significant local actions of the islet hormones on the exocrine pancreas, confirming of the existence of an insuloacinar portal system[53] (Table 14).

Hyperplasia, Islet Cell

Pathogenesis/cell of origin: islet cells

Table 12. Microscopic Findings of the Parathyroid Gland: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Congenital				
Aplasia/hypoplasia		X		
Cyst, ultimobranchial		X		
Duct, thyroglossal, persistent		X		
Non-proliferative				
Amyloid		X		
Angiectasis		X		
Apoptosis ǂ				
Atrophy		X		
Cyst		X		
Fibrosis		X		
Hemorrhage		X		
Hypertrophy		X		
Infarct		X		
Infiltrate, inflammatory cell [insert appropriate cell type]		X		
Inflammation		X		
Multinucleated giant cells			X	
Necrosis		X		
Pigment		X		
Single cell necrosis ǂ		X		
Tissue, ectopic *	X			
Thrombus		X		
Vacuolation		X		
Proliferative Non-neoplastic				
Hyperplasia			X	
Proliferative Neoplastic				
Adenoma			X	
Carcinoma			X	

* Terminology with diagnostic criteria or comments described in the text. ǂ Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

Diagnostic Features: Diffuse islet cell hyperplasia, characterized by increased numbers of otherwise unremarkable islet cells, resulting in variably increased cellularity and overall diameter of islet profiles

Comments: may be seen as an induced treatment related effect by test articles that cause hyperglycemia.

Table 13. Microscopic Findings of the Adrenal Gland: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Congenital				
Aplasia/hypoplasia		X		
Non-proliferative				
Amyloid		X		
Angiectasis		X		
Apoptosis [ǂ]		X		
Atrophy	X			
Cyst		X		
Degeneration, cystic		X		
Fibrosis		X		
Hematopoiesis, extramedullary		X		
Hemorrhage		X		
Hypertrophy, cortical, diffuse/focal		X		
Infarct		X		
Infiltrate, inflammatory cell [insert appropriate cell type]		X		
Inflammation		X		
Metaplasia, osseous		X		
Mineralization		X		
Necrosis		X		
Persistent X-zone				X
Pigment		X		
Single cell necrosis [ǂ]		X		
Tissue, ectopic		X		
Thrombus		X		
Vacuolation cortex decreased diffuse		X		
Vacuolation cortex decreased focal		X		
Vacuolation cortex increased diffuse		X		
Vacuolation cortex increased focal		X		
Proliferative Non-Neoplastic				
Hyperplasia, cortical/medullary			X	
Hyperplasia, subcapsular cell				X
Proliferative Neoplastic				
Adenoma, cortical cell			X	
Adenoma, subcapsular cell				X
Ganglioneuroma, benign			X	
Myelolipoma			X	
Pheochromocytoma, complex, benign			X	
Pheochromocytoma, benign			X	
Carcinoma, cortical cell			X	
Carcinoma, subcapsular cell				X
Neuroblastoma, malignant			X	
Pheochromocytoma, complex, malignant (adrenal gland)			X	
Pheochromocytoma, malignant			X	

[ǂ] Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

Table 14. Microscopic Findings of the Endocrine Pancreas: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Congenital				
Aplasia/hypoplasia		X		
Non-proliferative				
Amyloid, islet		X		
Angiectasis		X		
Apoptosis, islet cell [ǂ]		X		
Atrophy, islet cell		X		
Cyst		X		
Degranulation, islet cell		X		
Fibrosis, islet		X		
Hemorrhage, islet		X		
Hypertrophy, islet cell		X		
Infarct		X		
Infiltrate, inflammatory cell [insert appropriate cell type]		X		
Inflammation		X		
Metaplasia, hepatocyte			X	
Necrosis		X		
Pigment. islet		X		
Single cell necrosis		X		
Vacuolation, islet cell		X		
Proliferative Non-neoplastic				
Hyperplasia, islet cell [*#]		X		
Proliferative Neoplastic				
Adenoma, islet cell			X	
Adenoma, acinar-islet cell			X	
Carcinoma, islet cell			X	
Carcinoma, acinar-islet cell			X	

* Terminology with diagnostic criteria or comments described in the text. [#] Inducible lesion.
[ǂ] Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

Section 6: Hematopoietic and Lymphoid System

A. Anatomy of the Bone Marrow

During embryogenesis in rabbits, hematopoietic progenitors (Hematopoietic stem cells - HSCs) arise within several sites including the extraembryonic yolk sac and within the placenta. HSCs are also present in the fetal liver. Shortly before birth, HSCs and hematopoietic cells are both present in the bone marrow. Morphological studies by King and Ackerman conclusively indicated that erythrocytes develop extravascularly, arising from mesenchymal or reticular cells in the fetal bone marrow[54]. Mature erythrocytes enter the circulation through discontinuities in the sinusoidal walls. Neither endothelial cells nor blood-borne lymphocytes make an apparent contribution to erythropoiesis. The first hematopoietic cells to form in the fetal marrow are determined and develop along the erythrocytic line. These proerythroblasts initially arise randomly in the marrow parenchyma and are not in obvious association with the sinusoids. Subsequent maturation and proliferation of the primitive erythrocytic cells result in the formation of colonies of erythrocytic cells at all stages of development. As these colonies enlarge, the erythrocytic elements come in close association with the sinusoids. In later stages of marrow development, developing erythrocytic and granulocytic cells become intermixed and more randomly associated in the extravascular space of the marrow. In rabbits, extramedullary hematopoiesis (EMH) occurs primarily in the spleen[55].

Adipose cells begin to develop at 2 weeks of age and proceed so that the adult pattern of red and yellow marrow is fully established by 4 months of age. Adipose cell development occurs in both trunk and limb bones; the magnitude of the process, however, being considerably greater in the limb bones. Adipocyte precursors may be present in the marrow at birth with a differential distribution in the areas of prospective red and yellow marrow. Thus, fatty involution of marrow appears to be a programmed developmental event[56].

Bone marrow is variably distributed within the medullary cavity of long and flat bones. Bone marrow for microscopic evaluation in rabbits is typically collected from the femur. Tissue is processed by standard techniques for hematoxylin and eosin stained formalin fixed paraffin embedded decalcified bone. Additionally, marrow casts may be collected from femoral bone marrow and processed for histology. A general guidance for histopathology assessment of bone marrow tissue sections is available [57]. Romanowsky stained bone marrow smears may be made for cytology. Rabbit neutrophils (heterophils) have intracytoplasmic granules that cause them to resemble eosinophils. True rabbit eosinophils have larger darker granules. Lymphocytes are the predominant leukocyte. Basophils are more common than in other mammals, making up 2–7% of the leucocyte population of the rabbit (Table 15).

Leukemia

Comments: Leukemia is reported sporadically in research rabbits[58–61].

Lymphoma

Comments: Lymphoma is the most common neoplasm of juvenile and young adult rabbits. It has been reported in rabbits as young as 4 months of age[62] and appears to be more common overall in younger rabbits[63]. Reports have included tumors of both B-cell[64] and T-cell origin[61, 65].

B. Anatomy of the Thymus

The rabbit thymus develops bilaterally from the endoderm of the third pharyngeal pouch and the surrounding mesenchyme. It is recognized as the pacemaker of lymphopoiesis in that if it fails to develop prenatally, then the immune system cannot be established[66]. The rabbit thymus develops very late, at Embryonic Day (ED) 10 (about the third of gestation period). At ED29, the demarcation between the cortex and the medulla becomes easily distinct in all lobules. At this age, Hassall's corpuscles can be observed within the medulla. They are few in number, small in size and show different stages of their formation. Some Hassall's corpuscles are represented by collection of swollen epithelial cells, other corpuscles consist of few layers of concentrically arranged epithelial cells with centrally located keratin substance. At 1 and 2 weeks postnatally, the Hassall's corpuscles increase in size and number to be large, acidophilic, rounded bodies consisting of a central degenerated hyaline mass surrounded by concentrically arranged epithelial-reticular cells[67]. They are unique to the thymus[68]. The Hassall's bodies are structurally organized from medullary reticuloepithelial cells, which usually undergo hypertrophy prior to their inclusion in the outer cell layer of the corpuscles[69].

In rabbits, the thymus has two parts; thoracic and cervical. The rabbit thymus acquires the lobulated appearance at ED14. In the thorax, the thymus is separated into three lobes: the right dorsal thoracic lobe, the right ventral thoracic lobe, and the left thoracic lobe[70]. Grossly, the shape of the left lobe of the thymus is quadrilateral in outline with extended narrow craniomedial angle in the neck, while the right lobe is triangular in outline with its base cranially directed and extended narrow craniomedial angle in the neck. The dorsal aspect of both lobes is concave showing the cardiac impression which is larger on the left lobe. In addition, the right lobe shows a pulmonary impression laterally. Medially, the left lobe slightly overlaps the right one and both lobes are connected only by small amount of interlobar connective tissue. The ventral aspect is convex and related to the sternum. While the thymus remains relatively large in adult rabbits[13], with increasing age the thymus undergoes a proportional decrease in both cortical and medullary size[71] (Table 16).

C. Anatomy of the Spleen

There are no significant variations macroscopic structures or microarchitecture between the rabbit and rodent spleens[72]. Duplication of the spleen has been observed sporadically[73] (Rinke, pers. observation) (Table 17).

Table 15. Microscopic Findings of the Bone Marrow: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Congenital				
Agenesis/hypoplasia			X	
Non-proliferative				
Abscess		X		
Amyloid		X		
Apoptosis ǂ, increased, [insert appropriate cell type]		X		
Angiectasis		X		
Atrophy, serous, of fat #		X		
Cellularity, decreased, adipocyte		X		
Cellularity, decreased, bone marrow		X		
Dyshematopoiesis		X		
Fibrosis		X		
Hypersegmentation, granulocyte		X		
Infiltrate, inflammatory cell [insert appropriate cell type]		X		
Inflammation		X		
Metaplasia, osseous		X		
Mineralization		X		
Necrosis, lymphocyte		X		
Pigment, macrophage		X		
Pigment		X		
Serous atrophy of fat		X		
Single cell necrosis ǂ		X		
Proliferative Non-neoplastic				
Cellularity, increased, [insert appropriate cell type]		X		
Proliferative Neoplastic				
Eosinophil Granulocytic Sarcoma			X	
Histiocytic sarcoma			X	
Leukemia, erythroid/myeloid/megakaryocytic/mast cell/NOS *		X		
Lymphoma*		X		
Tumor, mast cell, benign			X	
Tumor, mast cell, malignant			X	

* Terminology with diagnostic criteria or comments described in the text. # Inducible lesion. ǂ Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

D. Anatomy of the Lymph Nodes

Lymph nodes are present at birth and develop upon antigenic stimulation. Knowledge about the area(s) drained by the lymph nodes is needed to interpret their morphology[74–77]. The mesenteric lymph nodes form a compact unit overlying the left side of the superior mesenteric artery[13]. Other intra-abdominal nodes include those near the posterior end of the mesoduodenum, adjacent to the portal vein near the lesser curvature of the stomach, and near the junction of the splenic and superior mesenteric veins[13]. There are no species-specific terms for lymph nodes in rabbits (Table 18).

E. Anatomy of the Mucosa-Associated Lymphoid Tissue (MALT)

The mucosal associated lymphoid tissue (MALT) is organized into congenital and acquired organized submucosal lymphoid accumulations associated with the mucosal epithelium. This can include loose clusters of lymphocytes or well-organized lymphoid follicles. Gut-associated, nasal-associated MALT and tonsils are congenital and lymphoid aggregates in other tissues are acquired with antigenic exposure (e.g. conjunctiva, oral, pharyngeal and nasal cavities, upper (larynx and trachea) and lower (bronchus/bronchial) respiratory tract, Eustachian tube, middle ear, stomach, gall bladder, cecum, colon, rectum, reproductive and urinary tracts). The ileocecal MALT is located at the ileocecal junction as an enlargement of the large intestine. The ileocecal MALT account for 50% of the total lymphoid tissue of the rabbit and are the reason for the small size of the spleen[30]. For detailed descriptions of the vermiform appendix and sacculus rotundus, please refer to the intestinal tract section.

The gut associated lymphoid tissue (GALT) should be examined in studies where the test article is administered orally, and is usually examined in a routine section of jejunum or il-

Table 16. Microscopic Findings of the Thymus: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Congenital				
Agenesis/hypoplasia			X	
Ectopic tissue		X		
Non-proliferative				
Abscess		X		
Amyloid		X		
Apoptosis ǂ, increased, lymphocyte		X		
Cellularity, decreased, lymphocyte		X		
Corticomedullary distinction, loss of		X		
Corticomedullary ratio, decreased		X		
Corticomedullary ratio, increased		X		
Cyst, epithelial		X		
Epithelial cell free zones, increased		X		
Hypoplasia		X		
Involution, age-related	X			
Infiltrate, inflammatory cell [insert appropriate cell type]		X		
Inflammation		X		
Metaplasia, osseous		X		
Mineralization		X		
Necrosis		X		
Pigment, macrophage		X		
Pigment		X		
Single cell necrosis ǂ		X		
Tissue, ectopic (specify tissue)		X		
Tissue, ectopic, parathyroid		X		
Tissue, ectopic, thyroid		X		
Thymic corpuscles, increased		X		
Tingible body macrophage, increased		X		
Vacuolation, macrophage		X		
Proliferative Non-neoplastic				
Cellularity, increased, [insert appropriate cell type]		X		
Proliferative Neoplastic				
Histiocytic sarcoma			X	
Lymphoma		X		
Thymoma, benign			X	
Thymoma, malignant			X	

ǂ Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

eum that contains Peyer's Patches, however one of the other MALTs - sacculus rotundus (ileocecal tonsils), vermiform appendix, colonic and rectal lymphoid aggregates, cryptopatches (CPs) and isolated lymphoid follicles (ILFs) - would suffice.

Rabbits develop a primary antibody repertoire through somatic diversification of Ig genes (dependent on intestinal microbial flora). Rabbits generate their antibody repertoire in three stages: (a) neonatal repertoire is generated by B lymphopoiesis in fetal liver and bone marrow (limited by preferential V(H) gene segment usage); (b) between 4 and 8 weeks after birth, gut-associated lymphoid tissue (GALT) develops a complex primary antibody repertoire, (c) the primary antibody repertoire is subsequently modified during antigen-dependent immune responses (the secondary repertoire)[78].

Most MALT is present at birth (gut, nasal and tonsils), and is acquired in other sites thereafter[79]. Age-related functional decline of the mucosal immune response and such age-related involution is not described below as a separate item; comparison with concurrent controls is needed to decide whether or not age-related changes have occurred in a study (Table 19).

Cellularity, Decreased, Lymphocyte

Comments: Rabbits are especially sensitive to lymphoid atrophy caused by glucocorticoid administration.

Table 17. Microscopic Findings of the Spleen: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Congenital				
Agenesis/hypoplasia			X	
Tissue, ectopic			X	
Non-proliferative				
Abscess		X		
Amyloid		X		
Angiectasis		X		
Apoptosis ǂ, increased, lymphocyte		X		
Cellularity, decreased, white pulp/red pulp		X		
Congestion	X			
Erythrophagocytosis		X		
Fibrosis		X		
Infiltrate, inflammatory cell [insert appropriate cell type]		X		
Inflammation		X		
Mineralization		X		
Necrosis, lymphocyte		X		
Pigment, macrophage		X		
Pigment		X		
Single cell necrosis ǂ		X		
Tingible body macrophages, increased		X		
Vacuolation, macrophage		X		
Proliferative Non-neoplastic				
Accumulation, adipocyte		X		
Aggregates, macrophage, increased		X		
Cellularity, increased, [insert appropriate cell type]		X		
Extramedullary hematopoiesis, increased		X		
Hyperplasia, nodular		X		
Hyperplasia, mast cell			X	
Proliferative Neoplastic				
Eosinophil Granulocytic Sarcoma			X	
Histiocytic sarcoma			X	
Leukemia, erythroid/myeloid/megakaryocytic/mast cell/ NOS		X		
Lymphoma		X		

ǂ Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

Table 18. Microscopic Findings of the Lymph Nodes: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Congenital				
Aplasia/hypoplasia			X	
Non-proliferative				
Abscess		X		
Amyloid		X		
Apoptosis ǂ, increased, lymphoid		X		
Cellularity, decreased, lymphocyte		X		
Dilatation, sinus		X		
Erythrocytes, intrasinusoidal		X		
Extramedullary hematopoiesis		X		
Fibrosis, (+ locator)		X		
Granuloma		X		
Hypertrophy/hyperplasia, high endothelial venule (HEV)		X		
Infiltrate, inflammatory cell [insert appropriate cell type]		X		
Inflammation		X		
Lymphangiectasis		X		
Metaplasia, osseous		X		
Mineralization		X		
Necrosis		X		
Pigment, macrophage		X		
Pigment		X		
Single cell necrosis ǂ		X		
Tingible body macrophages increased		X		
Vacuolation, macrophage		X		
Proliferative Non-neoplastic				
Accumulation, adipocyte		X		
Aggregates, increased, macrophage		X		
Cellularity, increased, (+ cell type)		X		
Extramedullary hematopoiesis, increased		X		
Hyperplasia, angiomatous			X	
Proliferative Neoplastic				
Eosinophil Granulocytic Sarcoma			X	
Histiocytic sarcoma			X	
Leukemia, erythroid/myeloid/megakaryocytic/mast cell/NOS		X		
Lymphoma		X		
Tumor, mast cell, benign			X	
Tumor, mast cell, malignant			X	

ǂ Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

Table 19. Microscopic Findings of the MALT: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Congenital				
Aplasia/hypoplasia			X	
Non-proliferative				
Abscess		X		
Amyloid		X		
Apoptosis[ǂ], lymphoid, increased		X		
Cellularity, decreased, lymphocyte *[#]		X		
Degeneration, follicle associated epithelium		X		
Hyaline material		X		
Infiltrate, inflammatory cell [insert appropriate cell type]		X		
Inflammation		X		
Lymphangiectasis		X		
Material, hyaline		X		
Mineralization		X		
Necrosis, (+ cell type)		X		
Pigment, macrophage		X		
Pigment		X		
Single cell necrosis [ǂ]		X		
Tingible body macrophages, increased		X		
Vacuolation, macrophage		X		
Proliferative Non-neoplastic				
Aggregates, macrophage, increased		X		
Cellularity, increased, (+ cell type)		X		
Extramedullary hematopoiesis		X		
Hyperplasia, follicle-associated epithelium		X		
Hypertrophy/hyperplasia, high endothelial venule (HEV)		X		
Metaplasia, squamous, follicle-associated epithelium		X		
Proliferative Neoplastic				
Eosinophil Granulocytic Sarcoma			X	
Histiocytic sarcoma			X	
Leukemia, erythroid/myeloid/megakaryocytic/mast cell/NOS		X		
Lymphoma		X		

* Terminology with diagnostic criteria or comments described in the text. # Inducible lesion. [ǂ] Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

Section 7: Hepatobiliary System (Liver and Gall Bladder)

A. Anatomy of the Liver

The liver is situated in the epigastric region reaching the level of the right 7th and left 9th ribs. The right hepatic, caudate and quadrate lobes are single, and the left lobe is divided into medial and lateral parts[80]. The caudate process of the caudate lobe is highly developed and overlies the right kidney (Table 20).

Cytoplasmic Alteration (Figure 12)

Other terms: Rarefaction, Glycogen accumulation.

Historical terms: Granular degeneration, hyaline degeneration, ground glass change.

Diagnostic features: Rabbit livers are often pale at necropsy. This cytoplasmic rarefaction is associated with glycogen accumulation and varies both between the sexes and diurnally.

Comments: Generally, rabbits not fasted before euthanasia show high levels of glycogen accumulation. This decreases during the day, as it is usual practice to remove access to food on the day of necropsy. Therefore, animals euthanized in the morning will have more glycogen in the liver than those euthanized in the afternoon. The Study Pathologist should be aware of this diurnal change and interpret any changes in glycogen accumulation with knowledge of whether the animal was fasted prior to euthanasia, for how long and at what time of day the necropsy occurred[81]. Electron microscopy or special stains are needed for a definitive diagnosis to distinguish between lipidosis (macrovesicular and/or microvesicular steatosis), phospholipidosis, and the gestational lipidosis seen in pregnant animals.

Infarct

Comments: Excess pressure from occlusive dressings, wrapping, sleeves or jackets used to enhance exposure to dermal therapeutics or to protect wound dressings and medical devices has been found to induce necrosis ("corset liver") in the liver[82] and regional infarction in the liver and spleen (Schuh, unpublished data) of rabbits.

Inflammation (Figure 13)

Comments: An autoimmune hepatitis, similar to that seen in man, has been reported in a 5-year-old rabbit. Portal areas were characterized by a marked infiltrate of plasma cells, and some lymphocytes that extended into the surrounding parenchyma with destruction of the limiting plate architecture. In some areas the lymphocytic infiltrate was more extensive and surrounded the bile duct. There were many macrophages with engulfed pigment and apoptotic bodies. Periportal hepatocytes were swollen with karyomegaly and prominent nucleoli[83].

Mineralization

Comments: Slight or advanced dystrophic mineralization of the liver may occur due to a calcium and Vitamin D imbalance, for example in cases of over-supplementation. Usually the change occurs first in the aortic arch and heart before it reaches other organs[11].

Necrosis

Comments: Multifocal hepatocellular necrosis may occur as a stress-related disease in young (6–12 weeks-old) animals caused by Gram-negative *Clostridium (Bacillus) piliformis* (Tyzzer's disease). Clinical symptoms are diarrhea, dehydration and death within 12–48 h. Bacterial detection is mainly difficult due to autolysis and *Escherichia coli* overgrowth; microbes can be found in living cells only (Periodic Acid Schiff, Giemsa, Warthin-Starry staining). Hepatic copper toxicosis is seen occasionally in laboratory rabbits that are fed a copper-rich diet, leading to hepatocellular copper storage. Animals that then undergo a stressful event (often coupled with anorexia) may acutely release the copper from the hepatocytes. Affected livers have an accentuated lobular pattern macroscopically and centrilobular to midzonal hepatocellular necrosis with mild periportal fibrosis and biliary hyperplasia[84].

Parasite

Comments: Parasites include nematodes, cestodes and protozoans, but are rarely a problem in well-managed barriered facilities. Protozoal parasites cause the most common and significant disease. Numerous species of *Eimeria* are capable of infecting rabbits (Figures 14, 15). Hepatic lesions caused by the microsporidian *Encephalitozoon cuniculi* are recognized in rabbits (Figure 16). Hepatic lesions often include granulomatous foci along with periportal infiltration by macrophages, multinucleated giant cells, lymphocytes, and plasma cells. Inflammation can extend into the hepatic portal veins and branches of the hepatic artery[2]. Parasite presence can be confirmed by real-time PCR[85].

Pigment (Figure 17)

Comment: This term should be used for material within hepatocytes or Kupffer cells only. Pigment in canaliculi should be termed 'Plug, bile'. Periportal and centrilobular storage of iron positive pigment has been observed, but rarely. The pigment deposition may be restricted to single lobes, but also within an entire lobe the distribution may vary significantly. Pseudomelanosis has been described previously[73]. The livers are grossly discolored from dark brown to black. Histologically, intracytoplasmic pigment granules are observed that contain iron and lipofuscins. This alteration is not known to be associated with lesions in other organs.

Vacuolation, Cytoplasm

Other terms(s): Gestational lipidosis

Comments: May be seen in rabbits on reproductive toxicity

Table 20. Microscopic Findings of the Liver: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Non-proliferative				
Abscess		X		
Amyloid		X		
Angiectasis		X		
Apoptosis ǂ		X		
Atrophy, hepatocyte		X		
Cholangiofibrosis		X		
Congestion	X			
Crystals		X		
Cyst, (+ locator)	X			
Cytoplasmic alteration *	X			
Degeneration, cystic		X		
Degeneration, hydropic	X			
Erythrocytes, intrahepatocellular		X		
Extramedullary hematopoiesis	X			
Fatty change	X			
Fibrosis		X		
Focus of cellular alteration				X
Hemorrhage		X		
Hepatocytes, intravascular		X		
Hepatodiaphragmatic nodule				X
Hypertrophy, hepatocyte/endothelial cell		X		
Hypertrophy/hyperplasia, Kupffer cell		X		
Hypertrophy/karyomegaly, endothelial cell		X		
Inclusions, intranuclear and cytoplasmic		X		
Infarct *		X		
Infiltrate, inflammatory cell [insert appropriate cell type]	X			
Inflammation *		X		
Intrahepatocellular erythrocytes		X		
Intravascular hepatocytes			X	
Karyocytomegaly and/or multinucleated hepatocytes		X		
Metaplasia, glandular		X		
Metaplasia, pancreatic acinar cell		X		
Mineralization *		X		
Necrosis, focal/multifocal *		X		
Necrosis, zonal		X		
Parasite *^		X		
Phospholipidosis			X	
Pigment *, hepatocyte/Kupffer cell		X		
Plug, bile		X		
Single cell necrosis ǂ		X		
Thrombus		X		
Tissue, ectopic		X		
Vacuolation, cytoplasm *		X		
Proliferative Non-Neoplastic				
Hyperplasia, bile duct		X		
Hyperplasia, angiomatous		X		
Hyperplasia, hepatocyte, non-regenerative		X		
Hyperplasia, hepatocyte, regenerative		X		
Hyperplasia, Ito cell			X	
Hyperplasia, oval cell			X	
Proliferative Neoplastic				
Adenoma, hepatocyte			X	
Adenoma, hepatocholangiocellular			X	
Carcinoma, hepatocyte			X	
Carcinoma, hepatocholangiocellular			X	
Hemangioma			X	
Hemangiosarcoma			X	
Hepatoblastoma			X	
Histiocytic sarcoma			X	
Tumor, Ito cell, benign			X	

* Terminology with diagnostic criteria or comments described in the text. ^ Described in systemic pathology section. ǂ Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

studies. Pregnancy toxemia is a metabolic disease primarily during late pregnancy (less frequently in postpartum, pseudopregnant, and nonpregnant females), characterized by low morbidity and high mortality, and exacerbated by an inability to consume adequate energy to match metabolic demands. Risk factors include: obesity, improper nutrition - such as a diet too low in fiber, sudden stress, and anorexia. Fat deposits become rapidly mobilized, resulting in hepatic lipidosis and ketosis.

B. Anatomy of the Gall Bladder

A gall bladder is present. The gall bladder has a cylindrical shape and does not reach the livers ventral edge. The bile duct enters the duodenum very close to the pylorus. Rabbits produce very large amounts of bile, about seven times as much as a dog on a weight basis[36]. Approximately 20–50% of rabbits produce atropinase in the bile[30]. Thus, atropine is not recommended during anaesthesia (Table 21).

Malformation

Comments: Bifurcate gall bladder or duplicated gall bladder is occasionally seen in rabbits[86]. It is clinically silent and an incidental finding at necropsy.

Calculus

Comments: Rabbits fed a diet containing 0.75% dihydrocholesterol for 7 days develop bile acid allodeoxycholic

Table 21. Microscopic Findings of the Gall Bladder: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Congenital				
Cyst			X	
Malformation *		X		
Non-proliferative				
Abscess		X		
Amyloid		X		
Apoptosis ǂ		X		
Calculus *		X		
Congestion	X			
Crystals		X		
Fibrosis		X		
Hemorrhage		X		
Hyalinosis		X		
Inclusions, intranuclear and cytoplasmic		X		
Infiltrate, inflammatory cell [insert appropriate cell type]		X		
Inflammation *		X		
Metaplasia		X		
Mineralization		X		
Necrosis, focal/multifocal		X		
Necrosis, single cell		X		
Parasite *		X		
Pigment		X		
Thrombus		X		
Tissue, ectopic, pancreas		X		
Single cell necrosis ǂ		X		
Vacuolation, macrophage		X		
Proliferative Non-Neoplastic				
Hyperplasia		X		
Metaplasia, glandular		X		
Proliferative Neoplastic				
Adenoma			X	
Adenocarcinoma			X	
Cholangioma			X	
Cholangiocarcinoma			X	

* Terminology with diagnostic criteria or comments described in the text. ǂ Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

(ADCA) and deoxycholic acid (DCA) stones in the gall bladder. In this model, inflammatory changes in the gall bladder mucosa are often observed even before stones are formed. Within 3 days of the lithogenic diet, abnormalities of platelet function are detectable. Platelet aggregation upon addition of adenosine diphosphate (ADP) is impaired. At the same time the red cells become crenated and develop thorny spicules (echinocytes). This morphological change is associated with intracellular dehydration and excessive loss of potassium. These changes coincide with a rise in serum ADCA and DCA and precede a slow rise in serum cholesterol. *In vitro* incubation studies also suggest that the bile acids probably caused membrane injury to the platelets and red cells. It is concluded that changes in the bile ADCA and DCA probably induce gall bladder epithelial injury in this model of experimental cholelithiasis[87].

Inflammation

Comments: Rabbits have well defined mucosa associated lymphoid tissue in the gall bladder and this should not be confused with inflammatory changes.

Parasite

Comments: Parasites are rarely a problem in well-managed barriered facilities. Protozoal parasites cause the most common and significant disease. *Eimeria stiedai (stiedae)* primarily damages the biliary system. After oral uptake of sporulated oocysts, the sporozoites penetrate the intestinal wall, reach the liver via blood vessels, and enter the epithelial cells of the bile ducts. The prepatent period is 15–18 days. Severe infections may produce abscessation, and bile duct swelling macroscopically, occasionally with hepatomegaly. Microscopically, multifocal granulomatous lesions surround bile ducts and often there is marked papillary ductule epithelial hyperplasia with intraluminal schizonts and zygotes[81]. Cured hepatic coccidiosis may be seen as areas of peribiliary fibrosis.

Section 8: Skin

Introduction

Rabbit skin is commonly used for *in vivo* and *in vitro* investigation and testing of many chemical agents, ranging from cosmetics to carcinogens[88–90]. The pathology of both spontaneous and induced conditions of the skin are similar in rabbits and humans, hence their use in vaccine studies. Careful recording of the nature, intensity and duration of the inflammatory response of the skin adjacent to implanted or injected substances is important in the assessment of the local tolerability of agents intended for contact with human tissues. The chemical and physical properties of injected chemicals or vaccines and their adjuvants as well as size, shape and surface texture of implanted biomaterials may modify the histological features and temporal pattern of the inflammatory and reparative responses[91–94]. Such studies in rabbits are conducted with descriptors following the ISO-10993 guidelines.

A. Anatomy

Rabbits are born hairless. The adult rabbit body is well furred except for a few sites which are covered with sparse or no hair: around external nares; mammary gland nipples; scrotum; inguinal folds; pinnae[12, 95]. Foot pads are absent, though the palmar and planter surfaces are thickly furred[25].

Mature rabbits have a large, fat-filled skin fold on the ventral surface of the neck called the dewlap[24, 25]. The dewlap is particularly well developed in older females. The upper lip is divided by the philtrum, a distinct cleft, confluent with the external nares, and the lips have multiple prominent vibrissae.

Normal rabbit fur is composed of three hair types, produced by different follicles[88, 96] that are arranged in clusters. A typical cluster consists of a single large central primary follicle (producing 50–60 µm diameter, 3–4 cm long guard hairs) surrounded by 2–4 somewhat smaller lateral primary follicles (which produce 25–30 µm diameter, 3.0–3.5 cm long awn hairs) and 20–50 much smaller secondary follicles (producing 15 µm diameter, 2.5–3.0 cm long down hairs). Down hairs are the most abundant type (90–95%) and form the dense "inner coat", while the coarser guard and awn hairs constitute the protective "outer coat"[88, 96].

The large, elongated pinnae (external ears) can represent up to 12% of the rabbit body surface area[24]. The pinna possesses a large central artery as well as marginal (lateral) veins that are frequently used for blood collection and intravenous injections[24, 97]. The density of hair follicles in the pinna (80/cm^2) is much lower than in many other body sites[90]. Due to the large surface area, well-developed vascularization (arteriovenous anastomoses), and relatively sparse hair coat, the pinna dissipates body heat well, and plays a major role in overall thermoregulation in rabbits[98, 99]. The epidermis of both pinna and body skin is thin[90, 100]. Rabbit pinna epidermis is about 16–18 µm thick, compared to about 58–64 µm thickness of pig ear skin[90].

Abundant dermal sebaceous glands are associated with hair follicles in pinna and body skin, but sudoriferous (sweat) glands appear to be absent or vestigial in rabbit skin[95, 100]. The rabbit is classified as a functionally "non-sweating" species[98].

Several specialized glands in or around the skin of rabbits produce externally released odiferous secretions that are important in social and sexual behavior modulation[101–103]. These include the submandibular (chin or mental) skin gland; the inguinal gland complex (brown and white glands); and the anal (rectal, perirectal) glands. These glands have also been collectively or singularly referred to as "apocrine" glands[104], though the actual mode of secretion remains unclear[105, 106]. As a result of this overlapping and sometimes contradictory terminology, when reviewing the literature, it is important to determine which gland(s) are being discussed, especially in older references.

The submandibular (mental) skin gland (Figures 18, 19) is located in the subcutis of the ventral mandible[102, 104]. Submandibular gland secretions are thought to function primarily as territorial markers. Rabbits distribute the secretions by rubbing their chins against inanimate objects and even other rabbits; this "chinning" behavior is more common in males[101, 103]. The submandibular gland is unpaired but multilobed, with a large central and two smaller lateral lobes; each lobe has an excretory duct opening onto the external skin[102]. The epithelium is cuboidal to low columnar, with epithelium of intact, sexually mature males being taller and more vacuolated than that of mature females[102, 105].

The submandibular skin gland is sexually dimorphic, with development function, and morphology strongly dependent on sex hormones. Intact males have much larger and heavier submandibular glands, with larger acini lined by taller epithelial cells[102, 104, 107]. In males, the oily submandibular secretions may coat the skin of the chin. In females, the gland is much less developed and may be difficult to find and sample in young animals. Gonadectomy of males reduces the size, weight, and secretory epithelium height of submandibular glands, while testosterone administered to castrated males reverses these effects[102, 107]. In females, ovariectomy has opposite effects, resulting in increased gland size and weight, as well as increased acinar diameter and epithelial height[102, 107].

Rabbits also have specialized glands in the nictitating membrane (see Special Senses section).

The paired inguinal gland complexes are located on either side of the penis or clitoris, and thus are sometimes referred to as "preputial" and "clitoral" glands (Figure 20) (see also Male Reproductive System and Female Reproductive System sections). Each gland complex is composed of two adjacent but morphologically different lobulated glands: the dorsolateral "white" gland and the medioventral "brown" gland. The white gland has typical sebaceous histomorphology, (Figure 21) while the brown gland is composed of branching tubules lined by simple cuboidal to columnar epithelium[106] (Figure 22).

Although closely apposed, the white and brown glands are separate structures with separate ducts (lined by keratinized stratified squamous epithelium) which open into the hairless

skin fold at the base of the penis and clitoris.

The strong-smelling combined inguinal gland secretion is considered to function in individual identification[103]. Compared to the submandibular skin gland, the brown and white inguinal glands respond similarly to gonadectomy and sex hormone administration, but the extent of response (sensitivity) is overall less pronounced[104, 105].

The inguinal glands (preputial and clitoral) are further discussed in the Male Reproductive System and Female Reproductive System sections, respectively.

Anal (or perirectal) glands, the third type of odiferous gland in rabbits, produce secretions considered important in territorial marking[103] (Figure 23). These glands are located in the anorectal submucosa (see also Peri-rectal tissue subsection in Digestive section).

B. Common Diseases of the Rabbit Skin

Based on its direct interaction with the environment, the skin is subject to many spontaneous and housing-related diseases. Morphological lesions should be described using the nomenclature listed below, however spontaneous diseases of the skin should be diagnosed in combination with clinical data. In a pathology report, the disease terms listed below could be used as "syndromes" to summarize and interpret morphological lesions.

Acariasis: Mite infestations of the skin can occur in laboratory rabbits[24, 108–110]. Ear mite (*Psoroptes cuniculi)* infestations can result in prominent epidermal hyperkeratosis and dermal inflammation of the external ear canal and pinna, often exacerbated by secondary bacterial and fungal infections. Fur mites (*Cheyletiella parasitovorax,* other *Cheyletiella spp., Leporacarus gibbus;* and other species*),* and mange mites such as *Sarcoptes scabei* (sarcoptic mange; scabies), and *Notoedres cati* (notedric mange) can also cause skin lesions in various sites, including alopecia, epidermal hyperkeratosis and ulceration, and dermal inflammation[24, 108, 109].

Aural hematoma: Hematoma of the pinna can occur due to various causes[111].

Ulcerative pododermatitis in rabbits: Also known as "sore hocks", ulcerative pododermatitis most commonly affects the plantar aspects of the tarsus and metatarsus. Inflammation (often with bacterial infection) is considered a sequel to a primary inciting cause of pressure necrosis of the skin (due to obesity, wire-bottomed cages, general lack of sanitation etc.) and is seldom observed with current husbandry standards [24, 109, 110].

Moist dermatitis: So-called moist dermatitis of the facial and neck (dewlap) skin can result from trapped moisture in large dewlaps or underlying dental disease with hypersalivation, often complicated by secondary bacterial infection[109, 112, 113]. Similar inflammatory changes can occur in other locations such as the perineal skin.

Virus-related skin and subcutaneous proliferative lesions of rabbits (such as those induced by myxoma virus, Shope fibroma virus, and various papillomaviruses) are beyond the scope of this paper, and the reader is referred to recent reviews[114, 115].

C. Dermatotoxicology

Testing of topically applied chemicals for acute dermal irritation/corrosion is typically performed in rabbits. However, as outlined in the supplement to the Organisation for Economic Co-operation and Development (OECD) test guideline 404 on dermal irritation/corrosion testing, consideration of existing data, structure activity relationships, physiochemical properties of the test item and testing in validated *in vitro* and ex vivo systems are recommended, before an *in vivo* study is conducted (Table 22).

Hamartoma, Collagenous

Comments: Collagenous hamartomas in the skin of rabbits are benign, solitary, poorly demarcated dermal nodules composed of dense collagen with interspersed fibrocytes[116, 117].

Inflammation

Comments: Generalized "exfoliative dermatitis" or "sebaceous adenitis" characterized by sebaceous gland atrophy, perifollicular, dermal, and/or epidermal lymphocytic infiltrates, and hyperkeratosis has been reported in rabbits[65, 83, 110, 118–120]. An association with concurrent thymoma or thymic lymphoma was noted in several cases[110, 118, 120]. Rabbits have been noted to be more sensitive to petroleum jelly-induced dermal irritation than rodents and minipigs, while rabbits and rats are more sensitive than minipigs to a topical antibiotic applied to abraded skin[121]. Conversely, rabbits exhibited decreased subcutaneous inflammation and biodegradation of polyurethane implants compared to rodents[122].

Xanthomatous Alteration

Comments: Xanthoma or xanthomatous alteration refers to non-neoplastic accumulations of lipid-laden macrophages ("foam cells") in the dermis. Due to their altered metabolism and genetic background, Watanabe heritable hyperlipidemic (WHHL) rabbits are prone to such xanthomatous lesions. In WHHL rabbits, xanthomatous alteration (xanthomas) most commonly occur in plantar tendons of the distal limbs and digits with occasional extension into adjacent subcutis or dermis[123–125]. Dermal xanthomatous alteration has also been reported in the hereditary high triglyceridemia (TGH) rabbit, an inbred rabbit strain which like the WHHL rabbit, has high blood cholesterol and lipids and a propensity to develop atherosclerosis[126]. It can be induced also by feeding high-fat diets to NZW rabbits[28].

Hyperplasia, Keratinocyte

Other terms: actinic keratosis

Pathogenesis/cell of origin: keratinocyte

Table 22. Microscopic Findings of the Skin: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Non-proliferative				
Abscess		X		
Accumulation, macrophage		X		
Adnexal dysplasia		X		
Amyloid		X		
Apoptosis ǂ		X		
Atrophy, epidermis/dermis/adnexa		X		
Congestion		X		
Cyst, squamous		X		
Degeneration		X		
Dilatation		X		
Edema, epidermis, intracellular/intercellular	X			
Elastosis		X		
Erosion/ulcer		X		
Fibrosis	X			
Hamartoma, collagenous *		X		
Hemorrhage		X		
Hyperkeratosis, epidermis/adnexa		X		
Infiltrate, inflammatory cell, [insert appropriate cell type]		X		
Inflammation, (+ locator) *		X		
Mineralization	X			
Necrosis, (+ locator)	X			
Pigment	X			
Pustule		X		
Single cell necrosis ǂ		X		
Thrombus	X			
Vesicle		X		
Xanthomatous alteration *#		X		
Proliferative Non-neoplastic				
Hyperplasia, epidermis/adnexa/melanocyte		X		
Hyperplasia, keratinocyte *		X		
Proliferative Neoplastic				
Adenoma, sebaceous cell			X	
Fibroma			X	
Keratoacanthoma			X	
Melanoma, benign			X	
Papilloma, squamous cell			X	
Tumor, basal cell, benign			X	
Tumor, hair follicle, benign			X	
Tumor, mixed, benign			X	
Adenocarcinoma			X	
Carcinoma, basal cell			X	
Carcinoma, eccrine gland			X	
Carcinoma, sebaceous cell			X	
Carcinoma, squamous cell			X	
Carcinosarcoma			X	
Histiocytic sarcoma			X	
Lymphoma, cutaneous			X	
Melanoma, malignant			X	

* Terminology with diagnostic criteria or comments described in the text. # Inducible lesion. ǂ Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

Comments: Actinic keratosis has been reported in the pinnae of a pet rabbit[127]. The affected animal, a Flemish male, spent considerable time exposed to sunlight. Clinically, there was pinnal erythema and scaling, with histopathologic findings considered consistent with early actinic keratosis: epidermal hyperkeratosis, epidermal hyperplasia with dysplasia, and dermal fibrosis. Actinic (solar) keratosis is an intraepidermal manifestation of abnormal keratinocyte proliferation and can progress to squamous cell carcinoma. Ultraviolet (UV) light is the causative agent. Although exposure to sunlight is not a factor in laboratory studies, actinic keratosis and drug-induced pruritis should be considered as a differential diagnosis in laboratory rabbits showing scaling or pruritis of the ear pinna in studies with test items that cause exacerbated photosensitivity.

Section 9: Mammary Gland

A. Anatomy of the Mammary Gland

Similar to humans, each mammary gland in the rabbit has several ducts (milk canals) which open independently in the nipple (rather than a single duct as in some other species such as mice)[95, 128, 129]. This important anatomical difference observed when comparing rabbits and humans to rodents occurs because when division of the mammary bud starts at rabbit ED26, each sprout which arises forms a primary milk canal[129] (Propper *et al.*, 2013). Rabbit mammary glands are paired, with usually four (sometimes five) pairs of mammae, each with a nipple, distributed along the ventral thorax and abdomen[25]. The presence of nipples in male rabbits has been documented in detail previously[95]. Newborns do not require colostrum as all immunity is acquired through the placenta. Rabbits have a unique pattern of nursing: it occurs only once a day, with circadian periodicity, throughout lactation[130]. Explants of pseudopregnant rabbit mammary glands in organ culture are used to investigate hormonal changes during pregnancy. Proliferative lesions in laboratory rabbits may arise from genotoxic test items, infectious agents and changes in hormonal homeostasis as part of the aging process or pseudopregnancy (Table 23).

Inflammation

Comments: Mammary gland inflammation (mastitis) is rarely encountered in modern laboratory facilities due to biosecurity and animal husbandry procedures operations[131, 132]. More commonly, histological changes are limited to infiltrates of foci of lymphocytes, neutrophils, macrophages, or plasma cells, alone or in combination.

Hyperplasia

Comments: In cases of pseudopregnancy, the entire mammary gland may be diffusely enlarged and hyperplastic and resemble feline fibroadenomatosis (M. Rinke, personal communication). Descriptions of mammary gland "cystic dilatation" in one cohort of untreated rabbits appeared consistent with mammary gland hyperplasia (with increased secretory activity)[133]. Findings consistent with mammary gland hyperplasia (described as mammary "cystic dilatation" with "epithelial infolding") were noted in female NZW rabbits with elevated serum prolactin levels and pituitary adenomas[134]. Mammary gland hyperplasia and dysplasia were noted in another female NZW rabbit with concurrent mammary gland adenocarcinoma and a prolactin-secreting pituitary adenoma[135]. These results suggested that mammary gland hyperplasia may have been related to elevated prolactin levels.

Experimental reversible mammary gland hyperplasia in rabbits has been induced by systemic administration of cyclosporine A. In one study, intravenous administration of cyclosporine A to nulliparous NZW female rabbits resulted in diffuse mammary hyperplasia characterized by increased numbers of alveoli, increased alveolar branching, increased secretion in alveolar lumens, and decreased fibrous stroma compared to control glands[136]. In another study, intravenous administration of cyclosporine A to male and female NZW rabbits resulted in diffuse mammary gland hyperplasia characterized by abundant ectatic, well-differentiated glands, but with increased fibrous stroma, and the change was termed "fibroadenomatous hyperplasia"[137]. In both studies, the mammary gland hyperplasia regressed after cessation of cyclosporine A administration.

Elevated plasma prolactin levels attributed to cyclosporine A were noted in one of these studies[136]. Thus, a possible role of prolactin in development of mammary gland hyperplasia was postulated[136, 137].

Gynecomastia has been found in a male rabbit that concurrently had a testicular Leydig cell tumor[138].

Table 23. Microscopic Findings of the Mammary Gland: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Non-proliferative				
Abscess		X		
Amyloid		X		
Angiectasis		X		
Apoptosis ǂ		X		
Atrophy		X		
Basophilia		X		
Congestion		X		
Corpora amylacea			X	
Cyst		X		
Degeneration		X		
Dilatation		X		
Edema		X		
Fibrosis	X			
Hemorrhage	X			
Hypertrophy, alveolar and/or ductal epithelial cell	X			
Infarct		X		
Infiltrate, inflammatory cell [insert appropriate cell type]	X			
Inflammation *		X		
Metaplasia			X	
Mineralization	X			
Necrosis		X		
Pigment		X		
Single-cell necrosis ǂ		X		
Thrombus		X		
Proliferative Non-Neoplastic				
Hyperplasia, lobuloalveolar *	X			
Proliferative Neoplastic				
Adenoma			X	
Adenomyoepithelioma			X	
Fibroadenoma			X	
Tumor, mixed, benign			X	
Adenocarcinoma			X	
Adenocarcinoma arising in fibroadenoma			X	
Carcinoma, adenosquamous			X	
Carcinosarcoma			X	
Sarcoma arising in fibroadenoma			X	

* Terminology with diagnostic criteria or comments described in the text. ǂ Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

Section 10: Nervous System

The neuroanatomy of the rabbit is covered in detail elsewhere[139]. The large brain size of the rabbit compared to rodents necessitates a different approach to trimming and embedding the brain. Pardo *et al.* have published a recommended trimming schemes for routine and neurotoxicity studies[140]. Although mature when on study, nervous system findings are not common in laboratory rabbits due to their young age.

This lexicon has been organized in tiers based on cell type (e.g., neuron, glia), and sometimes by cellular target (e.g., cell body, axon, myelin). A final set of terms has been included to demonstrate common artifacts which have been misidentified as neurodegenerative or neurotoxic lesions by inexperienced diagnosticians. Neural neoplasms are an important but very infrequent finding in non-rodents including rabbits evaluated on standard toxicity studies, due to the age group concerned. Conventional toxicity studies do not permit repeated assessment for lesion progression over time, so an appreciation of the true future biological behavior of neural neoplasms is unclear. Thus, in this lexicon we predict the impact on host function as "benign" or "malignant" based only on morphologic characteristics such as cellular differentiation, invasiveness, and proliferative rate. Certain lesions that have well-differentiated features but are biologically aggressive over time (e.g. glial neoplasms) have been termed "malignant" and "low grade" rather than "benign" to better address the usual clinical outcome of this category of neural tumors. Innovations in non-invasive imaging should help resolve questions regarding the biological behavior of these lesions in the future.

The most common non-proliferative anomalies in the CNS include damaged or dying cells (especially neurons, their axonal processes, and the myelin sheaths that insulate the axons) and the various reparative changes designed to minimize (in the CNS) or reverse (in the PNS) the damage. At the cellular level, the most important processes will involve neurons, various glial lineages, and blood vessels (Table 24).

Hydrocephalus

Comments: Cases of hydrocephalus in rabbits have been presumed to be related to a single autosomal recessive gene (hy/hy); however, occurrence with other abnormalities suggests that inheritance may be more complicated. In some cases, the condition appears to be inherited along with various ocular anomalies as an autosomal gene with incomplete dominance. Hydrocephalus may also occur in rabbits as a congenital condition related to hypovitaminosis A in pregnant females[141]. Hydrocephalus is also seen secondary to craniosynostosis. A strain of NZW rabbits with congenital, nonsyndromic coronal suture synostosis has been developed previously Mooney *et al.*, 1996, which mimics the pathology of human craniosynostosis[142].

Parasite (Figure 24)

Other terms: Encephalitis;

Comments: *Encephalitozoon cuniculi* is a common cause of neurological disease in pet rabbits, but nowadays is a rare occurrence in barriered colonies. *Encephalitozoon cuniculi* is a microsporidian pathogen of rabbits and other mammals that usually produces granulomatous encephalitis and interstitial nephritis. Severe systemic disease is rare except in immunosuppressed animals. Primary diagnosis is based on the presence of granulomatous encephalitis together with chronic interstitial nephritis and occasionally hepatitis but can be confirmed by serology or a combination of special staining methods, immunohistochemistry (IHC), and polymerase chain reaction (PCR). Real-time PCR is the most sensitive method for the confirmation of *E. cuniculi* infection. Differential diagnosis for *E. cuniculi* is *Toxoplasma gondii* infection. *E. cuniculi* infection is characterized by granuloma(s) composed of macrophages with large cytoplasm (epithelioid cells), which may be surrounded by inflammatory cells such as lymphocytes, plasma cells, and eosinophils, sometimes accompanied by fibrosis. The macrophages may form multinucleated giant cells. Focal lesions are largely restricted to the gray matter and primarily spare the white matter, with inner layers of the cerebral cortex more commonly affected than the middle or the outer layers. Lymphoplasmacytic meningoencephalitis, characterized by perivascular cuffs and leptomeningeal infiltrates consisting primarily of lymphocytes and plasma cells, is also usually present in affected animals. Spores are located in parasitophorous vacuoles in the parenchyma of the brain, either without inflammation or close to focal inflammatory lesions. Lesions can be categorized into 6 histopathological subtypes depending on the characteristics of the inflammatory response[85]. Rabbits affected with encephalitozoonosis most frequently exhibit multiple neurologic signs (head tilt, ataxia, circling, nystagmus, rotational movements around the body length axis, seizures, paresis, head tremors, swaying or nodding at rest, and behavior changes), kidney dysfunction (azotemia), and phacoclastic uveitis. Brain lesions may lead to altered cholinesterase values.

Vacuolation, Choroid Plexus (Figure 25)

Comments: Spontaneously occurring choroid plexus vacuolation in rabbits takes two forms, discrete microvacuoles within the epithelium of the choroid plexus or large macrovacuoles (adipocytes) within the stroma. Neither form is associated with clinical signs, both are considered incidental findings at histopathology and should not be recorded as a finding in preclinical studies unless the adipocytes are altered spontaneously (i.e. lipoma) or after xenobiotic treatment[143]. Vacuolated macrophages can be seen in the choroid plexus of animals dosed with PEGylated compounds. These are discrete macrovacuoles and are clearly within either macrophages and/or endothelial cells. Since removal of foreign bodies or materials from circulation is a normal function of macrophages, the resulting vacuolation is considered a normal physiological response in phagocytic cells. The inner core of the choroid plexus, containing the vacuolated

Table 24. Microscopic Findings of the Brain: Rabbit

Finding	Common	Uncommon	Not Recorded but Potentially Relevant	Not Applicable
Congenital				
Ectopic tissue, neuron		X		
Hydrocephalus *		X		
Non-proliferative				
Abscess		X		
Accumulation, laminar, Schwann cell		X		
Accumulation, matrix		X		
Amyloid		X		
Astrocyte swelling/vacuolation		X		
Astrocytosis		X		
Atrophy, axons		X		
Autophagy, neuron, ganglion		X		
Cellularity, decreased, neuron		X		
Cholesterol clefts		X		
Chromatolysis		X		
Cyst, squamous		X		
Decreased cellularity, neuron			X	
Degeneration, axon		X		
Degeneration, nerve fiber		X		
Demyelination		X		
Dystrophy, axon		X		
Edema, intramyelinic		X		
Extramedullary hematopoiesis, choroid plexus			X	
Gliosis, not otherwise specified (NOS)		X		
Hemorrhage		X		
Heterotopia, neuronal		X		
Infarct		X		
Infiltrate, inflammatory cell [insert appropriate cell type]		X		
Inflammation		X		
Microgliosis		X		
Mineralization		X		
Necrosis, neuron		X		
Necrosis/inflammation, media or wall, artery		X		
Parasite *		X		
Pigment, lipofuscin		X		
Satellitosis		X		
Single cell necrosis ǂ		X		
Syringomelia/hydromyelia		X		
Thrombus		X		
Tissue, ectopic, neuron		X		
Tissue, ectopic		X		
Type II astrocytes		X		
Vacuolation		X		
Vacuolation, neuron		X		
Vacuolation, white matter		X		
Vacuolation, choroid plexus *	X			
Proliferative Non-neoplastic				
Hamartoma, lipomatous			X	
Hyperplasia, glial cell, not otherwise specified (NOS)			X	
Proliferative Neoplastic				
Astrocytoma, malignant			X	
Carcinoma, choroid plexus			X	
Ependymoma, benign			X	
Ependymoma, malignant			X	
Glioma, mixed, malignant			X	
Glioma, not otherwise specified (NOS)			X	
Medulloblastoma			X	
Neuromyoblastoma, malignant			X	
Oligodendroglioma, malignant			X	
Papilloma, choroid plexus			X	

* Terminology with diagnostic criteria or comments described in the text. ǂ Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

Table 25. Microscopic Findings of the Spinal Cord: Rabbit

Finding	Common	Uncommon	Not Recorded but Potentially Relevant	Not Applicable
Congenital				
Ectopic tissue, neuron		X		
Hydromyelia		X		
Syringomyelia		X		
Syringomyelia/hydromyelia		X		
Non-proliferative				
Abscess		X		
Accumulation, matrix		X		
Accumulation, laminar, Schwann cell		X		
Astrocyte swelling		X		
Astrocyte vacuolation		X		
Astrocytosis		X		
Atrophy, axon		X		
Autophagy, neuron, dorsal root ganglion		X		
Cellularity decreased, neuron		X		
Cholesterol clefts		X		
Chromatolysis		X		
Cyst, squamous		X		
Degeneration, axon		X		
Degeneration, nerve fiber		X		
Demyelination *		X		
Dystrophy, axon		X		
Ectopic tissue			X	
Gliosis, not otherwise specified (NOS)		X		
Hemorrhage		X		
Heterotopia, neuronal			X	
Infarct		X		
Infiltrate, inflammatory cell [insert appropriate cell type]		X		
Inflammation		X		
Intramyelinic edema		X		
Microgliosis		X		
Mineralization		X		
Necrosis, neuron		X		
Necrosis/inflammation, media or wall, artery		X		
Neuronophagia		X		
Pigment, lipofuscin		X		
Radiculoneuropathy				X
Satellitosis		X		
Single cell necrosis ǂ		X		
Swelling, astrocyte		X		
Thrombus		X		
Type II astrocytes		X		
Vacuolation, neuron		X		
Proliferative Non-Neoplastic				
Hyperplasia, glial cell, not otherwise specified (NOS)			X	
Proliferative Neoplastic				
Astrocytoma, malignant			X	
Glioma, mixed, malignant			X	
Glioma, not otherwise specified (NOS)			X	
Oligodendroglioma, malignant			X	

* Terminology with diagnostic criteria or comments described in the text. ǂ Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

macrophages, is outside the CNS. There are two theories as to how the vacuolated macrophages arise: (i) hydrophilic PEG filters through the vasculature into the choroid plexus core and is kept there by the choroidal epithelial tight junctions and subsequently phagocytosed by resident macrophages, or (ii) circulating macrophages containing PEG filter out in this high blood flow area[144] (Table 25).

Demyelination, Nerve Fiber, Spinal Cord

Comments: New-born rabbits show an area in the dorsal part of the lateral funiculus of the first cervical segment of the spinal cord, from which myelinated nerves are few/absent[145]. Localised/focal unmyelinated axons are occasionally seen in the sections of lateral funiculus of the lumbar spinal cord of young adult rabbits. This is a normal anatomical difference in rabbits and there are no clinical signs (Table 26).

Pigment

Other terms: Melanosis

Comments: Spontaneously occurring melanosis of the meninges (especially those of the brain) may be seen in pigmented rabbit strains such as the NZW x New Zealand Red F1 Cross and Dutch Belted. It may be seen grossly at necropsy (Table 27).

Common Artifacts

Certain incidental changes are commonly misidentified as neuropathologic lesions by inexperienced researchers. The changes listed here are the most common of such findings – dark neurons and white matter vacuolation. Identified artifacts should be not reported in the pathology dataset. However, systematic artifacts where one dose group only is involved may be recognized and noted as a comment to the organ/tissue at the discretion of the study pathologist (Table 28).

Table 26. Microscopic Findings of the Meninges: Rabbit

Finding	Common	Uncommon	Not Recorded but Potentially Relevant	Not Applicable
Non-proliferative				
Abscess		X		
Aggregate, granular cell		X		
Angiectasis		X		
Cholesterol clefts		X		
Cyst, squamous		X		
Fibrosis		X		
Hemorrhage		X		
Infiltrate, inflammatory cell [insert appropriate cell type]		X		
Inflammation		X		
Mineralization		X		
Necrosis		X		
Necrosis/inflammation, media or wall, artery		X		
Pigment *		X		
Pigment, lipofuscin		X		
Single cell necrosis ǂ		X		
Thrombus		X		
Proliferative Non-neoplastic				
Meningioangiomatosis			X	
Proliferative Neoplastic				
Meningioma, benign			X	
Meningioma, malignant			X	
Tumor, granular cell, benign			X	
Tumor, granular cell, malignant			X	

* Terminology with diagnostic criteria or comments described in the text. ǂ Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

Table 27. Microscopic Findings of the Peripheral Nerves: Rabbit

Finding	Common	Uncommon	Not Recorded but Potentially Relevant	Not Applicable
Non-proliferative				
Accumulation, laminar, Schwann cell		X		
Accumulation, matrix			X	
Atrophy, axon		X		
Autophagy, neuron, dorsal root ganglion		X		
Cellularity, decreased, neuron		X		
Chromatolysis		X		
Cholesterol clefts		X		
Cyst, squamous		X		
Degeneration, nerve fiber		X		
Degeneration, axon		X		
Demyelination		X		
Dystrophy, axon		X		
Ectopic tissue		X		
Hemorrhage		X		
Infiltrate, inflammatory cell [insert appropriate cell type]		X		
Inflammation		X		
Intramyelinic edema		X		
Mineralization		X		
Necrosis/inflammation, media or wall, artery		X		
Pigment, lipofuscin		X		
Radiculoneuropathy				X
Renaut Body		X		
Single cell necrosis [ǂ]		X		
Proliferative Non-Neoplastic				
Hyperplasia, (+ cell type)			X	
Proliferative Neoplastic				
Schwannoma			X	

[ǂ] Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

Table 28. Artifactual Microscopic Findings of the Nervous System: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Artifact, dark neuron	X			
Bubbles, myelin		X		
Vacuolation, white matter	X			

Section 11: Female Reproductive System

Introduction

Standard INHAND nomenclature for non-proliferative and proliferative female reproductive system findings in rats and mice has previously been published[146] and should be used for the rabbit as appropriate. Generally, very few spontaneous or treatment induced microscopic changes are reported in the female reproductive tract of rabbits. Female rabbits become sexually mature at 5 months of age, and so rabbits on routine tox studies are fully mature.

A. Anatomy and Physiology of the Ovary

Rabbits are non-seasonally polyestrous. Female rabbits are induced ovulators and so decreased/absent corpora lutea and atretic follicles are normal. Ovulation can be induced in studies where vaginal swabs/dosing is a frequent event, and corpora hemorrhagica may be seen. Ovulation is triggered about 10 hours following copulation. Some animals are triggered into pseudopregnancy lasting 15–17 days, with or without galactopoiesis and endometrial hyperplasia.

Ovarian interstitial tissue is well developed in rabbits and was termed an "interstitial gland" in 1902[147]. This "gland" secretes progestogens. At 3 months of age, follicular atresia begins and the theca interna cells differentiate into the primary and then secondary interstitial gland[148]. The primary interstitial gland is composed of small polygonal cells with hyperchromatic nuclei and scant basophilic cytoplasm. It is highly vascularized. The ovary interstitium is almost completely composed of the secondary "gland" by 6 months old. This is composed of large polygonal cells with round vesicular nuclei and abundant eosinophilic cytoplasm containing numerous lipid droplets. There is high 3-β-hydroxysteroid dehydrogenase activity within the interstitial cells of secondary interstitial gland, which increases in activity with increase in size of the gland.

The ovaries of normal rabbits often have surface epithelial structures resembling ovarian papillomas[149]. The ovarian mesothelium (surface epithelium) may form short, broad papilla or papillae with slender villous processes. They have an inner core with few fibroblasts, small blood vessels, and loose or hyalinized connective tissues and are lined by pseudostratified or multi-layered epithelium. These structures should not be mistaken for neoplasms and occur only on the ovary and not on the surface of other abdominal organs or structures (Table 29, 30).

B. Anatomy of the Uterus and Cervix

Rabbits have a true bicornuate uterus, with no uterine corpus present. There are two separate cervices. Each uterine horn has a separate cervical canal and the tract is classified as uterus duplex, vagina simplex. The broad ligaments typically contain a large amount of adipose tissue. The light, transmission and scanning microscopic anatomy of the rabbit vagina, cervix and uterus have been comprehensively described by[150, 151]. Placentation is discoid labyrinthine hemodischorial with countercurrent fetomaternal blood flow; gestation lasts 25–30 days. Females give birth to a litter of 3–10. Neonates are weaned at about 6–8 weeks (Table 31).

Aneurysm

Comments: Endometrial venous aneurysms have been reported in three adult NZW rabbits with a history of intermittent severe urogenital bleeding (hematuria). The endometrium of all three rabbits had multiple blood-filled vesicles which projected into the uterine lumen, which were considered to be congenital or acquired defects in the vessel walls, as has occurred in humans[152].

Angiectasis

Comments: A focus of multiple, dilated thin walled blood vessels is occasionally seen as a congenital defect. They may occasionally rupture and bleed into the uterine lumen.

Decidual Reaction

Comments: Decidual reactions have been reported in non-pregnant rabbits given estrogens and progesterone as an early lesion in the development of deciduosarcoma[153, 154].

Hyperplasia

Comments: Spontaneous endometrial hyperplasia (polypoid and/or cystic) can be seen at 1 year of age[155], although it is more common in rabbits 4–5 years old.

Deciduosarcoma

Pathogenesis/cell of origin: Uterine stromal cells and uterine metrial gland cells.

Differential Diagnosis: Sarcoma, endometrial stromal; Mesenchymal proliferative lesion

Diagnostic Features: Rare malignant tumor of hypertrophied stromal cells with abundant PAS positive rarefied cytoplasm intermingled with numerous globular lymphocytes. Hypertrophied blood vessels characterize the lesion.

Comments: Deciduosarcomas are neoplasms unique to rabbits, and metastasis may occur. They are hormone-dependent and therefore may not actually be true neoplasms. Deciduosarcomas have been reported as induced tumors in rabbits on toxicity studies involving estrogen and progestin administration[153, 154, 156], and so because of this, the rabbit is a poor model for evaluating the effects of contraceptive steroids. In addition, a spontaneous deciduosarcoma has also been reported in a 6-year-old Dutch Belted rabbit[157]. Deciduosarcomas may appear after as little as 30 days of treatment of non-pregnant rabbits with estrogens and progesterone[154]. Exogenous estrogens are necessary for decidualization of the endometrium and to produce deciduosarcoma; exogenous progesterone promotes the process[156]. Withdrawal of the estrogen/progesterone treatment results in atrophy of decidual cells and tumors and disappearance

Table 29. Microscopic Findings of the Ovary: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Congenital				
Hypoplasia		X		
Non-proliferative				
Abscess		X		
Age related atrophy	X			
Amyloid		X		
Angiectasis		X		
Apoptosis [ǂ]		X		
Atrophy	X			
Atrophy, corpora lutea		X		
Corpora lutea, increased number		X		
Cyst, bursal/epithelial/follicular/luteal/paraovarian/rete ovarii, not otherwise specified (NOS)	X			
Decreased number/absent follicles/corpora lutea		X		
Degeneration, oocyte/corpora lutea		X		
Edema		X		
Follicle, luteinized/polyovular		X		
Fibrosis		X		
Granuloma		X		
Hemorrhage		X		
Hypertrophy, corpora lutea/ interstitial cell		X		
Immature		X		
Increased number, atretic follicles/corpora lutea		X		
Infiltrate, inflammatory cell [insert appropriate cell type]		X		
Inflammation		X		
Mineralization		X		
Necrosis		X		
Ovotestis			X	
Pigment		X		
Single cell necrosis [ǂ]		X		
Tissue, ectopic		X		
Vacuolation, corpora lutea/granulosa cell/theca cell/interstitial cell		X		
Proliferative Non-neoplastic				
Hyperplasia, epithelium/granular cell		X		
Adenosis		X		
Proliferative Neoplastic				
Adenoma			X	
Cystadenoma			X	
Leiomyoma		X		
Luteoma, benign			X	
Schwannoma, benign			X	
Teratoma, benign			X	
Thecoma, benign			X	
Tumor, Sertoli cell/granulosa cell, benign			X	
Tumor, sex cord stromal, mixed, benign			X	
Carcinoma, embryonal/tubulostromal/yolk sac			X	
Choriocarcinoma			X	
Cystadenocarcinoma			X	
Dysgerminoma			X	
Leiomyosarcoma			X	
Schwannoma, malignant			X	
Teratoma, malignant			X	
Thecoma, malignant			X	
Tumor, Sertoli cell/granulosa cell, malignant			X	
Tumor, sex cord stromal, mixed, malignant			X	

[ǂ] Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

Table 30. Microscopic Findings of the Oviduct: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Congenital				
Hypoplasia		X		
Non-proliferative				
Abscess		X		
Apoptosis ǂ				
Atrophy		X		
Cyst	X			
Dilatation		X		
Edema		X		
Fibrosis		X		
Granuloma		X		
Hemorrhage		X		
Immature		X		
Infiltrate, inflammatory cell [insert appropriate cell type]		X		
Inflammation, oviduct		X		
Mineralization		X		
Necrosis		X		
Salpingitis isthmica nodosa			X	
Single cell necrosis ǂ		X		
Proliferative Non-neoplastic				
Hyperplasia, epithelium		X		
Proliferative Neoplastic				
Leiomyoma			X	
Schwannoma, benign			X	
Schwannoma, malignant			X	

ǂ Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

of decidual tumors[154]. Transplantation of deciduosarcomas into nude mice as well as primary cell culture (in the absence of hormones) results in failure of cells to grow. Deciduosarcomas will invade the uterine walls and the uterine lymphatics and will metastasize to the lungs. Deciduosarcomas occurring in the spleen and other abdominal viscera may not be metastases, but instead are primary tumors, because treatment of castrated male rabbits with estrogen and progesterone will result in deciduosarcoma in the spleen at a high incidence. Induced deciduosarcomas are composed of large anaplastic decidual cells with large hyperchromatic nuclei. Multiple nuclei as well as bizarre giant nuclei may be observed. Most cells are vacuolated, containing multiple small or a few large vacuoles. Necrosis in the tumor is common. The spontaneously occurring deciduosarcoma is described as an invasive mass originating in the mesometrium of the endometrial stroma and invading the myometrium and mesometrium to form a large nodular mass. Cells are arranged in sheets and streaming bundles dissecting between the smooth muscle cells or arranged concentrically around large dilated blood vessels, with multiple foci of necrosis. Cells are anaplastic and consisted of two intermingling populations – spindloid cells with scant eosinophilic cytoplasm and cigar shaped nuclei with a single nucleolus, or epithelioid cells with abundant vacuolated eosinophilic cytoplasm, large oval eccentric nuclei with 1–2 nucleoli. Binucleate and multinucleate cells are common, as well as frequent giant cells, anisocytosis and nuclear pleomorphism. There are multiple mitotic figures per high power field.

Special Techniques: The neoplastic cells show positive cytoplasmic staining for vimentin, and nuclear staining for estrogen and progesterone receptors, and are negative for desmin, αsmooth muscle actin (αSMA), pancytokeratin, and CD10.

C. Anatomy of the Vagina

The vulva lies between the two inguinal sinuses; the vagina joins the urethra at the vestibule. The vestibule is surrounded by erectile tissue. The crura of the clitoris are present caudal to this erectile tissue, with the body and glans extending caudally to the vulva. The paired clitoral (inguinal) glands are located in the subcutis on either side of the base of the clitoris[106] (see Integument section) (Table 32, 33).

Table 31. Microscopic Findings of the Uterus and Cervix: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Congenital				
Hypoplasia			X	
Mesonephric duct remnants			X	
Non-proliferative				
Abscess		X		
Adenomyosis		X		
Aggregate, granular cell		X		
Amyloid		X		
Aneurysm *		X		
Angiectasis *		X		
Apoptosis ǂ		X		
Atrophy		X		
Basophilia			X	
Cyst, NOS	X			
Decidual reaction *		X		
Decidualization, focal			X	
Degeneration, epithelial		X		
Dilatation, luminal/glandular/cystic		X		
Edema		X		
Fibrosis		X		
Granuloma		X		
Hemorrhage		X		
Hypertrophy, epithelium/myometrium		X		
Immature		X		
Infarct		X		
Infiltrate, inflammatory cell [insert appropriate cell type]		X		
Inflammation		X		
Metaplasia, squamous cell		X		
Mineralization		X		
Necrosis		X		
Pigment		X		
Prolapse		X		
Pyometra		X		
Single cell necrosis ǂ		X		
Tissue, ectopic		X		
Vacuolation, epithelium		X		
Proliferative Non-neoplastic				
Hyperplasia, epithelium/granular cell *	X			
Hyperplasia, segmental cystic			X	
Neoplastic Lesions				
Adenoma, endometrial			X	
Keratoacanthoma			X	
Leiomyoma			X	
Papilloma, squamous cell			X	
Polyp			X	
Schwannoma, benign			X	
Tumor, granular cell, benign			X	
Adenocarcinoma, endometrial			X	
Carcinoma, squamous cell			X	
Deciduosarcoma #*		X		
Leiomyosarcoma			X	
Histiocytic sarcoma			X	
Schwannoma, malignant			X	
Tumor, granular cell, malignant			X	
Tumor, mixed Müllerian, malignant			X	

* Terminology with diagnostic criteria or comments described in the text. # Inducible lesion. ǂ Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

Table 32. Microscopic Findings of the Vagina: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Congenital				
Cyst (mesonephric duct remnants)			X	
Non-proliferative				
Abscess		X		
Adenosis		X		
Aggregate, granular cell		X		
Angiectasis		X		
Apoptosis ǂ		X		
Atrophy, epithelial	X			
Cyst, NOS	X			
Degeneration, epithelial		X		
Dilatation		X		
Edema		X		
Erosion/ulcer		X		
Fibrosis		X		
Granuloma		X		
Hemorrhage		X		
Hypertrophy		X		
Immature		X		
Infiltrate, inflammatory cell [insert appropriate cell type]		X		
Inflammation		X		
Keratinization, increased		X		
Metaplasia, squamous cell		X		
Mineralization		X		
Mucification, increased		X		
Necrosis		X		
Pigment		X		
Prolapse		X		
Rudiment, prostatic		X		
Single cell necrosis ǂ		X		
Vacuolation, epithelial		X		
Vagina, imperforate		X		
Proliferative Non-neoplastic				
Adenosis				X
Hyperplasia, epithelium/granular cell		X		
Proliferative Neoplastic				
Keratoacanthoma			X	
Leiomyoma		X		
Papilloma, squamous cell			X	
Polyp, vaginal			X	
Schwannoma, benign			X	
Tumor, granular cell, benign			X	
Carcinoma, squamous cell/adenosquamous			X	
Leiomyosarcoma		X		
Sarcoma, endometrial stromal			X	
Schwannoma, malignant			X	
Tumor, granular cell, malignant		X		

ǂ Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

Table 33. Microscopic Findings of the Clitoral (Inguinal) gland: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Non-proliferative				
Abscess		X		
Angiectasis		X		
Apoptosis ǂ			X	
Atrophy		X		
Basophilia			X	
Degeneration		X		
Dilatation		X		
Edema		X		
Fibrosis		X		
Granuloma		X		
Hemorrhage		X		
Immature		X		
Infiltrate, inflammatory cell [insert appropriate cell type]		X		
Inflammation		X		
Necrosis		X		
Pigment		X		
Single cell necrosis ǂ		X		
Proliferative Non-neoplastic				
Hyperplasia, squamous cell		X		
Hyperplasia		X		
Proliferative Neoplastic				
Adenoma			X	
Papilloma, squamous cell			X	
Tumor, basal cell, benign			X	
Adenocarcinoma			X	
Carcinoma, squamous cell			X	
Tumor, basal cell, malignant			X	

ǂ Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

Section 12: Male Repoductive System

Male rabbits become sexually mature at 6–7 months of age and so rabbits used on routine safety assessment studies are usually fully mature (Table 34).

Atrophy, Tubule

Comments: Tubular atrophy is an infrequent finding in the testis. It may be unilateral or bilateral but is generally localized affecting only a few tubules and has not been reported as affecting the whole testis. There is an accompanying oligospermia and sloughing of ductal epithelium in the epididymides[158].

Adenoma, (+ cell type)

Comments: Interstitial (Leydig) cell[138, 159] and granular cell tumors[160] are reported in adult/young adult rabbits (Table 35).

Cell Debris, Lumen

Comments: There is often more cellular debris in the lumen of rabbit epididymis than in other species (Table 36).

A. Anatomy of the Prostate, Proprostate and Paraprostate

In the male rabbit, two structures (termed "prostate" and "proprostate" in this review) analogous to the prostate of other species are located dorsal to the seminal vesicle, urethra, and urinary bladder (Figures 27, 28). These structures are two closely apposed bilobed glands which are considered separate organs with independent excretory ducts (rather than parts of a single multilobed gland)[161, 162]. The more caudally situated gland is generally designated as the "prostate"[162–164], and is composed of acini lined by uniform, very tall columnar epithelium with abundant pale eosinophilic cytoplasm and basally located oval nuclei. The more cranially situated gland has been most commonly designated as the "proprostate"[162, 163]. Proprostate acini are lined by low columnar epithelium with bright eosinophilic cytoplasm and centrally located oval to round nuclei (Figures 29, 30).

Male rabbits also have "paraprostate" glands associated with the urethra[161–163]. The paraprostate is comprised of small, club-shaped structures that lie on the dorsolateral aspect of the prostate and are embryologically derived from the urethral wall (Figure 31). These glands are histologically identical to the prostate (Figure 32). These are not routinely specifically sampled in toxicology studies but can appear fortuitously in cross-sections of the accessory sex-organ/urethral region as small clusters of prostate-like acini embedded in the periurethral connective tissue (Figure 33) (Table 37).

Metaplasia, Squamous Cell

Comments: Spontaneous focal keratinized squamous metaplasia of the prostate and proprostate epithelium is an infrequent finding peculiar to the rabbit and is clinically silent. It is important to recognize this as a spontaneous lesion when evaluating test articles with androgenic or estrogenic actions. The finding is well described in Dutch Belted and NZW rabbits [164]. It is characterized by generally small foci of increased numbers of lamellated squamous-like cells with or without superficial keratinization and sloughing of cornified debris into the gland alveolar lumen; the squamous metaplastic foci are located within the gland epithelium or can also extend into the underlying lamina propria.

B. Anatomy of the Seminal Vesicles

In most species, the paired seminal vesicles (vesicular glands) are dorsal to the ampullae. For consistency with nomenclature in rats, mice, and other species, this review uses the term "seminal vesicle" for the analogous structure in the male rabbit. Rather than separate paired organs as in other species, the rabbit seminal vesicle appears grossly as a single sac-like structure located dorsal to the urinary bladder and ventral to the prostate complex[162, 163]. The cranial (blind) end of the seminal vesicle has a distinctive grossly visible "dimpled" indentation, which corresponds a microscopic appearance of two side-by-side glands with separate lumens in the proximal portion (appreciable in cross-sections). In the more distal main body of the seminal vesicle, the central separating wall disappears to create a conjoined single lumen[161, 165]. The histologic appearance of seminal vesicle epithelium (basophilic cuboidal to low columnar cells) is similar to that in other species (Table 38).

C. Anatomy of the Bulbourethral Gland

The bilobed bulbourethral gland is located dorsal to the urethra and caudal to the prostate/proprostate[161–163, 166]. The histologic appearance of the bulbourethral gland epithelium is similar to that in other species. The two lobes of bulbourethral gland are subdivided into lobules by thick connective tissue septa and embedded entirely in the bulboglandularis muscle, portions of which penetrate the interlobar and interlobular septa of the gland. Excretory ducts of the bulbourethral gland exit ventrally to empty into the urethra. Each lobule of the bulbourethral gland has a substantial lamina propria with large central lumina lined by a simple cuboidal to columnar to pseudostratified epithelium (Table 39).

D. Anatomy of the Preputial Gland

So-called "preputial" glands (inguinal gland complex) are paired structures in the subcutis on either side to the base of the penis and prepuce[106], which are further described in the Skin section. Descent of the testes into the scrotum occurs at 2.5 to 3 months of age. However, males can retract their testes into the abdominal cavity via the inguinal ring (Table 40).

E. Anatomy of the Vas Deferens (Ampulla)

As the deferent ducts converge, their walls become thickened to form ampullae, connected to each other by the genital

Table 34. Microscopic Findings of the Testis: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Congenital				
Agenesis		X		
Aplasia		X		
Cryptorchidism		X		
Hypoplasia		X		
Non-proliferative				
Abscess		X		
Amyloid		X		
Angiectasis		X		
Apoptosis ǂ		X		
Atrophy, Leydig cell/tubular *	X			
Degeneration/atrophy, tubule		X		
Degeneration, germ cell/tubular		X		
Depletion, germ cell		X		
Dilatation, rete testis/tubule		X		
Edema		X		
Exfoliation, germ cell		X		
Fibrosis		X		
Hemorrhage		X		
Infiltrate, inflammatory cell [insert appropriate cell type]		X		
Inflammation		X		
Mineralization		X		
Multinucleated giant cell	X			
Necrosis		X		
Necrosis/inflammation, vascular/perivascular		X		
Pigment		X		
Residual bodies, atypical		X		
Single cell necrosis ǂ		X		
Sperm granuloma		X		
Sperm stasis		X		
Spermatid retention		X		
Spermatocele		X		
Vacuolation, macrophage		X		
Vacuolation, Leydig cell/tubule	X			
Proliferative Non-neoplastic				
Hyperplasia, (+ cell type)		X		
Proliferative Neoplastic				
Adenoma, (+ cell type) *		X		
Gonadoblastoma			X	
Seminoma, benign			X	
Teratoma, benign			X	
Tumor, granulosa cell, benign				X
Tumor, granular cell, benign			X	
Tumor, mixed Sertoli-Leydig cell, benign			X	
Tumor, Sertoli cell, benign			X	
Carcinoma, embryonal/Leydig cell/rete testis/yolk sac			X	
Choriocarcinoma			X	
Mesothelioma, malignant			X	
Seminoma, malignant			X	
Teratoma, malignant			X	
Tumor, Sertoli cell, malignant			X	

* Terminology with diagnostic criteria or comments described in the text. ǂ Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

Table 35. Microscopic Findings of the Epididymis: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Congenital				
Aplasia		X		
Hypoplasia		X		
Non-proliferative				
Abscess		X		
Amyloid		X		
Apoptosis ǂ		X		
Atrophy, duct	X			
Cell debris, lumen *	X			
Cribriform change		X		
Degeneration, epithelium		X		
Dilatation, duct		X		
Edema		X		
Fibrosis		X		
Granuloma, sperm		X		
Hemorrhage		X		
Infiltrate, inflammatory cell [insert appropriate cell type]		X		
Inflammation		X		
Karyomegaly		X		
Metaplasia, squamous cell	X			
Mineralization		X		
Necrosis		X		
Necrosis/inflammation, vascular/perivascular		X		
Single cell necrosis ǂ		X		
Sperm stasis		X		
Sperm, decreased, lumen		X		
Spermatocele		X		
Vacuolation, epithelium	X			
Proliferative Non-neoplastic				
Adenosis			X	
Proliferative Neoplastic				
Adenoma, Leydig cell			X	
Histiocytic sarcoma			X	

* Terminology with diagnostic criteria or comments described in the text. ǂ Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

fold. In contrast to rats and mice, the rabbit distal vas deferens has a very wide ampullary region[162, 163]. The ampullae can be so large that they have been mistaken for "paired" seminal vesicles at gross necropsy. Microscopically, the ampulla exhibits abundant, large lamina propria glands, which result in a distinctive "honeycomb" appearance (Figure 33) (Table 41).

Table 36. Microscopic Findings of the Efferent ducts: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Congenital				
Aplasia		X		
Hypoplasia		X		
Non-proliferative				
Amyloid		X		
Angiectasis		X		
Apoptosis [ǂ]		X		
Atrophy, duct	X			
Cell debris, lumen	X			
Cribriform change		X		
Degeneration, epithelium		X		
Dilatation, duct		X		
Edema		X		
Fibrosis		X		
Granuloma, sperm		X		
Hemorrhage		X		
Infiltrate, inflammatory cell [insert appropriate cell type]		X		
Inflammation		X		
Metaplasia, squamous cell	X			
Mineralization		X		
Necrosis		X		
Necrosis/inflammation, vascular/perivascular		X		
Single cell necrosis [ǂ]		X		
Sperm stasis		X		
Spermatocele		X		
Vacuolation, epithelium	X			
Proliferative Non-neoplastic				
Hyperplasia			X	

[ǂ] Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

Table 37. Microscopic Findings of the Prostate, Proprostate and Paraprostate: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Congenital				
Aplasia		X		
Hypoplasia		X		
Non-proliferative				
Abscess		X		
Amyloid		X		
Angiectasis		X		
Apoptosis ǂ		X		
Atrophy		X		
Basophilia		X		
Corpora amylacea		X		
Degeneration		X		
Dilatation, acinar/acinus/vesicle		X		
Edema		X		
Fibrosis		X		
Hemorrhage		X		
Infiltrate, inflammatory cell [insert appropriate cell type]		X		
Inflammation		X		
Metaplasia, squamous cell *	X			
Mineralization		X		
Necrosis		X		
Necrosis/inflammation, vascular/perivascular		X		
Pigment		X		
Single cell necrosis ǂ		X		
Vacuolation, epithelial		X		
Proliferative Non-neoplastic				
Hyperplasia, atypical/diffuse/reactive		X		
Proliferative lesion, mesenchymal			X	
Proliferative Neoplastic				
Adenoma			X	
Papilloma, squamous cell			X	
Tumor, granular cell, benign			X	
Adenocarcinoma			X	
Carcinoma, squamous cell			X	
Carcinosarcoma			X	
Tumor, granular cell, malignant			X	
Tumor, neuroendocrine, malignant			X	

* Terminology with diagnostic criteria or comments described in the text. ǂ Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

Table 38. Microscopic Findings of the Seminal Vesicle: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Congenital				
Aplasia		X		
Hypoplasia		X		
Non-proliferative				
Abscess		X		
Amyloid		X		
Angiectasis		X		
Apoptosis ǂ		X		
Corpora amylacea		X		
Degeneration		X		
Dilatation, acinar/vesicle		X		
Edema		X		
Fibrosis		X		
Hemorrhage		X		
Infiltrate, inflammatory cell [insert appropriate cell type]		X		
Inflammation		X		
Metaplasia			X	
Mineralization		X		
Necrosis		X		
Necrosis/inflammation, vascular/perivascular		X		
Pigment		X		
Single cell necrosis ǂ		X		
Vacuolation, epithelial		X		
Proliferative Non-neoplastic				
Hyperplasia, atypical/diffuse/reactive			X	
Proliferative lesion, mesenchymal			X	
Proliferative Neoplastic				
Adenoma			X	
Tumor, epithelial-stromal, benign			X	
Tumor, granular cell, benign			X	
Adenocarcinoma			X	
Tumor, granular cell, malignant			X	

ǂ Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

Table 39. Microscopic Findings of the Bulbourethral gland: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Congenital				
Aplasia		X		
Hypoplasia		X		
Non-proliferative				
Abscess		X		
Amyloid		X		
Angiectasis		X		
Apoptosis ǂ		X		
Atrophy		X		
Corpora amylacea		X		
Degeneration		X		
Dilatation, acinar/vesicle		X		
Edema		X		
Fibrosis		X		
Hemorrhage		X		
Infiltrate, inflammatory cell [insert appropriate cell type]		X		
Inflammation		X		
Metaplasia		X		
Mineralization		X		
Necrosis		X		
Necrosis/inflammation, vascular/perivascular		X		
Single cell necrosis ǂ		X		
Vacuolation, epithelial		X		
Proliferative Non-neoplastic				
Hyperplasia, atypical/diffuse/reactive			X	
Proliferative Neoplastic				
Adenoma			X	
Adenocarcinoma			X	

ǂ Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

Table 40. Microscopic Findings of the Preputial (Inguinal) gland: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Congenital				
Aplasia			X	
Hypoplasia			X	
Non-proliferative				
Abscess		X		
Apoptosis [ǂ]		X		
Atrophy		X		
Basophilia		X		
Degeneration		X		
Dilatation		X		
Edema		X		
Hemorrhage		X		
Infiltrate, inflammatory cell [insert appropriate cell type]		X		
Inflammation		X		
Necrosis		X		
Single cell necrosis [ǂ]		X		
Vacuolation, epithelial		X		
Proliferative Non-neoplastic				
Hyperplasia, atypical/diffuse/reactive/squamous cell			X	
Proliferative Neoplastic				
Adenoma			X	
Papilloma, squamous cell			X	
Adenocarcinoma			X	
Carcinoma, squamous cell, malignant			X	
Tumor, basal cell, malignant			X	

[ǂ] Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

Table 41. Microscopic Findings of the Ampullary gland: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Congenital				
Aplasia			X	
Hypoplasia			X	
Non-proliferative				
Abscess		X		
Angiectasis		X		
Apoptosis [ǂ]		X		
Degeneration		X		
Edema		X		
Hemorrhage		X		
Infiltrate, inflammatory cell [insert appropriate cell type]		X		
Inflammation		X		
Necrosis		X		
Necrosis/inflammation, vascular/perivascular		X		
Single cell necrosis [ǂ]		X		
Vacuolation, epithelial		X		
Proliferative Non-neoplastic				
Hyperplasia, atypical/diffuse/reactive			X	
Proliferative Neoplastic				
Adenoma			X	
Adenocarcinoma			X	

[ǂ] Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

Section 13: Respiratory System

Adult and juvenile rabbits are occasionally used for inhalation and intranasal safety assessment studies to test local tolerability and potential toxicity for drugs, chemicals and particulates. Rabbits are prone to atherosclerotic lesions in a variety of organs including the lung. For detailed description, see the cardiovascular section. Rabbits can be used as animal models for tuberculosis research, and they can be infected via snout only inhalation of the bacteria[167]. In addition, rabbits are used as animal models for induced hypertension and aspiration pneumonia, and for sinus research, i.e. study of surgical packing material or surgical techniques. Modern laboratory animal management practices within rabbit facilities are such that spontaneous infectious processes should only be infrequently encountered; thus, the lesions related to infectious respiratory tract diseases are not described in detail in this document.

A. Anatomy of the Nasal Cavity

The nostrils of rabbits contain sensory pads at the entrance, making the nose very sensitive to touch[168]. The nostrils are still when the rabbit is relaxed but can twitch at up to 150 twitches per minute. Rabbits are obligate nose breathers because the epiglottis is positioned rostrally to the soft palate, resulting in direct continuity of the nasopharynx, larynx, and trachea[25, 168].

The anatomy and histology of rabbit nasal cavity tissues have been described previously[169]. Four types of epithelia line the nasal cavity: squamous, transitional, respiratory and olfactory, and their distribution at various levels of the nasal cavity is described[169], along with recommended sectioning planes to be used for inhalation studies: Level I is sectioned immediately posterior to the incisors, Level II at the first palatal ridge, Level III immediately anterior to the first upper premolar teeth, and Level IV immediately anterior to the first upper molar. Level I is lined predominantly by squamous epithelium with small amounts of thick transitional epithelium, and examination is recommended only for studies involving test article administration via instillation. Level II is lined primarily with transitional and respiratory epithelia, whereas Levels III and IV are lined with respiratory and olfactory epithelia, and often contain nasal-associated lymphoid tissue. The vomeronasal organs are evident only in Level II (Table 42).

Cleft Palate

Comments: Cleft Palate is a common finding in rabbit teratogenicity studies. Congenital alveolar cleft is a malformation occurring as a result of non-fusion of primary palate during weeks 4–12 of gestation, and may be induced by glucocorticoids[31] (Table 43).

B. Anatomy of the Larynx

Iatrogenic damage may be noted after intubation, and so care should be taken in interpreting short term studies where surgical preparations have taken place. Intubation damage has been described previously[170]. Submucosal glands are scanty or absent in the larynx[171–173] (Table 44).

C. Anatomy of the Trachea and Bronchi

The upper (tracheobronchial) airways have very scanty mucous cells and relatively abundant club cells. For example, in rabbits, mucous cells constitute less than 2% of tracheal epithelium, while club cells constitute 17–25% of the upper airway epithelium[172]. Submucosal glands are scanty or absent in the trachea, and bronchi[171–173] (Table 45).

D. Anatomy of the Lungs (Alveoli and Bronchioles)

The left lung consists of only two lobes (cranial and caudal), whereas the much larger right lung has four lobes (cranial, middle, caudal, and accessory)[174]. Multiple generations of distal intrapulmonary airways (bronchioles) branch to the level of terminal bronchioles (respiratory bronchioles are not present)[175, 176]. Rabbit blood vessels are generally thin-walled and prone to collapse and hematoma formation on puncture – a feature important to remember for studies where test items have been given by intravenous administration. The exceptions to this are the pulmonary arteries which are enveloped in a prominent smooth muscle layer, which may be misinterpreted as hypertrophy[24, 25]. There is a relative paucity of bronchus associated lymphoid tissue (BALT) in laboratory rabbits compared to other species. BALT is acquired and increases with age and environmental antigen exposure. Due to modern husbandry systems, relatively little BALT is seen in the young animals on toxicology studies.

In rabbits (like other laboratory species and humans), ciliated cells constitute a high percentage (40–55%) of airway lining epithelium at all levels from the trachea to the distal bronchioles[172, 176]. In rabbits club cells (formerly known as Clara cells) are the predominant secretory cell of the distal airways (club cells and ciliated cells constitute about 50% each of the distal airway epithelium of rabbits)[172]. However, the upper (tracheobronchial) airways have very scanty mucous cells and relatively abundant club cells. For example, in rabbits, mucous cells constitute less than 2% of tracheal epithelium, while club cells constitute 17–25% of the upper airway epithelium[172]. Submucosal glands are scanty or absent in the trachea, larynx, and bronchi, and absent in bronchioles[171–173] (Table 46).

Atherosclerosis

Other term(s): Plaque, atheromatous

Comments: Cholesterol-rich diets have been used to induce wide-spread atheromatous lesions within a short time period (3 months) in NZW rabbits. Early foam cell accumulation to partly occlusive atheromatous plaques were observed in the larger lung arteries[28]. Unique proliferations are seen as age related changes in the pulmonary arteries of both sexes and can resemble iatrogenic lesions[177]. Genetically altered strains of the NZW rabbit such as the Watanabe rab-

Table 42. Microscopic Findings of the Nasal Cavity: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Congenital				
Cleft palate *		X		
Non-proliferative				
Abscess		X		
Amyloid		X		
Angiectasis		X		
Apoptosis ǂ		X		
Atrophy		X		
Congestion	X			
Corpora amylacea		X		
Degeneration		X		
Deviation, nasal septum		X		
Edema		X		
Embolus		X		
Eosinophilic globules		X		
Erosion/ulcer		X		
Hemorrhage		X		
Infiltrate, inflammatory cell [insert appropriate cell type]		X		
Inflammation [insert appropriate cell type]		X		
Metaplasia		X		
Necrosis		X		
Perforation, septum		X		
Regeneration		X		
Single cell necrosis ǂ		X		
Thrombus		X		
Proliferative Non-neoplastic				
Hyperplasia, (+ cell type)		X		
Proliferative Neoplastic				
Adenoma			X	
Papilloma, squamous cell			X	
Tumor, neuroendocrine cell, benign			X	
Adenocarcinoma			X	
Carcinoma, adenosquamous			X	
Carcinoma, neuroepithelium			X	
Carcinoma, squamous cell			X	

ǂ Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

bit (Watanabe heritable hyperlipidemia rabbit, WHHL) are also used extensively.

Fibrosis

Comments: A rabbit model of pulmonary fibrosis due to pneumoconiosis induced by a single instillation of a known amount of silica dust into the right lung, is available[178–180]. Affected lungs show diffuse areas of increased alveolar macrophages containing dark pigment (dust particles) and/or vacuoles, with few associated areas of alveolar wall thickening and increased reticular fibers. In this model, severity/distribution of unilateral fibrosis, is scored for each lung lobe.

Hernia, Diaphragmatic

Comments: Fox and Crary reported 55 cases of left diaphragmatic hernia in three related strains of rabbits kept at the Jackson Laboratory under normal colony conditions: strains AX, AX_{bubu} and III_c[181]. Associated abnormalities included hypoplasia of the ipsilateral lung and an increased incidence of ventricular septal defects. Death was attributable to respiratory insufficiency. Genetic analysis suggests recessive inheritance. The condition is neither sex limited nor sex linked. The authors believe that two autosomal recessive genes are involved and have proposed the symbols *dh 1* and *dh 2* for the two genes that must both be present in homozygous condition for the development of diaphragmatic hernia in these rabbit strains.

Table 43. Microscopic Findings of the Paranasal Sinuses and Nasopharynx: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Non-proliferative				
Apoptosis [ǂ]		X		
Congestion		X		
Edema		X		
Erosion/ulcer		X		
Hemorrhage		X		
Infiltrate, inflammatory cell [insert appropriate cell type]		X		
Inflammation		X		
Necrosis		X		
Single cell necrosis [ǂ]		X		
Proliferative Non-neoplastic				
Hyperplasia, (+ cell type)		X		
Metaplasia, squamous cell		X		
Proliferative Neoplastic				
Adenoma			X	
Papilloma, squamous cell			X	
Adenocarcinoma			X	
Carcinoma, adenosquamous			X	
Carcinoma, neuroepithelium			X	
Carcinoma, squamous cell			X	

[ǂ] Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

Table 44. Microscopic Findings of the Larynx: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Non-proliferative				
Abscess		X		
Apoptosis [ǂ]		X		
Congestion	X			
Degeneration		X		
Ectasia, submucosal glands		X		
Edema		X		
Epithelial alteration			X	
Erosion/ulcer		X		
Hemorrhage		X		
Infiltrate, inflammatory cell [insert appropriate cell type]		X		
Inflammation		X		
Necrosis		X		
Regeneration		X		
Single cell necrosis [ǂ]		X		
Proliferative Non-neoplastic				
Hyperplasia, (+ cell type)		X		
Metaplasia, squamous cell		X		
Proliferative Neoplastic				
Papilloma			X	
Tumor, neuroendocrine cell, benign			X	
Adenocarcinoma			X	
Carcinoma, squamous cell			X	
Tumor, neuroendocrine cell, malignant			X	

[ǂ] Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

Table 45. Microscopic Findings of the Trachea and Bronchi: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Non-proliferative				
Apoptosis [ǂ]		X		
Bronchiectasis		X		
Congestion	X			
Degeneration		X		
Ectasia, submucosal glands		X		
Edema		X		
Erosion/ulcer		X		
Fibrosis		X		
Hemorrhage		X		
Infiltrate, inflammatory cell [insert appropriate cell type]		X		
Inflammation		X		
Aggregates, macrophage, increased		X		
Metaplasia		X		
Necrosis		X		
Regeneration		X		
Single cell necrosis		X		
Proliferative Non-neoplastic				
Hyperplasia, (+ cell type)		X		
Metaplasia, squamous cell		X		
Proliferative Neoplastic				
Papilloma			X	
Tumor, neuroendocrine cell, benign			X	
Adenocarcinoma			X	
Carcinoma, squamous cell			X	
Tumor, neuroendocrine cell, benign/malignant			X	

[ǂ] Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

Infiltrate, Inflammatory Cell (Figures 34, 35)

Comments: Peribronchial/perivascular infiltrates of granulocytes and mononuclear cells are commonly seen around larger airways and their associated vessels as an incidental background finding in rabbits on routine toxicology studies[81]. Should be differentiated from Bronchus associated lymphoid tissue (BALT).

Inflammation

Comments: Cooper *et al.* reported a congenital surfactant pneumonia in the audiogenic (EIII/JC) strain of rabbits[177]. This pneumonia was frequently grossly visible as irregular firm tan nodules in the cranioventral portions of lung lobes. Histologically the lesions consisted of multifocal to coalescing intra-alveolar aggregates of large numbers of multinucleate giant cells, predominantly foreign body type, with epithelioid and foamy macrophages and few lymphocytes, plasma cells and heterophils. Lesions occasionally extended into smaller bronchioles. There was frequent type II pneumocyte hyperplasia (adenomatosis) and alveolar septal fibrosis. "Billups bodies" – globular to ring-like brown to gray acellular material – was free within the alveoli and cytoplasm of giant cells. This acellular material was Alcian blue and PAS positive. The material was immunoreactive for surfactant protein-A and had the ultrastructural appearance of multilamellar vesicles, suggesting a genetic defect in surfactant metabolism.

Macrophages Increased, Alveolar (Figure 36)

Comments: Tissue resident macrophages are the first responders to insults to tissues, and the "aggregates" are generally proliferation or hyperplasia of these responding macrophages. Barros *et al.* reported an infiltration of the mucosa and submucosa of the trachea and bronchi by macrophages, multinucleated giant cells, lymphocytes, and mast cells with associated basal lamina calcium deposits, in six rabbits after intoxication by the calcinogenic plant *Solanum glaucophyllum*[182]. Increased diffusely distributed macrophages may also occur in Dutch Belted rabbits that relatively frequently show cardiomyopathy of unclear origin.

Metaplasia, Osseous (Figure 37)

Comments: Osseous metaplasia is an incidental spontaneous background finding in rabbit lungs, which has a differing appearance depending on the stage of the lesion. In early stages, they are composed of a dense knot of small

Table 46. Microscopic Findings of the Lungs (Alveoli and Bronchioles): Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Congenital				
Cyst, congenital			X	
Diaphragmatic hernia *		X		
Hypoplasia			X	
Non-proliferative				
Abscess		X		
Alveolar emphysema			X	
Alveolar lipoproteinosis			X	
Apoptosis ǂ		X		
Atelectasis		X		
Atherosclerosis *		X		
Bronchiectasis		X		
Congestion	X			
Degeneration		X		
Ectasia, acinus/submucosal glands		X		
Edema		X		
Embolus		X		
Erosion/ulcer		X		
Fibrosis *		X		
Hemorrhage		X		
Hypertrophy, media, artery		X		
Infarct		X		
Infiltrate, inflammatory cell [insert appropriate cell type] *		X		
Inflammation *		X		
Lipoproteinosis, alveolus		X		
Macrophages increased, alveolar *		X		
Material, extracellular [insert morphology/color]		X		
Metaplasia, mucous cell/squamous cell		X		
Metaplasia, osseous *	X			
Mineralization		X		
Necrosis		X		
Pigment		X		
Pigment/foreign material		X		
Pyothorax		X		
Regeneration		X		
Single cell necrosis ǂ		X		
Thrombus *		X		
Proliferative Non-neoplastic				
Hyperplasia, (+ cell type)		X		
Metaplasia, mucous/squamous cell		X		
Proliferative Neoplastic				
Adenoma, bronchioloalveolar			X	
Papilloma			X	
Tumor, neuroendocrine cell, benign			X	
Adenocarcinoma			X	
Carcinoma, acinar			X	
Carcinoma, adenosquamous			X	
Carcinoma, bronchioloalveolar			X	
Carcinoma, squamous cell			X	
Histiocytic sarcoma			X	

* Terminology with diagnostic criteria or comments described in the text. ǂ Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

cells with hyperchromatic nuclei and scant eosinophilic cytoplasm within the wall of an alveolus. This progresses to a larger, sometimes papillomatous mass with a fibrous core and a dark, low spindle to cuboidal epithelial-like covering. As the lesion progresses, it changes into eosinophilic to basophilic, osteoid to mineralized bone, resembling the lesion classically seen in rodent lungs.

Thrombus (Figure 38)

Comments: Small thrombi, with an accompanying arteritis/periarteritis, are often seen as incidental findings in the lungs of rabbits on routine toxicity studies (Table 47).

Table 47. Microscopic Findings of the Pleura: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Congenital				
Cyst, congenital			X	
Non-proliferative				
Abscess		X		
Apoptosis [‡]		X		
Effusions, non-inflammatory		X		
Fibrosis		X		
Hemorrhage		X		
Infiltrate, inflammatory cell [insert appropriate cell type]		X		
Inflammation		X		
Macrophages increased		X		
Metaplasia		X		
Mineralization		X		
Pigment		X		
Pigment/foreign material		X		
Pyothorax		X		
Single cell necrosis [‡]		X		
Proliferative Non-neoplastic				
Hyperplasia, mesothelium			X	

[‡] Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

Section 14: Skeletal System (Bone, Joint, Tooth)

A. Anatomy of Bone

Compared to rodents, rabbit bone has a larger proportion of osteonal structures, with dense osteons within the center of cortical bone and a primary vascular structure running longitudinally[183]. Rabbits also have more cancellous bone than rodents and this cancellous bone shows a higher degree of remodelling into secondary bone[184]. The secondary bone retains the primary vascular structure with vascular canals of osteons on the periosteal and endosteal surfaces running parallel to the long axis of the medullary cavity[183, 185]. Compared to rodents, rabbits have relatively more trabecular bone mass that undergoes Haversian remodelling[184]. Rabbits do not have secondary centers of ossification present at birth[186]. NZW rabbits typically reach skeletal maturity at 8–11 months[187], with cartilage developing a mature appearance prior to epiphyseal closure[188]. Rabbits have significant cartilage healing ability at an early age[189], but periosteal support of cartilage declines markedly from 6–12 months and is very variable after one year[190]. Rabbit femoral condyle cartilage is relatively thin with 0.25–0.75 mm compared to 2.2–2.4 mm in humans[188].

Skull

Rabbit tympanic bullae are relatively larger than those of most mammals and rabbits have a longer and more tubular external auditory meatus. The orbits are very large, and joined by an interorbital foramen. The zygomatic arch has a prominent protuberance, called the zygomatic process that is at the caudal aspect of the arch[30]. The maxilla is fenestrated giving a lacy appearance on radiographs. Radiographic anatomy of the rabbit skull has been well described[191, 192].

Vertebrae and ribs

The most common vertebral formula is C7 T12 L7 S4 Ca16, but this can vary widely in the thoracolumbar region. A recent report found that 44% of rabbits had 12T/7L, 33% had 13T/6L, and 23% had 13T/7L. Additionally, the spinal cord terminated with S2 in 79% of rabbits but in S1 in 19% and in L3 in 2% of animals[193]. The lumbar vertebrae have prominent mammillary processes on the cranial articular process. Rabbits are unique among domestic animals for having the dorsal aspect of the lumbar vertebral mammillary processes level with and slightly ventral to the spinous process. S1–S3 are routinely fused in rabbits, while S3–S4 fusion is more variable[30]. The first 7 ribs articulate with the sternum and the final 5 are free. The costal cartilage sections of the 7th–9th ribs are attached. The sternum includes 6 sternebrae[30].

Limbs

Rabbits are digitigrade.

Forelimb

The rabbit has paired clavicles and the only direct attachment between the forelimb and the axial skeleton is the sternoclavicular ligament. The carpus includes two rows of carpal bones. In the 5 digits in the forelimb, P1 has two phalanges and P2–P5 have three phalanges[30].

Hindlimb

The femur articulates only with the tibia. The fibula fuses distally with the tibia for approximately half of its length. Six tarsal bones are arranged in three rows. P1–P5 all have three phalanges[30]. The rabbit stifle joint is considered to have minimal to no resemblance to the human stifle anatomy[194].

Non-hematopoietic marrow

Rabbits have relatively fatty bone marrow which is not an ideal for autogenous bone and marrow harvesting or transplantation[184] (Table 48).

Malformation, Skeletal

Comments: Syringomyelia, hypoplasia pelvis, femoral luxation, and distal foreleg curvature are occasionally seen together as a hereditary defect in fetuses in Developmental and Reproductive Toxicology (DART) studies.

Bone Increased, Trabeculae

Comments: Osteopetrosis has been recorded in Dutch Belted rabbits; feed formulation errors have historically caused vitamin A toxicity-related increased bone deposition, sometimes leading to hydrocephalus[195].

Necrosis (Figures 39, 40)

Comments: Osteonecrosis can be induced with steroid therapy, as there may be infarction from fat or lipid-laden fibrin and platelet-containing emboli[196, 197].

Fracture

Comments: The combination of a light skeleton (6–8% of body weight [24, 30]) and ample skeletal muscle (>50% of body weight) predisposes rabbits to vertebral, sometimes even spontaneous, fracture[24, 195], often at the 7th lumbar vertebrae[30]. Lumbosacral fractures may also be seen as sequelae to convulsions/seizures induced by CNS active test articles. Avulsion of the tuberositas tibiae has been reported[198].

Hyperplasia, Chondrocyte

Comments: Chondrocyte hyperplasia, cartilage degeneration and necrosis are seen with fluoroquinolone antibiotics[199].

B. Anatomy of Joints

Spontaneous lesions of the joints and synovium are rare in rabbits used in nonclinical toxicology studies. The relative lack of changes in the joints of the rabbit is most likely related to the young age of the animals used. The most frequently used trimming plane to prepare femorotibial joints for microscopic eval-

Table 48. Microscopic Findings of Bone: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Congenital				
Malformation, skeletal *		X		
Non-proliferative				
Apoptosis ǂ		X		
Bone decreased, trabeculae and/or cortex		X		
Bone increased, trabeculae and/or cortex *		X		
Callus		X		
Cyst, bone		X		
Eroded surface, increased		X		
Fibro-osseous lesion (FOL)				X
Fibrous osteodystrophy (FOD)		X		
Fracture *		X		
Fracture/Callus		X		
Growth plate closed		X		
Growth plate partially closed		X		
Growth plate open		X		
Hemorrhage		X		
Infiltrate, inflammatory cell [insert appropriate cell type]		X		
Inflammation		X		
Necrosis *		X		
Osteoblastic surface increased		X		
Osteoclasts increased		X		
Osteoid increased		X		
Physeal dysplasia		X		
Physis, decreased thickness		X		
Physis, increased thickness		X		
Single cell necrosis ǂ		X		
Proliferative Non-neoplastic				
Hyperplasia, chondrocyte *		X		
Hyperplasia, osteoblast, focal		X		
Proliferative Neoplastic				
Chordoma			X	
Chondroma			X	
Osteoma			X	
Osteoblastoma			X	
Osteofibroma			X	
Chondrosarcoma			X	
Fibrosarcoma, osteogenic			X	
Osteochondroma			X	
Osteosarcoma			X	

* Terminology with diagnostic criteria or comments described in the text. ǂ Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

uation is parasagittal orientation (taken off-center through one femoral condyle), a portion of meniscus, and the corresponding tibial plateau.

Typical scoring systems used in toxicology studies are the International Cartilage Research Society (ICRS) visual Histological Assessment Scale[200] and the Osteoarthritis Research Society International (OARSI) score[201]. These are more appropriate for use in animal models than the Mankin scoring system used in man (Table 49).

Degenerative Joint Disease (DJD)

Comments: Induced models are used for research i.e. partial lateral meniscectomy[202].

Table 49. Microscopic Findings of the Joint and Synovium: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Non-proliferative				
Abscess		X		
Apoptosis ǂ		X		
Degeneration, articular cartilage		X		
Degeneration, chondromucinous		X		
Degenerative Joint Disease (DJD) *		X		
Hemorrhage		X		
Infiltrate, inflammatory cell [insert appropriate cell type]		X		
Inflammation		X		
Metaplasia		X		
Necrosis		X		
Osteophyte		X		
Single cell necrosis ǂ		X		
Proliferative Non-neoplastic				
Hyperplasia, synovial cell		X		
Proliferative Neoplastic				
Sarcoma, synovial			X	

* Terminology with diagnostic criteria or comments described in the text. ǂ Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

C. Anatomy of Teeth

The maxilla contains 4 incisors, no canines, six premolars, and 4–6 molars. The mandible contains 2 incisors, no canines, 4 premolars, and 6 molars. Unlike rodents, rabbits have two pairs of maxillary incisors caudal to the main incisors ("peg teeth") and have a total of 26–28 teeth. A slight degree of brachygnathism is normal in the rabbit so that the large pair of inferior incisors usually contact the small superior pair during occlusion. The large incisor teeth are adapted for gnawing and continue to erupt throughout life. There are no canine teeth and a large diastema exists between the incisors and premolars. Incisors consist of crown only, with extra-alveolar and intra-alveolar parts. Rabbits are hypsodonts and have a long crown without a true tooth root[30].

The labial or convex side of the incisors is covered by a layer of enamel. The lingual or concave side of the incisors is enamel-free but does have a very thin layer of cementum into which fibers of the periodontal ligament are embedded. Enamel is not formed over the top of the incisors. Before eruption, the tip is filled with dentin produced by odontoblasts of the pulp. As the tip wears away with use, the odontoblasts form more dentin (secondary dentin) so that the pulp is never exposed. Incisors have a widely open apical foramen (Table 50).

Malocclusion

Comments: Erosions of the mucosa may occur due to irregular growth or sharp edges of broken teeth.

Table 50. Microscopic Findings of the Tooth: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Congenital				
Malocclusion *	X			
Non-proliferative				
Abscess		X		
Alteration, dentin matrix			X	
Apoptosis ǂ		X		
Concretion, pulp			X	
Cyst			X	
Degeneration		X		
Dental dysplasia		X		
Denticle			X	
Dentin matrix alteration			X	
Dentin, decreased			X	
Dentin, niches			X	
Fracture		X		
Necrosis		X		
Periodontal pocket			X	
Pulp concretion			X	
Resorption			X	
Single cell necrosis ǂ		X		
Thrombus		X		
Proliferative Neoplastic				
Ameloblastoma			X	
Ameloblastic odontoma			X	
Fibroma, cementifying/ossifying			X	
Fibroma, odontogenic			X	
Odontoma			X	
Tumor, odontogenic, benign			X	
Tumor, odontogenic, malignant			X	

* Terminology with diagnostic criteria or comments described in the text. ǂ Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

Section 15: Soft Tissue (Soft Tissue, Mesothelium, Adipose, Skeletal and Smooth Muscle)

The pathology of both spontaneous and induced conditions of soft tissues are similar in rabbits and humans, hence their use in vaccine studies. Careful recording of the nature, intensity and duration of the inflammatory response of the soft tissues to implanted or injected substances is important in the assessment of the local tolerability of agents intended for contact with human tissues. The chemical and physical properties of injected chemicals or vaccines and their adjuvants as well as size, shape and surface texture of implanted biomaterials may modify the histological features and temporal pattern of the inflammatory and reparative responses[91–94]. Such studies in rabbits are conducted with descriptors following the ISO-10993 guidelines (Table 51).

A. Anatomy of Adipose Tissue

Brown fat is converted to white fat in the interscapular region of the rabbit as it ages, which correlates with the disappearance of catecholamines from the sympathetic nerve fibers in arterial blood vessels in both brown and white fat[203]. The peritoneal mesothelium of the anterior abdominal wall of the rabbit is characterized by flattened mesothelial cells with tight junctions, desmosomes, cytoplasmic pinocytic vesicles and microvilli[204]. It has been shown that adipose tissue may have an important paracrine function in smooth muscle cell proliferation in blood vessels[205] (Table 52).

Hyperplasia

Comments: Hyperplasia of adipose tissue (obesity) has been reported associated with pregnancy toxemia, but also with ketosis in non-pregnant NZW rabbits[24].

B. Anatomy of Muscle

The distribution of lesions of smooth muscle generally parallels the normal distribution of smooth muscle in the body so that lesions occur mostly in the female genital tract, the gastrointestinal tract and skin but only rarely in deep soft tissue. However, it has been shown that adipose tissue may have an important paracrine function in smooth muscle cell proliferation in blood vessels[205]. In soft tissues, particularly in inflammatory processes, smooth muscle cells may be difficult to distinguish from myofibroblasts. They both express smooth muscle actin but smooth muscle cells usually contain desmin[206] (Table 53).

Atrophy

Comments: Destruction and denervation atrophy in skeletal muscle caused by injection of local anesthetics i.e. lidocaine or bupivacaine is reported in the muscles adjacent to the facial nerve in rabbits[207].

Degeneration

Comments: Vitamin E deficiency causes skeletal muscle hyaline degeneration and mineralization, as does ketamine and xylazine intramuscular injection in Dutch Belted rabbits. The preferred site for intramuscular injection is the dorsal lumbar muscle. Alum granulomas or minimal focal myofiber degeneration are often seen at vaccination sites[81, 208].

Mineralization

Comments: Hypervitaminosis D as well as vitamin E deficiency cause widespread mineralization[209].

Necrosis

Comments: Afifi *et al.* reported muscle necrosis seen with 1,1'-methylenebis[4-[(hydroxyimino)methyl]-pyridinium] dimethanesulfonate intramuscular injection to NZW rabbits[210]. Sequestration of non-viable fat tissue (fat necrosis) transplanted into NZW rabbits has been reported[211]. Abscesses are common in the skin of domestic rabbits[110]. Rabbits restrained for six hours a day for 35 days developed focal, small necrotic areas in the skeletal muscle[212].

Parasite

Comments: Sarcocystosis, presumably caused by *Sarcocystis cuniculi*, was recently reported in 2 purpose-bred, SPF Dutch Belted laboratory rabbits[213]. Sarcocysts were found in the eyelid of one rabbit and the tongue of the other (Table 54).

Table 51. Microscopic Findings of the Soft Tissue: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Non-proliferative				
Abscess		X		
Amyloid		X		
Apoptosis ǂ		X		
Atrophy		X		
Degeneration		X		
Fibroplasia		X		
Fibrosis		X		
Hemorrhage		X		
Infiltrate, inflammatory cell [insert appropriate cell type]		X		
Inflammation		X		
Metaplasia, osseous/cartilaginous		X		
Mineralization		X		
Necrosis		X		
Single cell necrosis ǂ		X		
Proliferative Non-neoplastic				
Hyperplasia		X		
Proliferative Neoplastic				
Fibroma			X	
Hibernoma			X	
Leiomyoma			X	
Lipoma			X	
Rhabdomyoma			X	
Fibrosarcoma			X	
Leiomyosarcoma			X	
Liposarcoma			X	
Mesenchymoma, malignant			X	
Rhabdomyosarcoma			X	
Sarcoma, NOS (Not otherwise specified)			X	

ǂ Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

Table 52. Microscopic Findings of the Adipose Tissue: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Non-proliferative				
Abscess		X		
Apoptosis ǂ		X		
Atrophy		X		
Degeneration		X		
Fibrosis		X		
Hemorrhage		X		
Infiltrate, inflammatory cell [insert appropriate cell type]		X		
Inflammation		X		
Inflammation, lipogranulomatous		X		
Mineralization		X		
Necrosis		X		
Single cell necrosis ǂ		X		
Proliferative Non-neoplastic				
Hyperplasia *		X		
Proliferative Neoplastic				
Hibernoma			X	
Lipoma			X	
Liposarcoma			X	
Sarcoma, NOS (Not otherwise specified)			X	

* Terminology with diagnostic criteria or comments described in the text. ǂ Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

Table 53. Microscopic Findings of the Smooth and Skeletal Muscle: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Non-proliferative				
Abscess		X		
Apoptosis ǂ		X		
Atrophy *		X		
Degeneration *		X		
Fibrosis		X		
Hemorrhage		X		
Hypertrophy		X		
Infiltrate, inflammatory cell [insert appropriate cell type]		X		
Inflammation		X		
Metaplasia, osseous/cartilaginous		X		
Mineralization *		X		
Necrosis *		X		
Parasite *		X		
Single cell necrosis ǂ		X		
Vacuolation, myocyte		X		
Proliferative Non-neoplastic				
Hyperplasia		X		
Proliferative Neoplastic				
Rhabdomyoma			X	
Rhabdomyosarcoma			X	
Sarcoma, NOS (Not otherwise specified)			X	

* Terminology with diagnostic criteria or comments described in the text. ǂ Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

Table 54. Microscopic Findings of the Mesothelium: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Non-proliferative				
Abscess		X		
Apoptosis ǂ		X		
Fibrosis		X		
Fibroplasia		X		
Hemorrhage		X		
Infiltrate, inflammatory cell [insert appropriate cell type]		X		
Inflammation		X		
Metaplasia		X		
Single cell necrosis ǂ		X		
Proliferative Non-neoplastic				
Hyperplasia		X		
Proliferative Neoplastic				
Mesothelioma, malignant			X	

ǂ Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

Section 16: Special Senses

The otic (ear) and olfactory systems are not routinely evaluated in toxicity studies in the rabbit. The ocular system is subdivided into the eye and the ocular adnexa (glands and other eye-associated tissues). At necropsy, Davidson's fixative is usually the fixative of choice for the eyes and optic nerves. For a thorough examination of the ocular system, at a minimum, the eyes, optic nerves, and major ocular adnexa (eyelids, lacrimal glands, nictitating membrane with nictitans gland, and Harderian glands) should be examined.

A. Anatomy of the Eye

At birth, the eye is developmentally immature, and differentiation continues and is substantially complete when the eyelids open at about post-natal days 10–11[214–218].

The rabbit eye is relatively large in proportion to body size and slightly flattened along the antero-posterior plane[217]. The circular, rather shallow orbits are at an approximately right angle to the sagittal plane of the head, so the eyes protrude prominently[217, 219–222]. Each of the eyes of the rabbit has approximately 190-degree field of view, but they also work together to have a small amount of binocular vision. Because of their lateral placement, the angle between the eyes is 150–175 degrees, and the overall visual field is extremely wide (330 – to almost 360 degrees)[217, 219–224]. In contrast, the binocular field of vision is correspondingly quite narrow (10–35 degrees wide)[221].

B. Anatomy of the Eyelids

Rabbits are born blind with closed eyelids, which open at about post-natal days 10–11. The superior eyelid (palpebra) of the rabbit is shorter and thicker and has larger and more abundant eyelashes than the inferior eyelid[219]. The outer surfaces of the eyelids are lined by typical keratinized stratified squamous epithelium. As in other skin regions of the rabbit, the eyelid skin lacks sweat glands.

Meibomian (tarsal) glands are present in the superior and inferior eyelids, embedded as linear arrays in the tarsal plate (Figure 41). In one study of NZW rabbits, Meibomian gland numbers/eyelid averaged from 32.30 +/– 3.43 and 27.15 +/– 2.35 in the superior and inferior eyelids, respectively[225]. In each Meibomian gland, the sebaceous holocrine acini are aligned along and empty via short ductules into a single central duct via short ductules. The central duct in turn opens at the conjunctival margin[219, 226]. The central excretory duct is normally lined by keratinized stratified squamous epithelium[226, 227].

Small clusters of accessory lacrimal gland acini (glands of Wolfring) have been described in the superior eyelid of rabbits[228] (Figure 42). These are located submucosally, and anterior to the Meibomian gland arrays (Figures 43, 44).

Extraocular muscles involved in movement of the eyelids include the levator superior palpebrae and orbicularis oculi[219, 229–233], as well as the depressor palpebrae inferioris (present in rabbits but not in most other mammalian species)[220, 234, 235] (Table 55).

C. Anatomy of the Conjunctiva

Compared to humans and many other species, the precorneal tear film of rabbits is thicker, more stable, and has a substantially different composition (i.e., types and proportions of lipid and mucins)[236–239].

Conjunctival submucosal lymphoid cell aggregates, with or without germinal centers (conjunctiva-associated lymphoid tissue [CALT]) are normally present in rabbits[240–242]. CALT aggregates are more abundant in the palpebral and fornical conjunctivae versus the bulbar conjunctiva. They are also more abundant in the inferior than superior eyelid[219, 240, 242]. CALT

Table 55. Microscopic Findings of the Eyelid: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Non-proliferative				
Abscess		X		
Apoptosis ǂ		X		
Atrophy, Meibomian gland		X		
Congestion		X		
Infiltrate, inflammatory cell [insert appropriate cell type]		X		
Inflammation (+ locator)		X		
Metaplasia		X		
Single cell necrosis ǂ		X		
Proliferative Non-neoplastic				
Hyperplasia, squamous cell			X	
Proliferative Neoplastic				
Papilloma, squamous cell			X	
Carcinoma, squamous cell			X	

ǂ Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

aggregates are absent in neonatal rabbits, develop rapidly after the eyes open (at about post-natal day 10–11), reach maximum numbers and size in mature rabbits (7–20 months), and then decline in aging animals[240] (Table 56).

Hyperplasia, Conjunctiva

Other terms: *Pseudopterygium; aberrant conjunctival overgrowth; ankyloblepharon; circumferential conjunctival hyperplasia; conjunctival centripetalization; conjunctival hyperplasia; conjunctival stricture; corneal occlusion; epicorneal conjunctival membrane; precorneal membranous occlusion; pinguecula bilateralis; pseudosymblepharon; pterygium; pterygium conjunctivae.*

Comments: Infrequently, the rabbit cornea is progressively covered by hyperplastic conjunctiva around the entire perimeter. Of unknown etiology, the condition appears to be unique to rabbits[222, 243–248]. Conjunctival hyperplasia can be unilateral or bilateral, and is characterized clinically by a circumferential, nonadherent membranous flap which arises from the perilimbal bulbar conjunctiva and grows centripetally and symmetrically across the anterior corneal surface. Microscopically, the membranes consist of a collagenous central stroma lined by conjunctival mucosa[247].

D. Anatomy of the Cornea

The rabbit cornea is relatively large and slightly elliptical (slightly longer along the horizontal axis)[219–221, 243]. Although there are breed and age variations, central corneal thickness in the living rabbit ranges from about 0.35–0.44 mm[249–256], which is thinner than the human cornea (0.53–0.58 mm)[257].

Most authors concur that the rabbit corneal stroma lacks a Bowman's layer, a subepithelial condensation of the collagenous stroma present in humans and certain other species[219, 258–261]. Differently from rats and mice, the nuclei of rabbit corneal keratocytes are visible as hyperreflective structures. Thus, their density can be easily evaluated. Endothelial cell density is higher than in rats and mice, and the endothelium regenerates in response to injury or loss[262, 263] (Table 57).

Attenuation, Endothelium

Comments: Unlike many other species, the rabbit corneal endothelium has rather robust capacity to proliferate to cover defects or loss of individual endothelial cells. Following insult, the rabbit corneal endothelium generally undergoes endothelial proliferation and regenerates, with occasional multinucleate cell formation, rather than endothelial attenuation[263].

Dermoid, Cornea

Comments: A case of a corneal dermoid in a dwarf rabbit[264], and a limbic dermoid in a NZW rabbit[265] have been reported. Although uncommon, dermoids should be on the list of differential diagnoses for corneal masses in rabbits. Animals exhibiting these changes on pre-study examination should be removed from the study cohort before dosing commences.

Table 56. Microscopic Findings of the Conjunctiva: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Non-proliferative				
Abscess		X		
Apoptosis ǂ		X		
Atrophy, epithelium		X		
Cyst, inclusion		X		
Dermoid		X		
Edema		X		
Erosion/ulcer		X		
Infiltrate, inflammatory cell [insert appropriate cell type]	X			
Inflammation	X			
Metaplasia		X		
Pigment		X		
Single cell necrosis ǂ		X		
Proliferative Non-neoplastic				
Hyperplasia, conjunctival *		X		
Hyperplasia, squamous cell			X	
Proliferative Neoplastic				
Papilloma, squamous cell			X	
Carcinoma, squamous cell			X	

* Terminology with diagnostic criteria or comments described in the text. ǂ Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

Table 57. Microscopic Findings of the Cornea: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Congenital				
Dermoid, corneal *		X		
Non-proliferative				
Abscess		X		
Apoptosis ǂ		X		
Atrophy		X		
Attenuation endothelium *		X		
Cyst, inclusion		X		
Degeneration		X		
Descemetocele		X		
Dystrophy, corneal *		X		
Edema		X		
Erosion/ulcer		X		
Fibroplasia		X		
Fibrosis		X		
Hypertrophy, Descemet's membrane		X		
Infiltrate, inflammatory cell [insert appropriate cell type]		X		
Inflammation		X		
Keratinization		X		
Metaplasia		X		
Mineralization *		X		
Neovascularization		X		
Necrosis		X		
Single cell necrosis ǂ		X		
Vacuolation, lipid, cornea *#		X		
Vacuolation, epithelium or endothelium		X		
Proliferative Non-neoplastic				
Hyperplasia, endothelium		X		
Hyperplasia, squamous cell		X		
Proliferative Neoplastic				
Papilloma, squamous cell			X	
Carcinoma, squamous cell			X	

* Terminology with diagnostic criteria or comments described in the text. # Inducible lesion. ǂ Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

Dystrophy, Cornea

Pathogenesis/cell of origin: Corneal epithelium and associated basement membrane and stroma.

Differential Diagnosis: Corneal dysplasia

Diagnostic Features: Thickened, elevated epithelium interspersed with areas of abnormally thin epithelium.

Comments: When precisely used, the term "corneal dystrophy" describes a disease process of mineralization in the cornea (especially the epithelial basement membrane), with the lesions being spontaneously occurring, non-inflammatory, usually involving the central cornea, and are often bilateral and symmetrical[266]. The Dutch Belted rabbit can exhibit such a corneal dystrophy[266], sometimes referred to as "anterior corneal dystrophy". This is a spontaneous, possibly inherited condition characterized by clinically observed central to peripheral corneal opacities which correspond microscopically to the focal areas of epithelial basement thickening and irregularity[266, 267]. This true corneal dystrophy is comparable to Thiel-Behnke corneal dystrophy (TBCS) caused by defects in transforming growth factor beta (TGFβ) in humans[267].

However, most reports of rabbit "corneal dystrophy" do not describe such true corneal dystrophy, because in rabbits, the term "corneal dystrophy" has been used to describe several apparently unrelated non-inflammatory conditions of uncertain etiology, which are characterized by various changes in the corneal epithelium, stroma, and/or endothelium.

For example, a morphologically different condition termed "corneal epithelial dystrophy" has been described in two

4-month-old NZW rabbits[268]. The affected animals had clinically observed unilateral circumferential corneal opacities extending from the limbus to the central cornea. Microscopically, the opacities consisted of alternating areas of corneal epithelial thinning and thickening (hyperplasia) with unremarkable basement membranes. It is unclear if this is a true corneal dystrophy or not[268].

Another apparently distinct condition termed "pre-Descemet's membrane corneal dystrophy" has been described in adult NZW rabbits[269]. Microscopically, focal peripheral to central accumulations of ectopic corneal endothelial cells were present subjacent to Descemet's membrane, and corresponded to clinically observed corneal opacities. By electron microscopy these cells were found to be secreting matrix material based on the cells' intracytoplasmic content, presence of a dense and homogenous material associated with the outer cell membrane, location of these cells close to Descemet's membrane, and the cells' linear organization. The change was assumed to be present at birth because it was seen in 2-week-old rabbits. The nomenclature of dystrophy for this lesion reflects the nomenclature of a similar lesion in humans. No mineralization has been reported with this lesion in rabbits.

Vacuolation, Lipid, Cornea

Other terms: corneal lipidosis; lipid keratopathy

Pathogenesis/cell of origin: lipid-laden keratocytes, foamy macrophages, sterol clefts, and/or multinucleated giant cells in the corneal stroma.

Differential Diagnosis: vacuolation, mucopolysaccharides; vacuolation, NOS; edema.

Diagnostic Features: Microscopic changes in the cornea are primarily in the stroma (especially anteriorly), and include lipid-containing keratocytes and foamy macrophages, sterol clefts, and/or multinucleated giant cells, often associated with secondary neovascularizaton and inflammatory cell infiltrates[270–273]. Similar lesions have also been described in the nictitating membrane[273].

Comments: Corneal lipid vacuolation has been described in various rabbit breeds with high serum cholesterol levels due to familial predisposition (in Watanabe heritable hyperlipidemic [WHHL] rabbits [270] or resulting from high dietary cholesterol in various other rabbit breeds[271, 273]. In one study of "New Zealand" rabbits fed high-cholesterol diets, the typical corneal stromal changes were present but other lesions were also observed: lipid accumulation in corneal epithelium and endothelium, as well as lipid-laden macrophages in the iris stroma, ciliary body, ciliary processes, and choroid, and increased lipid staining in the retina[271]. Other studies with rabbits fed high-cholesterol diets have also demonstrated light and transmission electron microscopic effects in other regions of the globe including: lipid-laden macrophages in the choroid and suprachoroid; lipid accumulation in the retinal pigment epithelium (RPE) and astrocytes; Bruch's membrane thickening; RPE hypertrophy; Müller cell and astrocyte activation; and degeneration and/or necrosis of choroidal vessel endothelium and retinal neurons[274–277]. Instillation of cationic amphiphilic drugs in juvenile white rabbits induce corneal phospholipidosis[278].

Mineralization

Comments: Albino and pigmented rabbits can exhibit "calcific" or "band keratopathy"-like subepithelial and stromal mineralization following corneal injury from various causes[220, 279–281]. Hypervitaminosis D can also result in corneal mineralization, but in rabbits seems to occur only in eyes compromised by concurrent ocular inflammation[282, 283].

E. Anatomy of the Anterior Chamber and Aqueous Humor

Many features of the rabbit uvea (iris, ciliary body, and choroid), aqueous filtration system, and anterior chamber are related to the low accommodative ability. The rabbit anterior chamber is large, being 2.3 - fold larger than that of the cynomolgus macaque even though the eyes of both species are of similar size[284] and having a slightly greater diameter than the much larger human eye[285]. Compared to humans, the rabbit anterior chamber is shallower and more curved due to the displacement of the iris anteriorly by the large lens[220, 285]. Yüksel *et al.*[256] reported that mean anterior chamber depth of young "New Zealand" rabbits is 2.08 +/– 0.16 mm, which is very similar to the 2.161 +/– 0.11 mm noted by Werner *et al.*[285] in male NZW rabbits (Table 58).

F. Anatomy of the Filtration Angle

The rabbit iridocorneal (filtration) angle is relatively large and deep, partly because of the small ciliary muscle. Rabbits have multiple slit-like venous collector channels known as the angular aqueous plexus, rather than a singular canal of Schlemm[233, 286–291] (Table 59).

Malformation, Filtration Angle

Other terms: Buphthalmos; buphthalmia

Comments: A type of developmental glaucoma, inherited as an autosomal recessive trait with incomplete penetrance, has long been recognized in rabbits[24, 292–298]. This hereditary glaucoma has been most commonly recognized in NZW albino rabbits[295, 297, 298], but can also occur in other albino strains such as AXBU/J[296] and in "pigmented" rabbits[293]. The fundamental phenotypic defect is incomplete and/or abnormal development of iridocorneal angle structures (i.e., goniodysgenesis), resulting in impaired drainage of aqueous humor from the eye[295]. Clinical signs generally become evident early in life, around 2–3 months of age or even earlier, and include elevated intraocular pressure (IOP), corneal edema, increased corneal diameter, and eventually

Table 58. Microscopic Findings of the Anterior Chamber and Aqueous Humor: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Non-proliferative				
Proteinaceous fluid			X	
Inflammation			X	
Proliferative Non-neoplastic and Neoplastic				
-				

Table 59. Microscopic Findings of the Filtration Angle: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Congenital				
Malformation, filtration angle *		X		
Non-proliferative				
Narrowed filtration angle *		X		
Single cell necrosis		X		
Proliferative Non-neoplastic				
Proliferation, trabecular meshwork			X	

* Terminology with diagnostic criteria or comments described in the text.

grossly detectable enlargement and excessive protrusion of the globe[243, 292–295, 297, 298]. Most cases are bilateral, but unilateral involvement has been reported[294, 295, 297]. Microscopically, aqueous outflow structural abnormalities include a narrowed, truncated, or absent ciliary cleft, shrunken or compressed trabecular meshwork, absent or poorly developed pectinate ligaments, and posterior displacement of the angular aqueous plexus[292, 293, 295–299]. The ciliary body can also be hypoplastic. Associated changes can include pathologic optic nerve head cupping, optic nerve atrophy, and retinal changes ranging from decreased or degenerate ganglion cells to extensive full thickness retinal atrophy[292, 294].

Narrowed Filtration Angle

Comments: Experimentally induced glaucoma in rabbits has been studied as an animal model of human disease[220, 292, 300]. Glaucomatous changes can also be secondary to ocular inflammation, trauma, and other causes[248], and would therefore be considered acquired and having a normally formed, but possibly obstructed, filtration angle.

G. Anatomy of the Uvea (Iris, Ciliary Body and Choroid)

Many features of the rabbit uvea (iris, ciliary body, and choroid), are related to the low accommodative ability. The ciliary body is divided into the anterior pars plicata (ciliary processes and ciliary muscle) and the posterior pars plana. In keeping with the low accommodative ability, the rabbit ciliary body muscle (smooth muscle) is small and poorly developed[219, 235, 243, 287, 291]. The pars plicata ciliary processes are radially arranged leaflike folds which arise from the anterior ciliary body and extend along the posterior iris surface. In the rabbit, long and short ciliary processes alternate, with the longer processes often interconnected by lateral, epithelium-covered stromal bridges to each other and to the posterior iris, forming the so-called "ciliary web", "circular ledge", or "sims" (Figure 45)[220, 235, 301–304].

The pars plana of rabbits is relatively narrow, so the lens and pars plana are in closer proximity in the rabbit compared to the cynomolgus macaque[284, 304, 305]. The junction of the pars plana and the peripheral retina in rabbits and many non-primate species is unindented and smooth, and thus more appropriately referred to as the ora ciliaris retinae rather than as the ora serrata. The ora ciliaris retinae of rabbits is situated relatively more anteriorly than is the ora serrata of the cynomolgus macaque[284].

The rabbit choroid exhibits increased thickness in a horizontal nasotemporal band inferior to the optic nerve head (along the retinal visual streak; see Retina section below)[217, 220]. A choroidal tapetum lucidum is not present in rabbits[243] (Table 60).

Metaplasia, Osseous

Comments: Ciliary body osseous metaplasia consists of small, irregular, non-mineralized osteoid masses in the ciliary body of otherwise unremarkable eyes. This has been noted as a rare incidental change in NZW rabbits[306]; whether it also occurs in other strains is unknown. Although the etiology is unknown, these may be minor developmental anomalies, similar to the uveal "heterotopic ossification" in other species such as guinea pigs and dogs[307–309]. Scleral osseous metaplasia was also reported as a reaction to intraocular osteoinductive hydroxyapatite and polyethylene polymer implants in experimentally manipulated (eviscerated) eyes of NZW rabbits[310].

Table 60. Microscopic Findings of the Uvea (Iris, Ciliary Body and Choroid): Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Congenital				
Adhesion, iris			X	
Hypoplasia, choroid		X		
Hypoplasia, ciliary body		X		
Malformation, iris			X	
Persistent pupillary membrane		X		
Non-proliferative				
Apoptosis ǂ		X		
Atrophy		X		
Congestion		X		
Edema		X		
Hemorrhage		X		
Infiltrate, inflammatory cell [insert appropriate cell type]		X		
Inflammation		X		
Metaplasia, osseous *		X		
Neovascularization		X		
Pigment, increased/decreased, iris		X		
Single cell necrosis ǂ		X		
Vacuolation, lipid *		X		
Vacuolation, cytoplasm, epithelium		X		
Proliferative Non-neoplastic				
Hyperplasia, melanocyte			X	
Proliferative Neoplastic				
Adenoma, ciliary body, iris			X	
Leiomyoma, uvea			X	
Melanoma, uvea, benign			X	
Schwannoma, intraocular/optic nerve, benign			X	
Melanoma, uvea, malignant			X	
Adenocarcinoma, ciliary body, iris			X	
Meningioma, malignant, optic nerve			X	
Schwannoma, intraocular/optic nerve, malignant			X	

* indicates terminology with diagnostic criteria or comments described in the text. ǂ Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

Vacuolation, Lipid

Comments: Accumulations of foam cells, extracellular lipid and occasional cholesterol clefts have been found in the iris and ciliary body of the eyes in about 50% of NZW rabbits fed a cholesterol-rich diet over three months[28]. Similar ocular lesions were described for WHHL rabbits[311].

H. Anatomy of the Lens

The rabbit lens is large compared to that of haplorhine primates[219, 234]. The rabbit lens is 3.9- fold larger than that of cynomolgus macaques, even though the eyes of both species are of similar size[284]. The rabbit lens is also larger and thicker than the human lens, even though the human eye is overall much larger[217, 220]. NZW rabbits have mean lens thickness and diameter of 6.36 +/– 0.13 mm and 10.47 +/– 0.31 mm, respectively, while humans have mean lens thickness and diameter of 4.24 +/– 0.46 mm and 9.58 +/– 0.27 mm, respectively[285]. Rabbits are distinctive in having linear shaped sutures, with the anterior and posterior sutures oriented vertically and horizontally, respectively[219, 312] (Table 61).

Degeneration, Lens Fiber (Figure 46)

Comments: Lens fiber degeneration is a microscopic finding that is usually correlated with ophthalmic examination findings of lens opacity. Spontaneous lens opacities can occur at different ages in rabbits and can exhibit breed or strain specificity[24, 313–317]. Congenital lenticular opacities of uncertain etiology have been reported in neonates, but most spontaneous cataracts occur in adult or even aged animals[222]. In a study involving rabbits ranging in age from about 2.7 to 9.6 months, Munger *et al.* reported lens opacity incidences of 5.7% in albino NZW and 1.1% in pigmented NZW × NZ Red F1 hybrids[314]. In two NZW inbred strains

Table 61. Microscopic Findings of the Lens: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Non-proliferative				
Apoptosis ǂ		X		
Degeneration, lens fiber *		X		
Dislocation, lens, anterior or posterior			X	
Fibroplasia, lens epithelium		X		
Hypertrophy, lens capsule/epithelium/fiber		X		
Inflammation		X		
Mineralization, lens fiber		X		
Necrosis, lens epithelium		X		
Parasite *		X		
Rupture, lens capsule		X		
Single cell necrosis ǂ		X		
Vacuolation, lens epithelium/fiber		X		
Proliferative Non-neoplastic				
Hyperplasia, lens epithelium		X		

* Terminology with diagnostic criteria or comments described in the text. ǂ Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

(EII/JC and EIIJC-HLA-A2), spontaneous lens opacities had an overall much later onset, being noted only in animals 37 months or older[315]. Nuclear sclerosis (increased compaction of inner cortical lens fibers) was noted only in older animals (average age 6.0 +/– 2.9 years in one series[222] and 3.5–4.0 years in another series)[318]. Lens fiber degeneration and more extensive lesions can develop as sequelae of many non-heritable spontaneous or experimentally induced conditions that secondarily affect the lens (i.e., diabetes, glaucoma, posterior synechia, and proliferative vitreoretinopathy) [24, 248, 300, 319–321].

Many cases of spontaneous lenticular opacities in rabbits are suspected to be of heritable (genetic) origin[314, 315]. A recent study has demonstrated that experimentally induced mutations of the α-crystallin gene result in heritable opacities in knockout rabbits and their offspring[322].

Experimentally induced lens fiber degeneration in rabbits occurs with administration of various chemical test articles; exposure to microwaves, UVA radiation, or electric current; hyperoxia; and dietary imbalances[220, 294, 320, 321, 323–325]. Lens fiber degeneration in rabbits in toxicity studies can also result from extraneous physical trauma to the lens (i.e., from misplaced hypodermic needles during intravitreal injections or from cage accidents or other misadventure).

Parasite

Comments: The common microsporidian parasite *Encephalitozoon cuniculi* can infect many tissues of rabbits, including the eye. Ocular infections can result in multiple pathologic changes including corneal ulceration, edema, and epithelial and endothelial necrosis; iris and ciliary body edema and epithelial degeneration; retinal atrophy; and generalized inflammatory cell infiltrates[326, 327]. In the lens, infections can also result in degeneration of the lens, which in turn sometimes ruptures, resulting in secondary uveal inflammation (phacoclastic uveitis)[85, 222, 326, 328–331]. The route of infection for the lens is unclear, though transplacental vertical transmission has been proposed[328, 331].

I. Anatomy of the Vitreous

The vitreous cavity of the rabbit eye is relatively small, with a vitreous-to-globe area ratio of 0.4 compared to a 0.7 ratio in the similarly sized eye of the cynomolgus macaque[284]. In rabbits, strong vitreal attachment occurs along the retinal medullary rays[332].

The collagen fibrils of the rabbit vitreous are condensed into funnel-like lamellae which are more prominent and uniform than those in humans. The lamellae generally extend anteroposteriorly from the vitreous base to the optic nerve head[333]. Cloquet's canal, a conduit for hyaloid vessels during fetal development, is retained consistently in adult rabbits[333], even though most authors agree that this structure does not routinely persist in adult human eyes[334] (Table 62).

J. Anatomy of the Retina

Further maturation of the retina continues post eyelid opening for several weeks more or even to adulthood[215, 216, 335, 336]. Regression of ocular fetal vessels (hyaloid vessels and vasculosa lentis) has been reported to be complete by about postnatal days 14–20[337, 338], but persistence of embryonic vessel remnants is common in rabbits[339–341].

The rabbit retina exhibits many anatomical and histologic differences compared to that of humans and other primates and non-primate mammalian species. The medullary rays are

Table 62. Microscopic Findings of the Vitreous: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Congenital				
Aplasia, vitreous		X		
Persistent hyperplastic primary vitreous		X		
Persistent hyaloid vessels	X			
Non-proliferative				
Fibroplasia		X		
Hemorrhage		X		
Infiltrate, inflammatory cell [insert appropriate cell type]		X		
Inflammation		X		
Metaplasia, bone or cartilage		X		
Mineralization, vitreous		X		
Pigment, macrophage, hemosiderin		X		
Proliferative Non-neoplastic and Neoplastic				
-				

easily visible ophthalmoscopically as two broad, pale, wing-like bands that emanate from the optic nerve head and extend horizontally across the temporal and nasal fundus to just posterior to the equator[219, 220, 222]. Histologically, the medullary rays consist of myelinated nerve fibers (axons of the retinal ganglion cells)[336, 342–347]. In typical sagittal histologic sections, the medullary rays appear as focal elevations of the inner retinal surface due to the collectively increased thickness of their myelinated nerve fibers. Unlike most species, the rabbit retina has oligodendrocytes, which are localized in the medullary rays[343, 344]. Rabbit retinal astrocytes are confined to the medullary rays, especially the nerve fiber and ganglion cell layers, with some astrocytes closely associated with the blood vessels overlying the medullary rays[345, 347].

Although not visible ophthalmoscopically, the visual streak is well developed in the rabbit[220, 335, 343, 347–352]. Histologically, in typical sagittal sections, the rabbit visual streak is a discrete nasotemporal linear zone of increased ganglion cell density, located inferior to the optic nerve head and medullary rays[220, 348, 350–353].

The area centralis is a specialized focus of increased ganglion cell density distinct from the linear visual streak which is present in the retina of many mammals[335, 354]. Whether the rabbit possesses an area centralis is a subject of some controversy, with some authors[348, 351, 353], but not others[217, 350] reporting its presence.

Rabbits are presumed to have dichromatic color vision[355, 356]. Density gradients are present in the rabbit retina, with the "blue" S-cones concentrated in small zones in the inferior retina[335, 355, 356]. Dual-opsin cones (which co-express both "blue" and "green" opsins) have been demonstrated in rabbits[357]. The intrinsically photosensitive retinal ganglion cells (ipRGC) are a recently discovered third class of nonciliary retinal photoreceptor[358]. The recent identification of melanopsin gene expression in the rabbit retina suggests the possibility that iprGC may also occur in this species[359].

Compared to many other species, the Müller macroglial cells of the rabbit retina are especially prominent[220, 360], with the entire transretinal span of individual Müller cells and their processes often easily traceable on routine H&E sections. The Müller cells are distributed throughout the rabbit retina, including the medullary rays[215, 345, 347, 361].

Bruch's membrane is a laminated extracellular matrix located between the retinal pigmented epithelium (RPE) and the adjacent choriocapillaris and is composed of the RPE and choriocapillaris capillary basement membranes and associated collagen and elastin layers[362, 363]. Bruch's membrane in rabbits is thinner than that of humans[364]. The RPE contain melanosomes, which lack melanin granules in albino rabbits such as the NZW strain. RPE melanin granules tend to diminish in number (due to fusion) and accumulate lipofuscin as aging-related changes. The Dutch Belted rabbit and NZW F1 cross rabbits offer the ability to test potential effects of xenobiotics on the eye of pigmented rabbits.

Retinal and choroidal arterial supply is dual and variable among rabbits, arising from the external carotid artery as it feeds the external ophthalmic artery or from the internal carotid artery as it feeds the internal ophthalmic artery[365]. The rabbit retina is partially vascularized (merangiotic vascularization), which is unique among the domestic and common laboratory species[342, 366, 367]. The central retinal artery enters the optic nerve and then passes into the globe, where it divides into nasal and temporal arteries that extend horizontally across the fundus (parallel to and overlying the medullary rays; other regions of the retina are avascular)[342, 366, 367].

In rabbits, the exit point of the optic nerve from the globe is superior to the antero-posterior pole axis and horizontal-most meridian plane of the globe[219, 234, 333, 360, 367, 368]. Thus, the rabbit optic nerve head is located in the superior rather than central fundus.

The rabbit optic nerve head is horizontally oval and normally deeply indented (physiologic cupping), which is ap-

preciable both ophthalmoscopically and in histologic preparations[217, 219, 220, 234, 368]. In many species such as humans, macaques, horses, and pigs, the scleral exit channel at the optic nerve head is multi-fenestrated due to a well-developed lamina cribrosa, a sieve-like network of collagenous plates[366, 369–371]. Rabbits have a poorly developed lamina cribrosa, and the optic nerve head contains neuronal tissue and astrocytes in addition to oligodendroglia[219, 234, 360, 366, 368, 369]. This connective tissue meshwork also contains elastin and lends support for the nerve tissue.

In rabbits, a central retinal artery enters the optic nerve ventrally, just posterior to the optic nerve head[219, 366, 368]. Main veins from the two medullary rays also exit via the optic nerve[372] (Table 63).

Deposits, Extracellular Matrix, Subretinal

Pathogenesis/cell of origin: RPE

Diagnostic Features: Discrete, focal, rounded eosinophilic deposits located between the RPE and Bruch's membrane, sometimes resulting in a focal "dome"-like inward elevation of the RPE.

Comments: These deposits between the RPE and Bruch's membrane are not common but can occur as spontaneous findings in otherwise unremarkable rabbit eyes[373], and morphologically resemble drusen though they have not been biochemically characterized in rabbits.

Table 63. Microscopic Findings of the Retina: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Congenital				
Arteriolar loop, pre-retinal		X		
Non-proliferative				
Apoptosis ǂ		X		
Atrophy, retinal, global/inner/outer		X		
Congestion		X		
Deposits, extracellular matrix, subretinal *		X		
Detachment, retina		X		
Displacement, photoreceptor nuclei		X		
Edema		X		
Eosinophilic bodies, retina *		X		
Fibroplasia, retinal, subretinal or epiretinal		X		
Folds, retina	X			
Glial cells, increased		X		
Hemorrhage		X		
Hypertrophy, retinal pigment epithelium (RPE) *	X			
Inclusions (intracytoplasmic accumulation), RPE		X		
Infiltrate, inflammatory cell [insert appropriate cell type]		X		
Inflammation		X		
Mineralization		X		
Myelin, increased		X		
Necrosis		X		
Necrosis, single cell		X		
Neovascularization		X		
Pigment, increased		X		
Pigment, decreased		X		
Polarity loss, RPE		X		
Retinal rosettes		X		
Single cell necrosis ǂ		X		
Vacuolation, cytoplasmic/extracellular		X		
Proliferative Non-neoplastic				
Hyperplasia, retinal pigmented epithelium		X		
Proliferative Neoplastic				
-				

* Terminology with diagnostic criteria or comments described in the text. ǂ Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

Eosinophilic Bodies, Retina (Figure 47)

Pathogenesis/cell of origin: retinal neurons (horizontal cells)

Diagnostic Features: Occasional, round to oval, pale pink, circular structures with indistinct outlines, located in the inner nuclear layer (INL) and outer plexiform layer (OPL).

Comments: The pale eosinophilic round structures in the rabbit retina termed "eosinophilic bodies" have been demonstrated by immunohistochemistry and transmission electron microscopy to be neurofilament accumulations in horizontal cell neurites (dendrites) [374]. Affected retinas were otherwise histologically unremarkable. The retinal eosinophilic bodies occur in several rabbit breeds including NZW, Japanese White, and Dutch Belted, with higher incidences in older animals, suggesting that they are an aging-related change.

Hypertrophy, Retinal Pigment Epithelium (RPE) (Figure 48)

Diagnostic Features: Small foci of enlarged and often displaced RPE in the subretinal space. The RPE aggregates are frequently located near the optic nerve head (peripapillary) or at the peripheral margins of the retina but can also be found less frequently in other retinal regions. The swollen RPE cells have abundant pale basophilic, granular cytoplasm, which often has a brownish tinge attributed to lipofuscin[373]. Pigment granules for pigmented breeds are concentrated around these vacuoles[375].

Comments: Young adult rabbits sometimes exhibit this spontaneous RPE change unassociated with any concurrent ocular pathology[373]. The exact etiology is undetermined. This spontaneous RPE hypertrophy was first recognized in a pigmented rabbit breed (Dutch Belted) but can also occur in other pigmented breeds (e.g. New Zealand Red) as well as in albino breeds (Table 64).

K. Anatomy of the Sclera

The rabbit sclera is thicker at the limbus (0.5 mm) and thinner at the posterior pole (approximately 0.18–0.2 mm) [219, 234]. In comparison, human sclera thickness is similar at the limbus (approximately 0.5–0.53 mm), but much greater at the posterior pole and near the optic nerve (0.86 mm–1.0 mm)[376, 377].

In rabbits, a large orbital venous sinus (also called the orbital "venous plexus") is located posterior to the globe and receives the venous drainage from the eye and orbital contents[219, 220, 233, 378, 379].

Arteries supplying the rabbit eye (such as the long and short posterior ciliary arteries) generally enter the sclera in the posterior globe near the optic nerve, while the central retinal artery enters within the optic nerve itself[233, 367, 378] (Table 65).

Metaplasia Osseous

Comments: Scleral osseous metaplasia has been reported as a reaction to intraocular osteoinductive hydroxyapatite and polyethylene polymer implants in experimentally manipulated (eviscerated) eyes of NZW rabbits[310].

Table 64. Microscopic Findings of the Optic Nerve: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Non-proliferative				
Atrophy		X		
Degeneration, axon		X		
Demyelination		X		
Infiltrate, inflammatory cell [insert appropriate cell type]		X		
Inflammation		X		
Necrosis		X		
Single cell necrosis [ǂ]		X		
Vacuolation		X		
Proliferative Non-neoplastic				
Glial cells, increased number		X		
Proliferative Neoplastic				
Glioma, benign			X	
Meningioma, benign			X	
Meningioma, malignant			X	
Schwannoma, benign			X	
Schwannoma, malignant			X	

[ǂ] Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

Table 65. Microscopic Findings of the Sclera: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Non-proliferative				
Apoptosis ǂ		X		
Atrophy		X		
Hemorrhage		X		
Infiltrate, inflammatory cell [insert appropriate cell type]		X		
Inflammation		X		
Metaplasia, osseous *		X		
Single cell necrosis ǂ		X		
Proliferative Non-neoplastic and Neoplastic				
-				

* Terminology with diagnostic criteria or comments described in the text. ǂ Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

L. Anatomy of the Ocular Adnexa - Glands and Ducts

The gross anatomical terminology of the rabbit ocular adnexal glands has been the subject of some confusion in the scientific literature, with many different, often inconsistent, and even contradictory nomenclature schemes promulgated by various authors. Thus, caution is warranted when reviewing published terminology schemes and descriptions for these structures.

The rabbit zygomatic salivary gland is located along the zygomatic arch near the inferior portion of the lacrimal gland[234, 380, 381]. Portions of the zygomatic salivary are sometimes sampled along with the adjacent lacrimal gland, appearing in routine histologic preparations as clusters of deeply basophilic mucous-cell acini with tiny lumens.

The ocular adnexa, especially the Harderian gland and most of the extraocular muscles are closely associated with the large venous sinus (or plexus) present in the posterior orbit of rabbits[219, 233, 378].

Harderian Gland

The rabbit Harderian gland is large, located in the medial ventral orbit, and attached to the base of the nictitating membrane[219, 220, 234, 382, 383]. The rabbit Harderian gland is composed of two closely apposed but grossly and histologically distinct lobes, surrounded by a thin fibrous capsule[219, 234, 384]. A single excretory duct opens on the concave surface of the base of the nictitating membrane[219, 379, 385].

Histologically, the Harderian gland is classified as tubuloacinar (tubuloalveolar). Acinar epithelial cells of both lobes are characterized by abundant cytoplasmic lipid vacuoles, and the secretions of both lobes are predominantly lipid[383, 385–390].

Based on their grossly visible coloration, the two lobes are known as the "white" lobe and the "pink" (or "red") lobes[219, 383–385, 391] (Figure 49). The more inferiorly situated pink lobe (Figure 50) is about twice as large as the more superiorly located white lobe[219, 383, 384, 391, 392]. In the white lobe (Figure 51), acinar cell lipid vacuoles are small, more uniform and very densely packed, imparting a typically darker, more eosinophilic microscopic appearance in routine H&E sections. In contrast, in the grossly pink lobe acinar cells contain larger, clear vacuoles, and thus appear paler microscopically[234, 382–384, 390–392].

Unlike rats, mice, and hamsters, the rabbit Harderian glands does not appear to exhibit histologic sexual dimorphism and/or porphyrin secretion[390, 393]. However, intact male rabbits have particularly large Harderian glands, which increases further in size during the breeding season.

Lacrimal Glands

The rabbit lacrimal gland is large, long, thin, and multilobulated, with pink to pale red macroscopic coloration[217, 220] (Figure 52). Its lobes fill most of the inferior orbit and extend into the posterior superior orbit[290]. Although most of the lacrimal gland is intraorbital, portions may extend onto the lateral zygomatic arch and even extraorbitally onto the zygomatic bone[234, 382]. Most authors describe a single excretory duct, which opens into the superior eyelid conjunctiva at the lateral canthus[382, 394, 395].

As in several other species, the rabbit lacrimal gland exhibits a degree of sexual dimorphism, with adult males exhibiting larger acini and greater numbers of acinar cells than females[396].

Nictitating Membrane and Nictitans Gland

The rabbit has a well-developed nictitating membrane (third eyelid)[217, 219, 382]. It consists of a crescentic conjunctival fold reflected from the medial canthus molded to the contours of the globe, and adjacent to the Harderian gland. A central hyaline cartilage plate, embedded in fibrous loose connective tissue, reinforces the nictitating membrane[217, 219, 234, 382].

The inner surface of the nictitating membrane is lined by goblet-cell containing conjunctival mucosa, while the more external surface is lined by non-keratinized stratified squamous epithelium (Figure 53).

The nictitans gland (gland of the third eyelid) is thin and flat, and surrounds most of the length of the central cartilage. It is a modified lacrimal-type gland with serous acini[382]. Several ducts extend through the cartilage plate to open on the inner surface of the nictitating membrane[219, 382, 397] (Table 66).

Cytoplasmic Alteration, Harderian Gland or Lacrimal Gland

Other terms: Metaplasia, Harderization; Ectopic gland.

Comments: Cytoplasmic alteration of the lacrimal gland or of the Harderian gland occur relatively commonly in the rabbit[398]. In the Harderian gland, it is possible to observe small islands of normal lacrimal gland, while less frequently, islands of normal Harderian gland acini may be observed in the lacrimal gland (Figure 54). The lacrimal gland alteration in the Harderian gland has been reported as early as 3 weeks of age and increases in incidence with age in the lacrimal glands of males and females but occurs with a greater incidence and extent in males. Harderian gland alteration in the lacrimal gland is recognized less commonly and is not well characterized.

Necrosis, Harderian Gland or Lacrimal Gland

Comments: Necrosis and acute to subacute inflammation in the Harderian and/or lacrimal glands consistent with infarction due to embolism of microthrombi associated with medial auricular artery catheterization has been reported[33].

Nasolacrimal Duct

In adult rabbits, the nasolacrimal duct (NDL) has the same three regions as described in other mammals (orbital lacrimal canaliculi and sac, bony NDL canal, and non-bony NDL canal in nasal cavity).

In the rabbit, a single lacrimal punctum is located in the inner surface of the inferior eyelid near the medial canthus about 3 mm from the lid margin[219, 222, 382, 399]. This opens into a poorly developed lacrimal sac-like dilatation which widens into the nasolacrimal duct[222, 399–402]. The nasolacrimal duct terminates just caudal to the mucocutaneous junction of the nares[18, 220, 222].

According to most authors, the rabbit nasolacrimal sac and duct are lined by stratified to pseudo-stratified columnar epithelium, which in many areas has a conspicuously bilayered appearance[399–402]. Some of the epithelial lining cells

Table 66. Microscopic Findings of the Harderian, Lacrimal, and Nictitans Glands: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Non-proliferative				
Apoptosis ǂ		X		
Atrophy		X		
Congestion		X		
Cyst		X		
Cytoplasmic alteration, acinar, Harderian gland or lacrimal gland *		X		
Degeneration		X		
Dilatation		X		
Edema		X		
Hemorrhage		X		
Hypertrophy		X		
Infiltrate, inflammatory cell [insert appropriate cell type]		X		
Inflammation		X		
Karyomegaly		X		
Necrosis *		X		
Necrosis, single cell		X		
Porphyrin increased				X
Regeneration		X		
Single cell necrosis ǂ		X		
Proliferative Non-neoplastic				
Hyperplasia, acinar		X		
Neoplastic				
Adenoma			X	
Adenocarcinoma			X	

* Terminology with diagnostic criteria or comments described in the text. ǂ Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

Table 67. Microscopic Findings of the Nasolacrimal Duct: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Non-proliferative				
Apoptosis ǂ		X		
Atrophy		X		
Congestion		X		
Cyst, inclusion		X		
Degeneration		X		
Edema		X		
Erosion/ulceration		X		
Fibrosis		X		
Hemorrhage		X		
Infiltrate, inflammatory cell [insert appropriate cell type]		X		
Inflammation		X		
Metaplasia		X		
Necrosis		X		
Single cell necrosis ǂ		X		
Proliferative Non-neoplastic				
Hyperplasia, epithelial		X		
Proliferative Neoplastic				
Papilloma, squamous cell			X	
Carcinoma, squamous cell			X	

ǂ Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

secrete mucins[399, 402]. In rabbits, portions of the nasolacrimal duct are surrounded by a prominent cavernous body with large blood vessels in a loose stroma[402] (Table 67).

M. Anatomy of the External Ear

The lesions of the convex surface of the external ear (pinna) are largely those of haired skin and are discussed with the Integumentary section. The external ear (pinna) is easily assessed during macroscopic examination. The large veins in the rabbit pinna are often used for blood collection or Test Article administration, and if the latter are sampled for histopathology as the "Injection/Treatment Site".

The concave external areas of the pinnae have a thin epidermis and dermis with a paucity of hair follicles. In the external ear canal just outside of the bony collar (i.e. at about the level of the obtuse-angle turn), the ear canal retains the thin epidermis but has a circumferential zone containing sebaceous glands (ceruminous glands) but lacking hair follicles. These glands are absent at this site in rodents. Within the internal acoustic meatus, defined by the presence of the bony collar, the dermis is very thin to non-existent with the epidermis almost lying upon the temporal bone. Rabbits have multiple small ceruminous glands (simple sebaceous glands that secrete cerumen, or "ear wax") (Table 68, 69, 70).

Table 68. Microscopic Findings of the External Ear: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Non-proliferative				
Apoptosis [ǂ]		X		
Congestion		X		
Cyst. tympanic membrane		X		
Debris, external ear canal		X		
Edema		X		
Erosion/ulceration		X		
Fibrosis		X		
Hemorrhage		X		
Infiltrate, inflammatory cell [insert appropriate cell type]		X		
Inflammation, auricular cartilage		X		
Inflammation, external ear canal		X		
Metaplasia		X		
Perforation, tympanic membrane		X		
Single cell necrosis [ǂ]		X		
Proliferative (non-neoplastic)				
Hyperplasia, epithelium		X		
Neoplastic				
Papilloma, squamous cell			X	
Carcinoma, squamous cell			X	

[ǂ] Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

Table 69. Microscopic Findings of the Middle Ear: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Non-Proliferative				
Apoptosis [ǂ]		X		
Atrophy, bone		X		
Cholesteatoma		X		
Congestion		X		
Cyst		X		
Edema		X		
Fibrosis		X		
Hemorrhage		X		
Infiltrate, inflammatory cell [insert appropriate cell type]		X		
Inflammation, granulomatous/catarrhal		X		
Metaplasia, squamous cell		X		
Mineralization		X		
Necrosis, bone		X		
Necrosis, tympanic membrane		X		
New bone formation		X		
Perforation, tympanic membrane		X		
Single cell necrosis [ǂ]		X		
Tissue, granulation		X		
Ulcer		X		
Proliferative Non-neoplastic				
Fibrosis		X		
Proliferative Neoplastic				
-				

[ǂ] Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

Table 70. Microscopic Findings of the Inner Ear: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Non-proliferative				
Apoptosis [ǂ]		X		
Cellularity decreased, spiral ganglion/spiral limbus/spiral ligament, and/or stria vascularis		X		
Congestion		X		
Degeneration, axon/hair cells and/or epithelium		X		
Edema		X		
Erosion/ulceration		X		
Fibrosis		X		
Hair cell, decreased number		X		
Hemorrhage		X		
Infiltrate, inflammatory cell [insert appropriate cell type]		X		
Inflammation, inner ear		X		
Loss, disorganization or disruption, otolith		X		
Metaplasia		X		
Necrosis cartilage/hair cell		X		
Necrosis neuronal/vestibular organ		X		
New bone formation		X		
Otolith loss, disorganization or disruption		X		
Single cell necrosis [ǂ]		X		
Vacuolation, hair cell/supporting cell		X		
Vacuolation, stria vascularis		X		
Proliferative Non-neoplastic and Neoplastic				
-				

[ǂ] Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

Section 17: Urinary System

Calcium absorption and metabolism in the rabbit is poorly understood. Rabbits normally have a higher blood calcium range than other laboratory animal species and are predisposed to cystic, urethral, ureteral and renal calculi. Rabbits excrete 45–60% excess calcium though the urine as calcium carbonate. Mineralized foci are commonly seen throughout the urinary tract. Urine is normally alkaline, and cloudy to pigmented, caused by the presence of albumin, fine calcium carbonate and ammonium magnesium phosphate crystals. The fact that rabbits are horizontal quadrupeds may also predispose the anterior wall to retention of microcrystals and other particles as compared to humans. Rabbit urine varies in color from creamy yellow to dark red depending on the presence of porphyrin pigments derived from the diet or xenobiotics e.g. antibiotics. Care must be taken to differentiate between red urine caused by porphyrin excretion and hematuria. While modern laboratory animal management practices have limited the incidence of infectious processes in the kidney, inflammatory conditions related to infectious disease may still occur (Table 71).

Cyst

Comments: Renal lesions resembling human polycystic kidney disease were reported in a retrospective evaluation of NZW rabbit kidney tissue[403].

Glomerulopathy

Comments: Rabbits are susceptible to a glomerulopathy induced by corticosteroids[404–406]. The initiating lesion is a glomerulopathy characterized by aneurysmal capillary dilatation with nodular changes of eosinophilia and cellular loss in the glomeruli. Bowman's space often contains erythrocytes or eosinophilic material. Bowman's capsule may be necrotic. Ultrastructurally, glomerular capillaries may be occluded with a proteinaceous coagulum, endothelium may be swollen, and podocytes have loss of foot processes. Basement membranes may be thickened or tortuous. Epithelial cells of the glomerular tufts may have hyaline globules, vacuoles or be intensely osmophilic. Renal tubules may have fatty infiltration, hyaline droplets, and cellular necrosis. Tubules contain erythrocytes and protein casts. Clinical pathology parameters may demonstrate increased BUN, glycosuria, albuminuria, and hematuria with clinically red urine. Kidney weights may be increased. It is important to recognize the susceptibility of rabbits to corticosteroid glomerulopathy as it may be confused with a test article-related effect if animals are given corticosteroids for palliative purposes during a toxicology study.

Mineralization (Figure 55)

Comments: Mineralized foci are commonly seen in the collecting ducts and medulla of rabbit kidneys. Mineralized foci in the tubules or interstitial areas of the cortex are present in 60% of male and female rabbits evaluated[81, 407]. Focal mineralization is also occasionally recorded in the urothelium of the urinary bladder.

Nephropathy, Spontaneous

Pathogenesis/cell of origin: Proximal and distal tubules

Diagnostic Features: The histological findings are generally recorded separately (basophilia tubules, dilated/cystic tubules, pigmented tubules, interstitial inflammatory cell infiltrate), and the term nephropathy is only used when at least three of the aforementioned components are present. A spontaneous nephropathy syndrome is commonly seen in clinically normal apparently healthy rabbits from colonies free from *Encephalitozoon cuniculi*. There are no clinical signs accompanying these lesions and no evidence of progression/greater severity of the findings on longer term studies i.e. the lesion is not thought to be progressive unlike the nephropathy in rats. It is considered to be a syndrome particular to the NZW rabbit as similar findings have not been recorded in mixed breed pet rabbits. The renal findings are observed in 80% of apparently healthy young rabbits, more frequently in females than males[81]. Spontaneous findings of mineralization, tubular basophilia and dilatation have been reported previously in young laboratory rabbits less than 1 year of age[408, 409], but the incidence of this lesion seems to be increasing in the NZW population. Basophilic tubules, dilated/cystic tubules, pigmented tubules, interstitial inflammatory cell infiltration, and mineralization have been reported in juvenile NZW rabbits as little as 8 weeks old (Bradley, unpublished data). Study pathologists should exercise caution when interpreting kidney findings in apparently healthy rabbits as these renal nephropathy findings may mask nephrotoxic effects.

Vacuolation

Comments: Vacuolation of the proximal convoluted tubule epithelium is a regular finding in young non-pregnant females (35%). These vacuoles stain positively with Oil red O stain for neutral lipids. Vacuolation of the proximal convoluted tubule epithelium has been recorded in juvenile NZW rabbits as little as 8 weeks old (Bradley, unpublished data) (Table 72, 73, 74).

Table 71. Microscopic Findings of the Kidney: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Congenital				
Aplasia		X		
Renal dysplasia		X		
Non-proliferative				
Abscess		X		
Accumulation, glycogen		X		
Accumulation, hyaline droplets		X		
Accumulation, adipocytes, interstitium		X		
Amyloid, glomerulus/interstitium		X		
Angiectasis		X		
Apoptosis ǂ		X		
Atrophy, glomerulus/tubule		X		
Basophilia, tubule	X			
Basophilic granules			X	
Calculus	X			
Cast (+ modifier)	X			
Chronic progressive nephropathy				X
Crystals	X			
Cyst *	X			
Degeneration, tubule	X			
Degeneration/regeneration	X			
Dilatation, Bowman's space/tubule	X			
Edema, interstitium		X		
Erosion		X		
Extramedullary hematopoiesis		X		
Fibrosis, interstitium	X			
Glomerulonephritis	X			
Glomerulopathy, hyaline/mesangioproliferative		X		
Glomerulopathy *	X			
Glomerulosclerosis		X		
Granuloma, Foreign material		X		
Hemorrhage		X		
Hyperplasia/metaplasia, Bowman's capsule	X			
Hypertrophy, tubule		X		
Immature glomerulus	X			
Inclusion bodies		X		
Infarct		X		
Infiltrate, inflammatory cell [insert appropriate cell type]	X			
Inflammation, interstitium	X			
Interstitial nephritis			X	
Karyomegaly		X		
Mesangiolysis		X		
Metaplasia, osseous/squamous cell		X		
Microabscess	X			
Mineralization * (+ locator)	X			
Multinucleated giant cells		X		
Necrosis, (+ modifier, locator)		X		
Nephropathy, obstructive/retrograde		X		
Nephropathy, alpha2u-globulin				X
Nephropathy, spontaneous *	X			
Parasite		X		
Pigment	X			
Pyelonephritis	X			
Regeneration, tubule	X			
Single cell necrosis ǂ		X		
Tissue, ectopic, adrenal		X		
Vacuolation *, tubular	X			
Proliferative Non-neoplastic				
Hyperplasia, oncocyte			X	
Hyperplasia, mesangium			X	
Hyperplasia, juxtaglomerular			X	
Hyperplasia, tubule		X		
Hyperplasia, urothelium		X		
Nephroblastematosis			X	
Proliferative Neoplastic				
Adenoma			X	
Nephroblastoma		X		
Oncocytoma			X	
Papilloma			X	
Renal mesenchymal tumor			X	
Adenocarcinoma			X	
Carcinoma		X		
Carcinoma, squamous cell/urothelium			X	
Sarcoma, renal			X	

* Terminology with diagnostic criteria or comments described in the text. ǂ Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

Table 72. Microscopic Findings of Ureter: Rabbit

Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Congenital				
Aplasia, ureter			X	
Non-proliferative				
Abscess		X		
Apoptosis ǂ		X		
Calculus		X		
Crystals		X		
Dilatation		X		
Edema		X		
Erosion/ulcer		X		
Fibrosis		X		
Hemorrhage		X		
Infiltrate, inflammatory cell [insert appropriate cell type]		X		
Inflammation		X		
Single cell necrosis ǂ		X		
Proliferative Non-neoplastic				
Hyperplasia, urothelium		X		
Metaplasia, glandular/squamous cell			X	
Proliferative Neoplastic				
Papilloma, squamous cell/urothelial			X	
Adenocarcinoma			X	
Carcinoma, squamous cell/urothelial			X	

ǂ Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

Ethical Practices: All procedures used to prepare macroscopic and microscopic images of animal specimens for this article were performed in accordance with regulations and established guidelines for humane treatment of research animals and were reviewed and approved in advance by the relevant Institutional Animal Care and Use/Ethics Committee.

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Table 73. Microscopic Findings of the Urinary Bladder: Rabbit

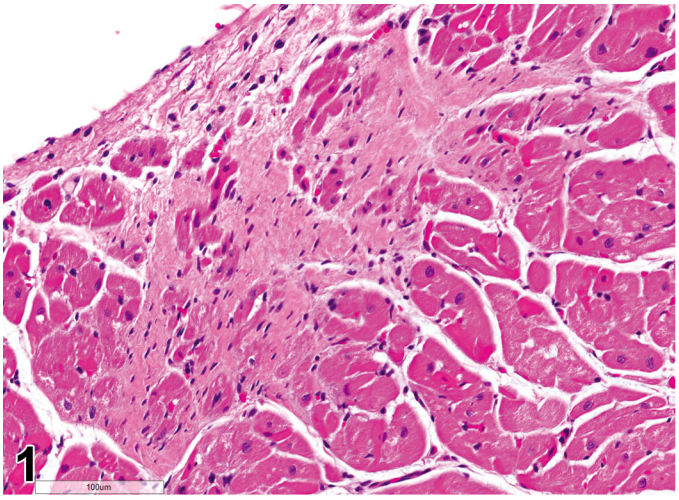
Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Congenital				
Diverticulum			X	
Non-proliferative				
Abscess		X		
Angiectasis		X		
Apoptosis ǂ		X		
Calculus		X		
Crystals	X			
Dilatation		X		
Edema		X		
Erosion		X		
Fibrosis		X		
Hemorrhage		X		
Hypertrophy, urothelium		X		
Inclusions, urothelium				X
Infiltrate, inflammatory cell [insert appropriate cell type]		X		
Inflammation		X		
Metaplasia		X		
Mineralization, urothelium		X		
Necrosis		X		
Parasite		X		
Proteinaceous plug				X
Single cell necrosis ǂ		X		
Ulcer		X		
Uropathy, obstructive		X		
Vacuolation, urothelium		X		
Proliferative Non-neoplastic				
Hyperplasia, urothelium			X	
Metaplasia, glandular/squamous cell			X	
Proliferative Neoplastic				
Proliferative lesion, mesenchymal				X
Papilloma, squamous cell/urothelial			X	
Adenocarcinoma			X	
Carcinoma, squamous cell/urothelial			X	

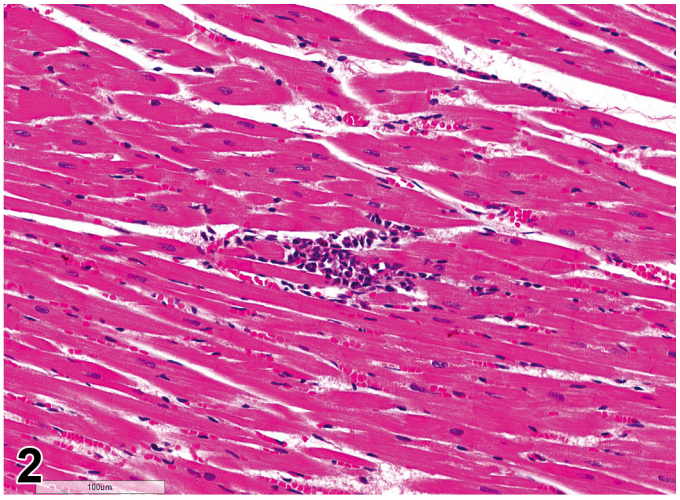
ǂ Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.

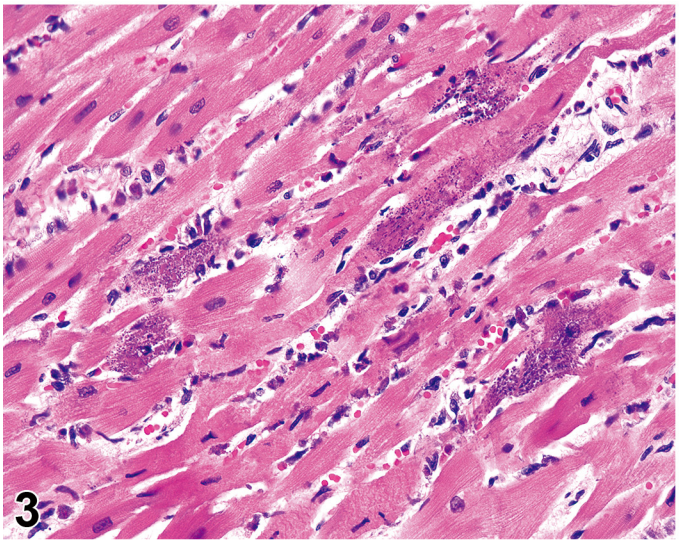
Table 74. Microscopic Findings of the Urethra: Rabbit

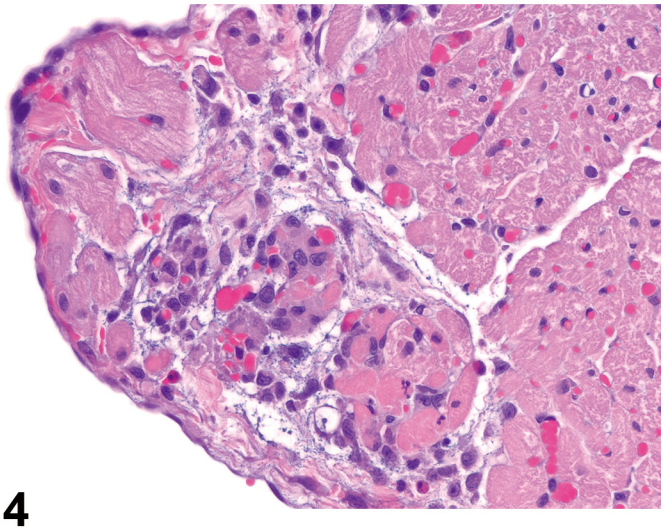
Finding	Common	Uncommon	Not Observed but Potentially Relevant	Not Applicable
Non-proliferative				
Abscess		X		
Apoptosis [ǂ]		X		
Congestion		X		
Edema		X		
Erosion		X		
Fibrosis		X		
Hemorrhage		X		
Hypertrophy, urothelium		X		
Infiltrate, inflammatory cell [insert appropriate cell type]		X		
Inflammation		X		
Metaplasia		X		
Obstruction		X		
Plug, proteinaceous				X
Single cell necrosis [ǂ]		X		
Proliferative Non-neoplastic				
Hyperplasia, urothelium		X		
Metaplasia, glandular/squamous cell		X		
Proliferative Neoplastic				
Proliferative lesion, mesenchymal				X
Papilloma, squamous cell/urothelial			X	
Adenocarcinoma			X	
Carcinoma, squamous cell/urothelial			X	

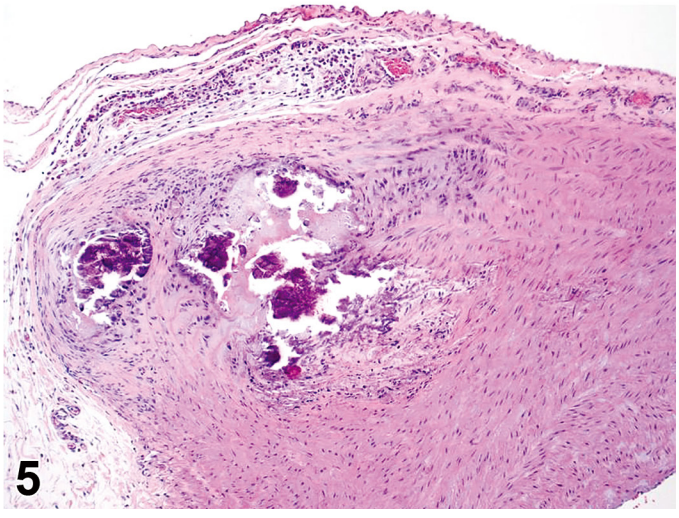
[ǂ] Refer to [4] for diagnostic criteria and use of the terms apoptosis and single cell necrosis.











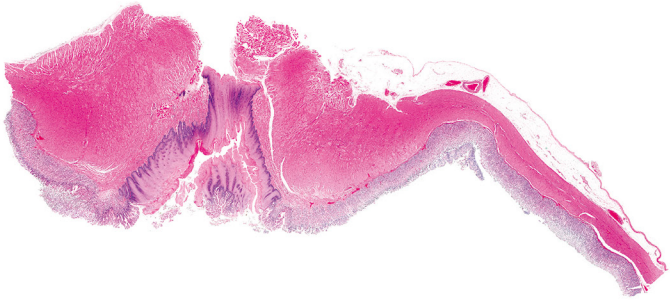
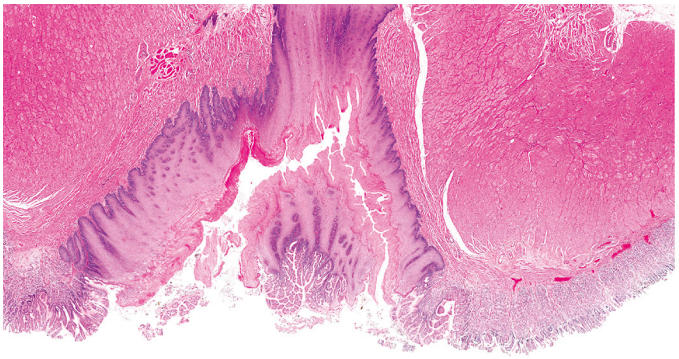


Figure 1.——Heart, Fibrosis Myocardium, H&E.
Figure 2.——Heart, Infiltrate, inflammatory cells, H&E.
Figure 3.——Heart, Mineralization myocardium H&E.
Figure 4.——Heart, Necrosis myocardium, H&E.
Figure 5.——Aorta, Mineralization, H&E.
Figure 6.——Stomach, Cardioesophageal junction, H&E.



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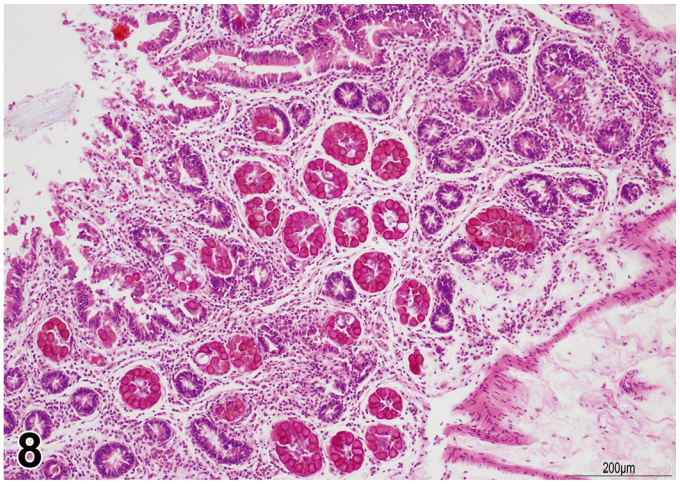

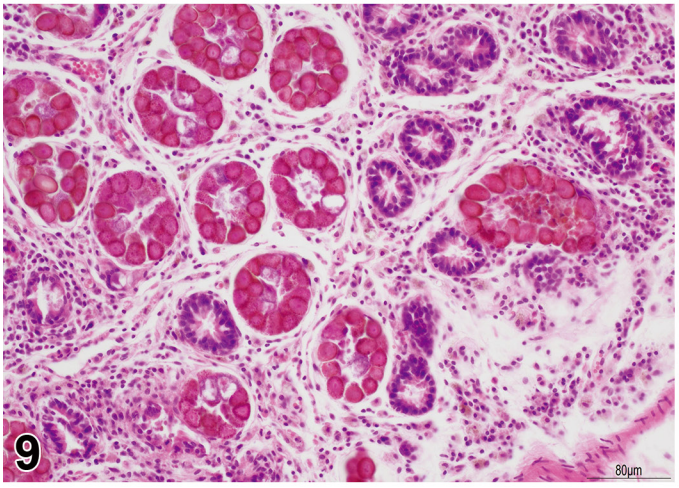

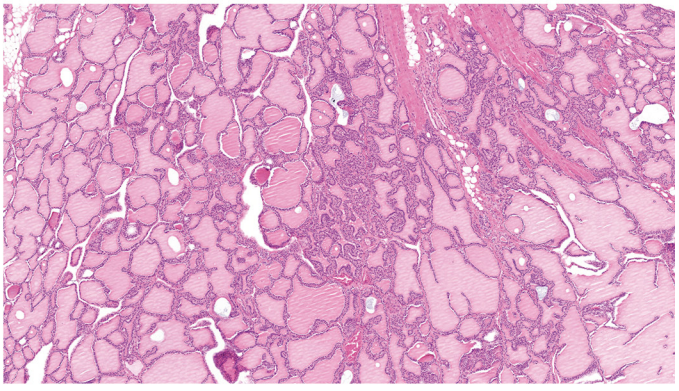

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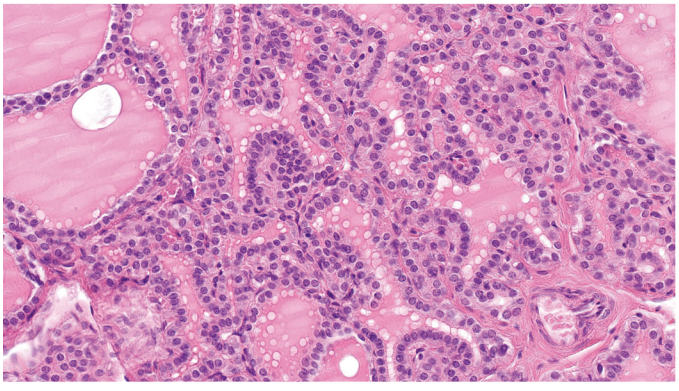

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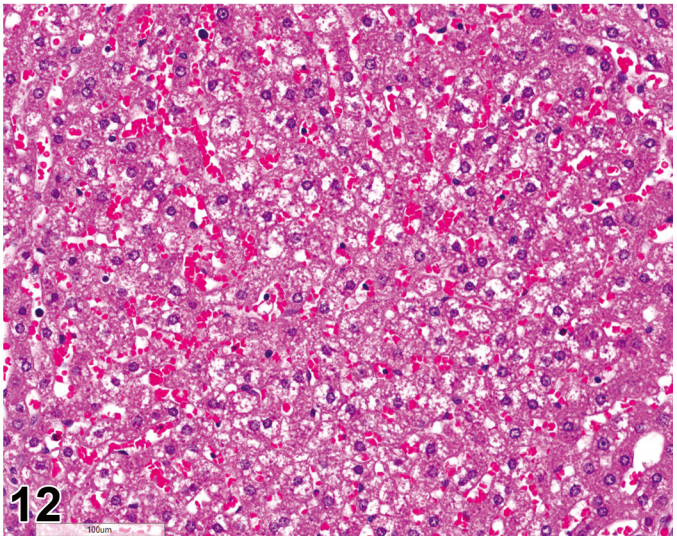
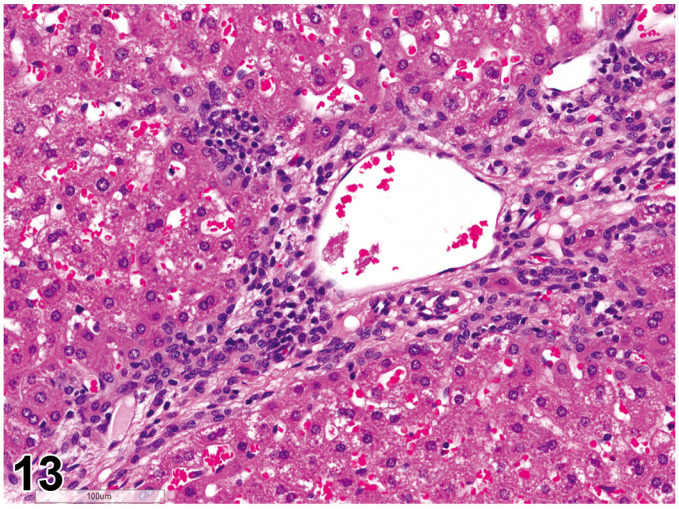
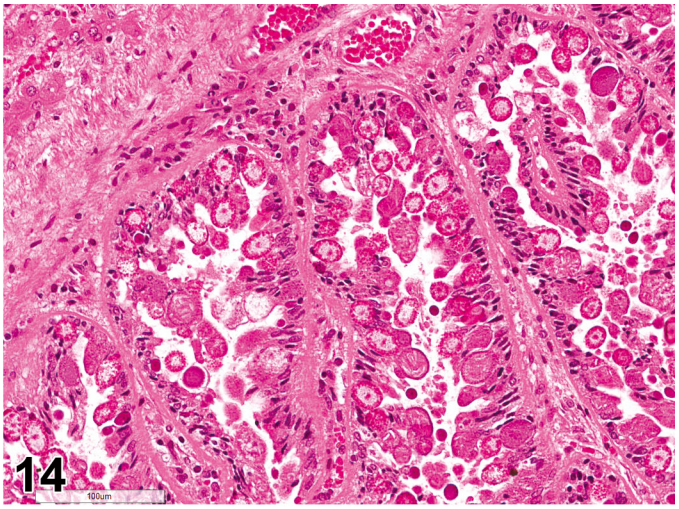
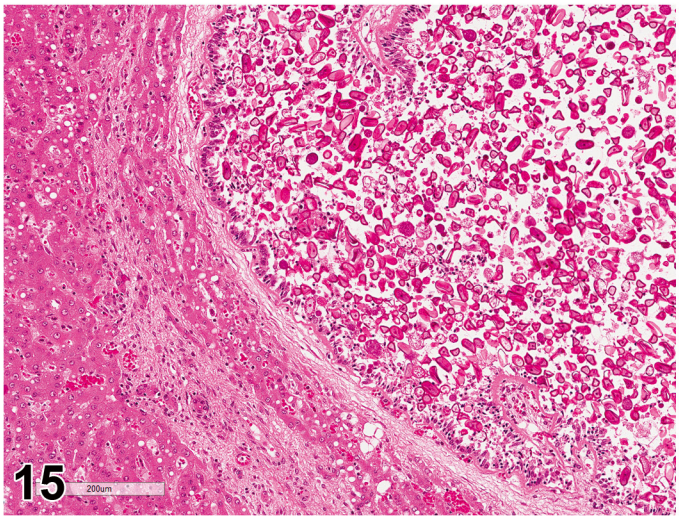
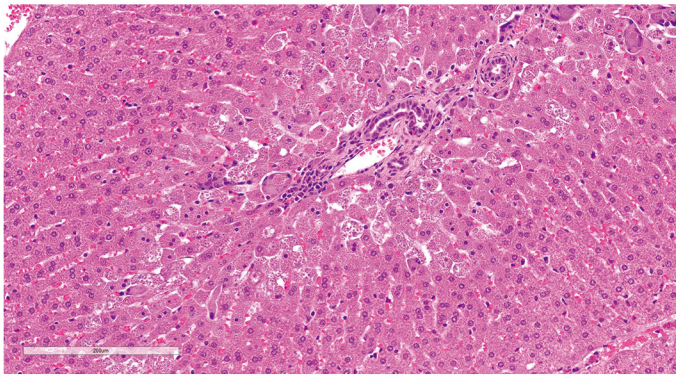


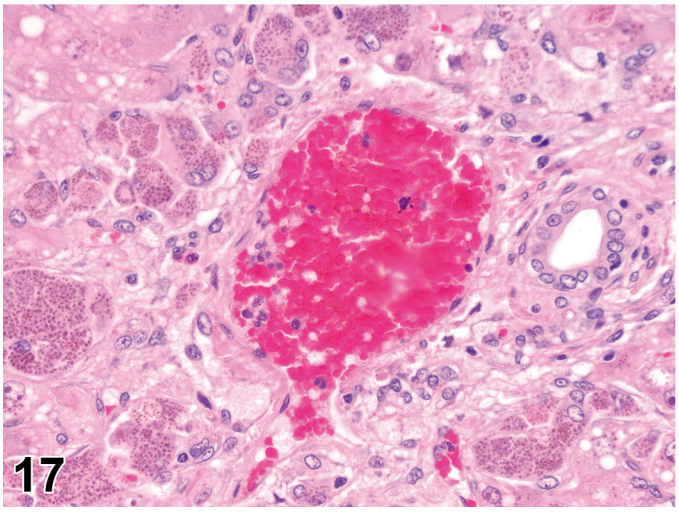
FIGURE 7.—Stomach, Cardioesophageal junction, H&E.
FIGURE 8.—Gastrointestinal tract, Parasite (*Eimeria*), H&E.
FIGURE 9.—Gastrointestinal tract, Parasite (*Eimeria*), H&E.
FIGURE 10.—Thyroid, Diffuse Hyperplasia, H&E.
FIGURE 11.—Thyroid, Diffuse Hyperplasia, H&E (high mag).
FIGURE 12.—Liver, Cytoplasmic alteration, H&E.











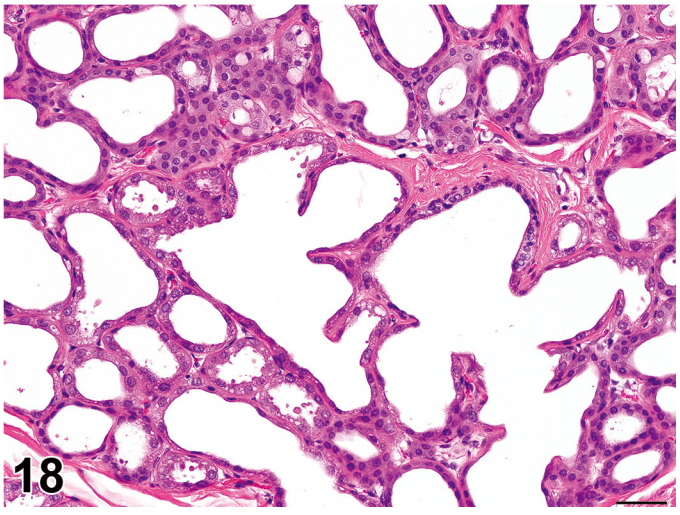
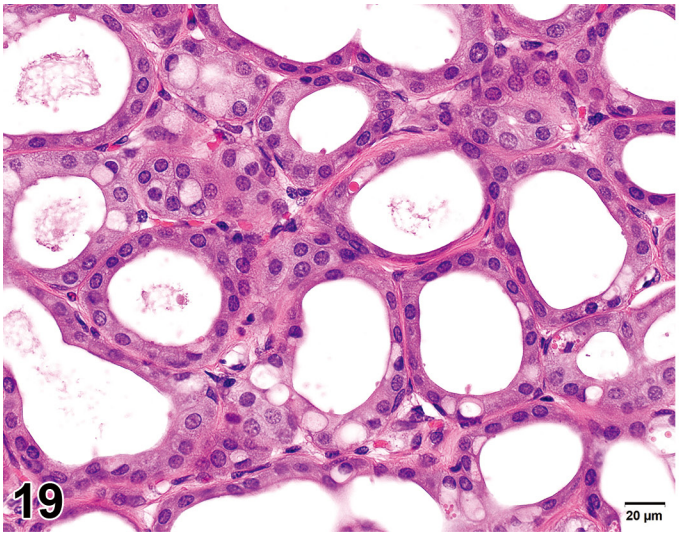
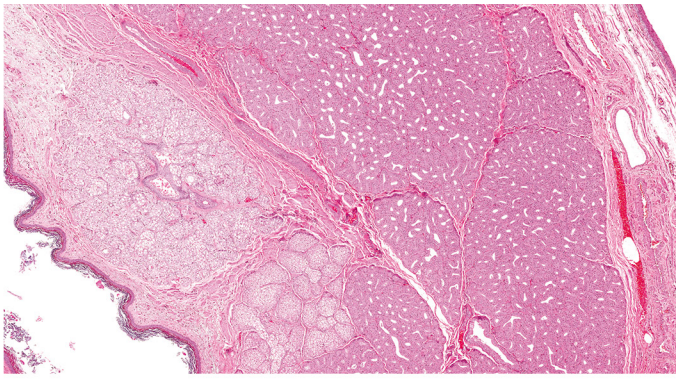
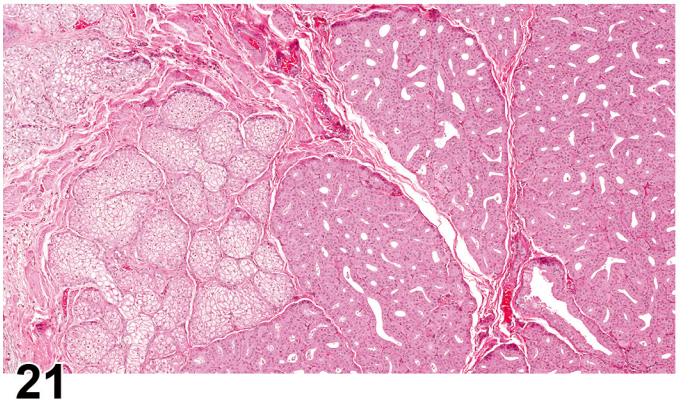
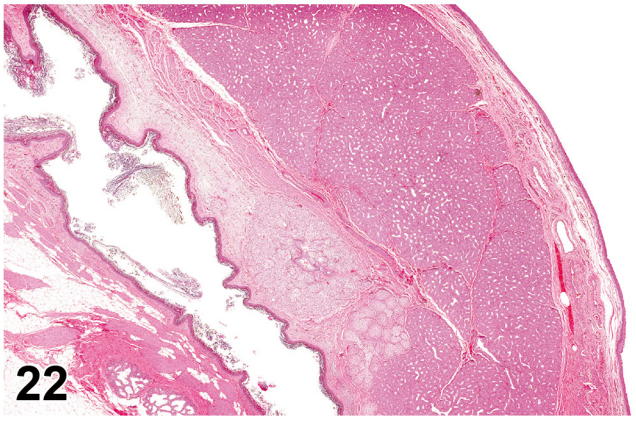


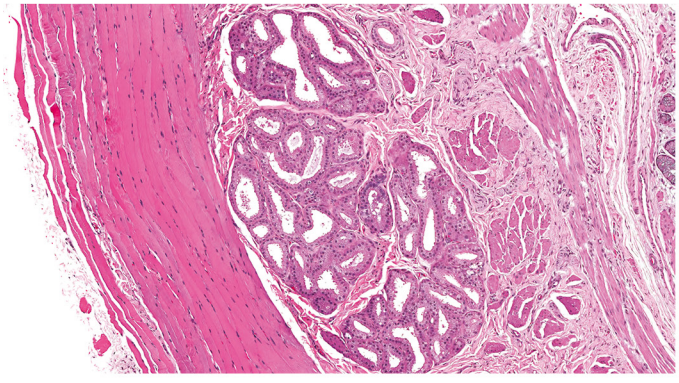
FIGURE 13.—Liver, Inflammation, liver periportal, H&E.
FIGURE 14.—Liver, Parasites (*Eimeria*), H&E.
FIGURE 15.—Liver, Parasite (*Eimeria*), H&E.
FIGURE 16.—Liver, Parasite (*Encephalitozoon*), H&E (Courtesy of Aaron Sargeant).
FIGURE 17.—Liver, Pigment (Liver toxicosis), H&E.
FIGURE 18.—Submandibular skin (mental) gland, H&E.











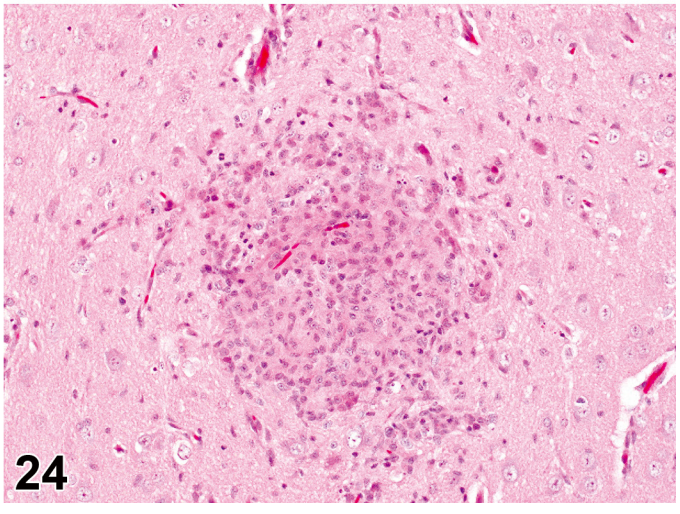
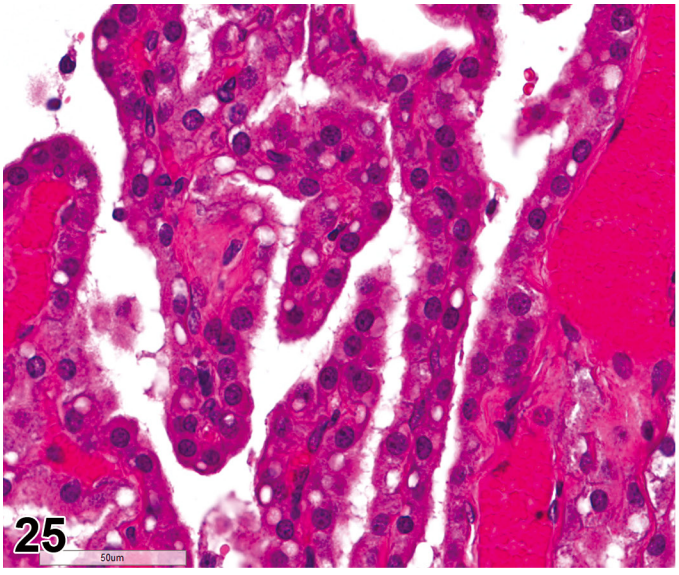
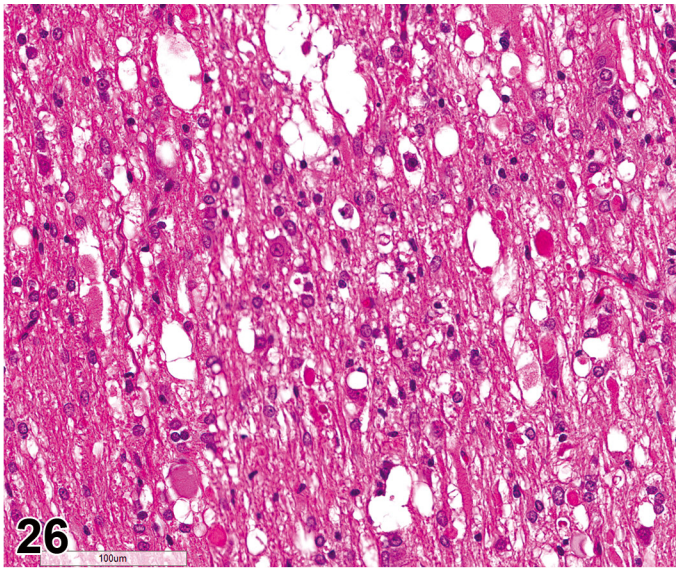
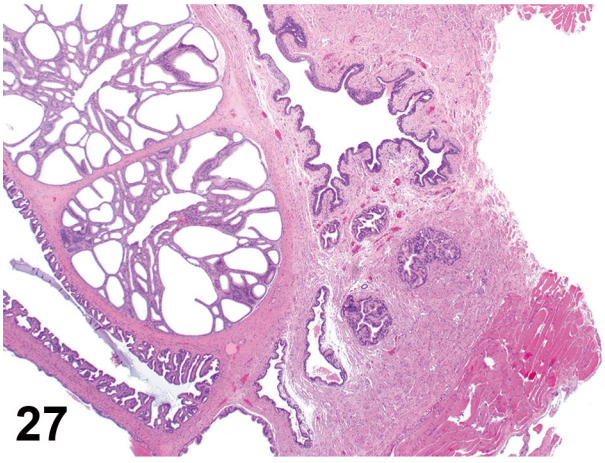
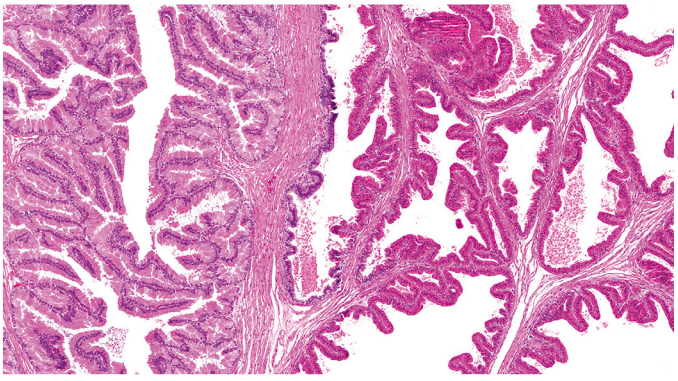


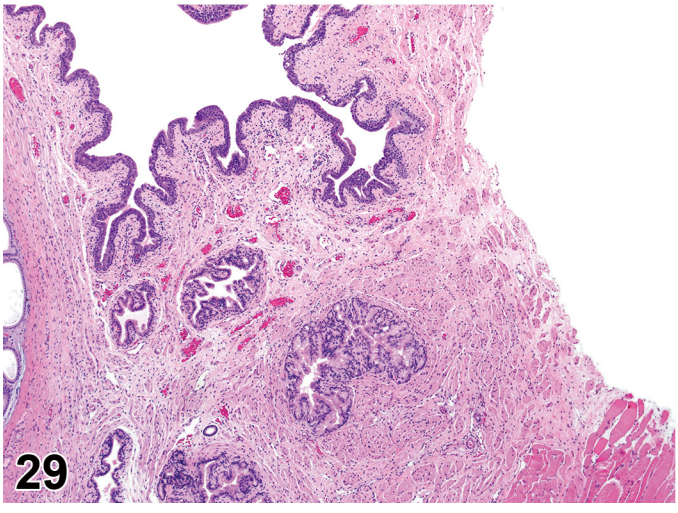
FIGURE 19.—Submandibular skin (mental gland), H&E (high mag).
FIGURE 20.—Inguinal gland complex: sebaceous (left), apocrine (right), H&E.
FIGURE 21.—Inguinal gland complex: sebaceous (left), apocrine (right), H&E (high mag).
FIGURE 22.—Female, Inguinal gland complex (apocrine), vagina, H&E (high mag).
FIGURE 23.—Rectum, Anal gland, H&E.
FIGURE 24.—Brain, Parasitic encephalitis, H&E.











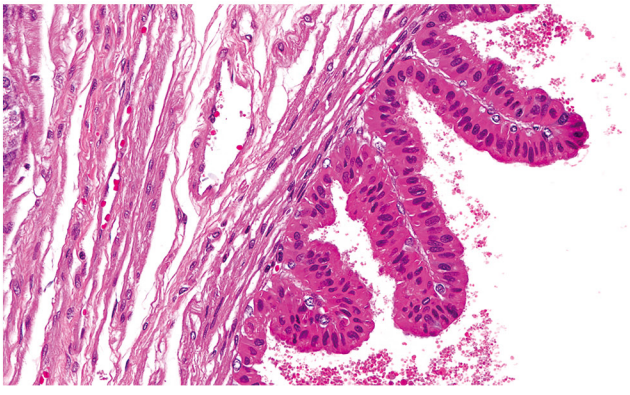
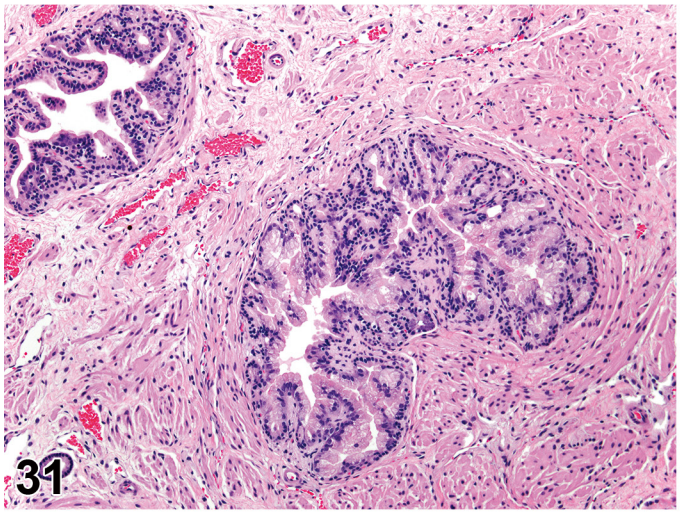
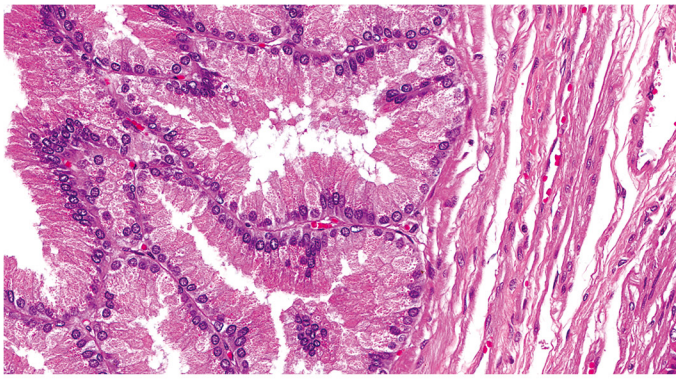
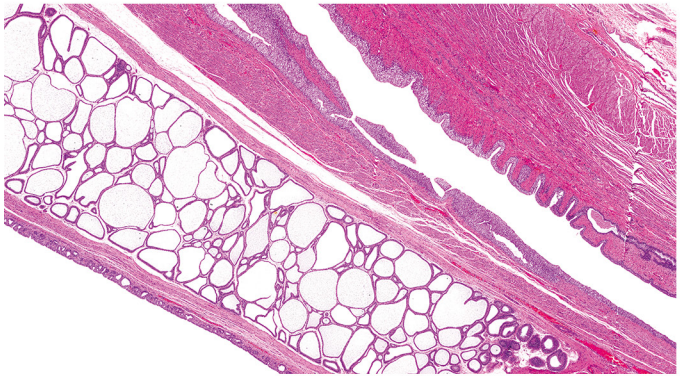
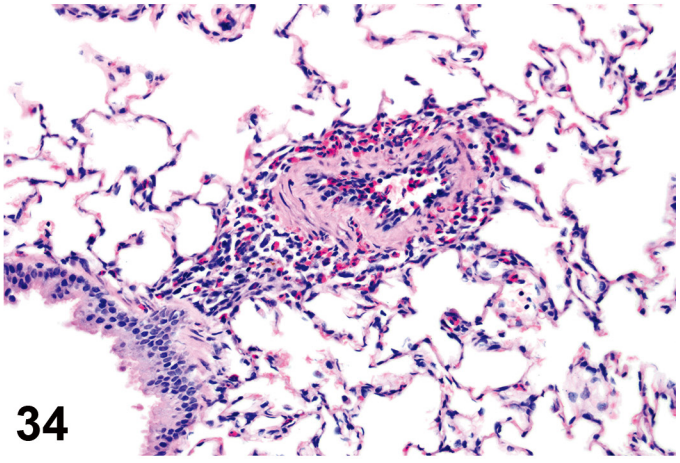


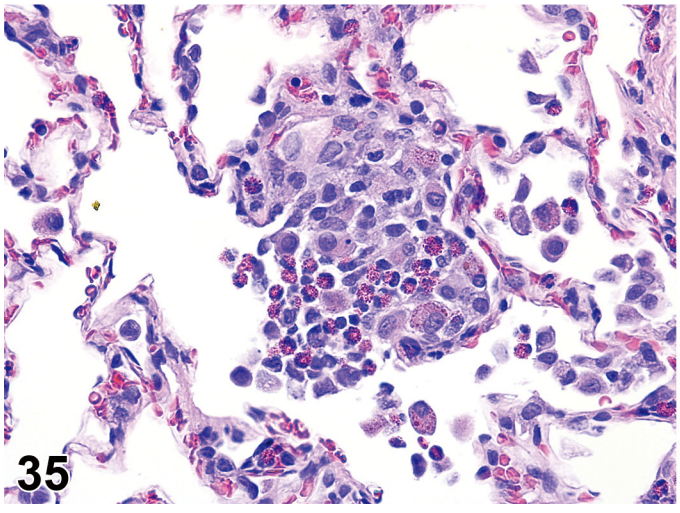
Figure 25.—Brain, Vacuolation, choroid plexus, H&E.
Figure 26.—Peripheral Nerve, Demyelinization fibres, H&E.
Figure 27.—Prostate, and associated glands, H&E.
Figure 28.—Prostate (left) and Proprostate (right), H&E.
Figure 29.—Proprostate, H&E.
Figure 30.—Proprostate, H&E.











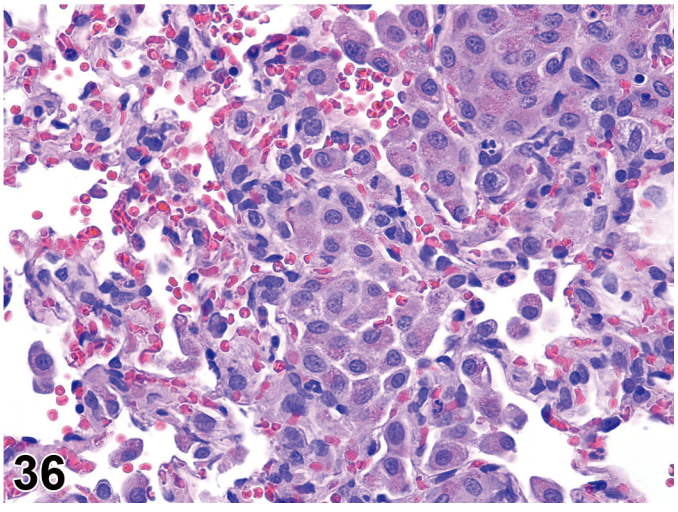
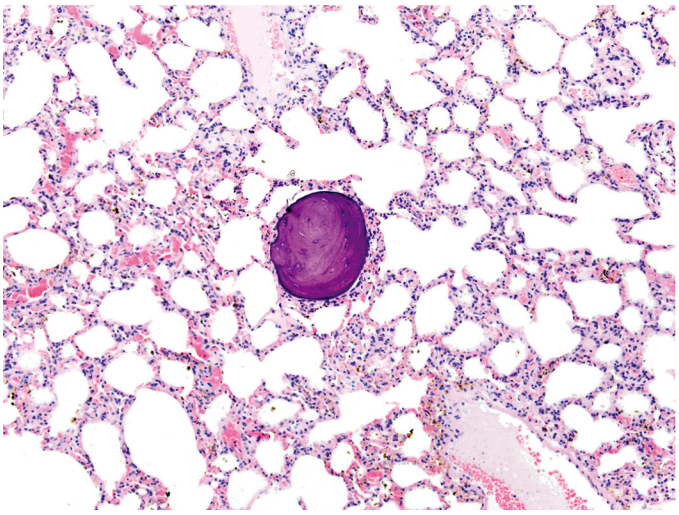
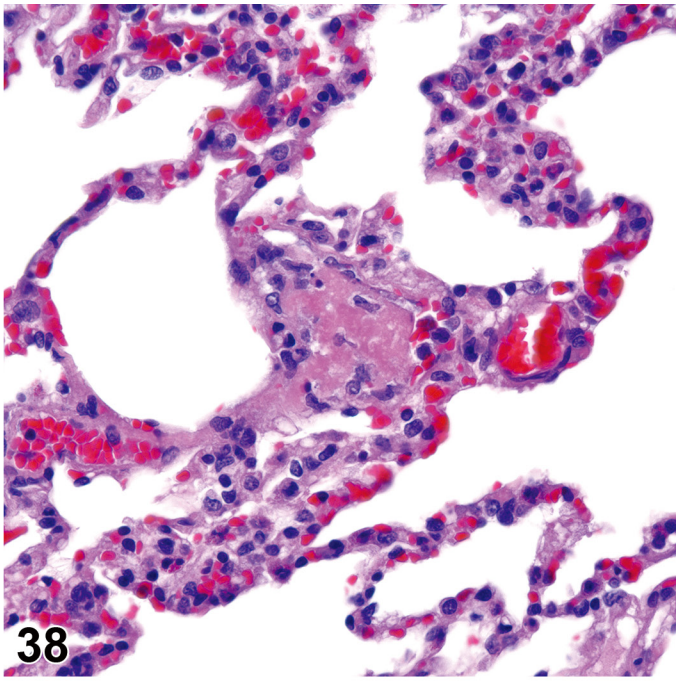
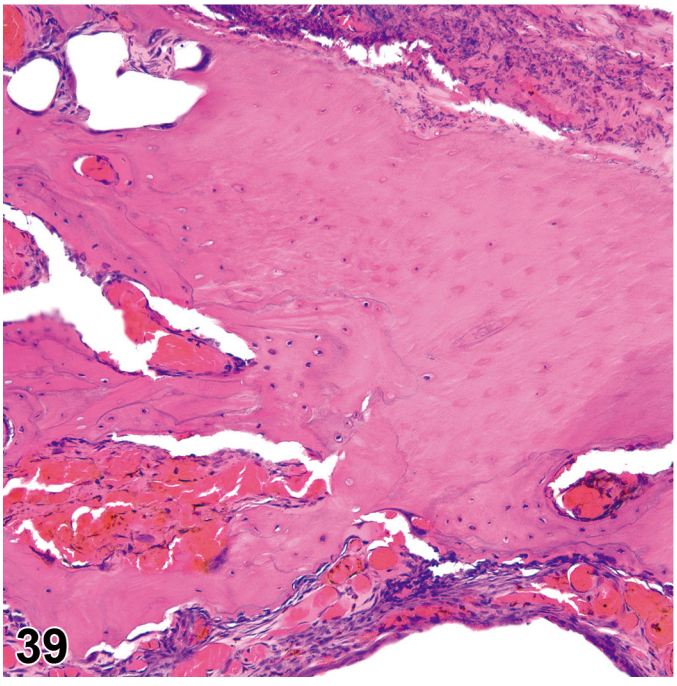


FIGURE 31.—Paraprostate, H&E.
FIGURE 32.—Prostate, H&E.
FIGURE 33.—from left to right: Seminal vesicle, Vas deferens, Ampulla, Urethra, H&E.
FIGURE 34.—Lung, Infiltrate, inflammatory cell, H&E.
FIGURE 35.—Lung, Infiltrate, heterophil, H&E.
FIGURE 36.—Lung, Macrophages increased, alveolar H&E.







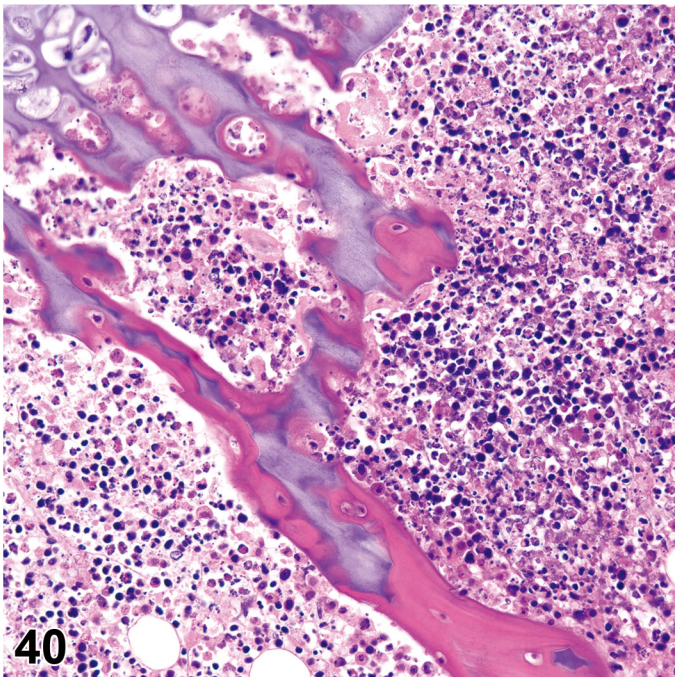
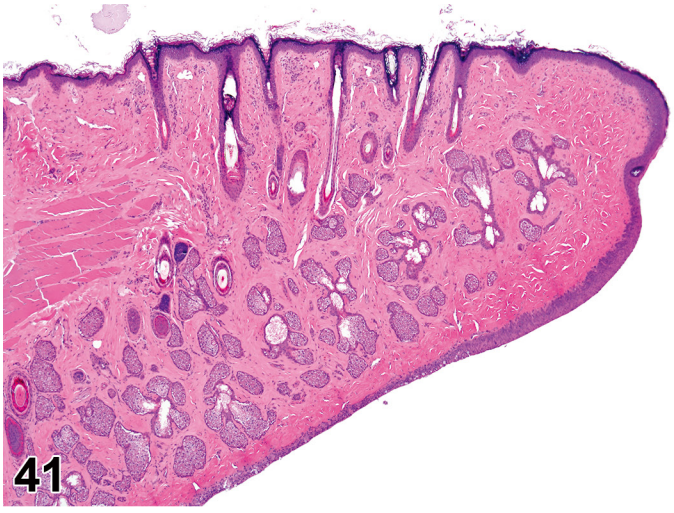
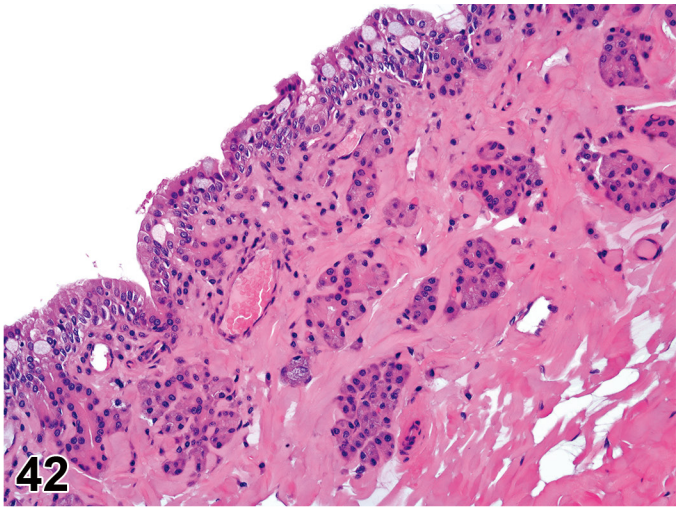
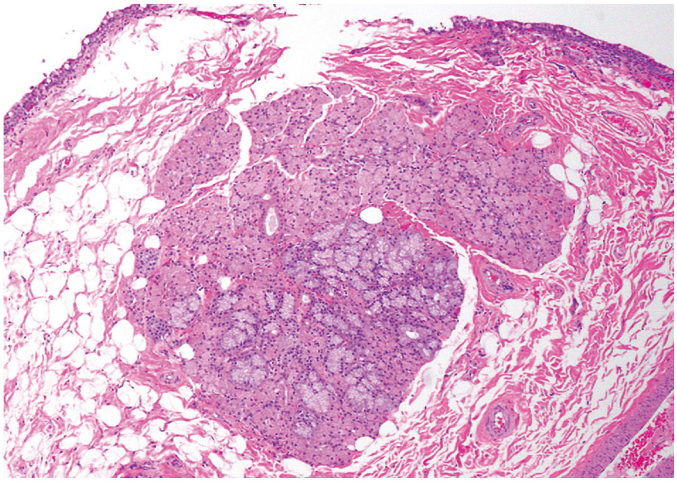
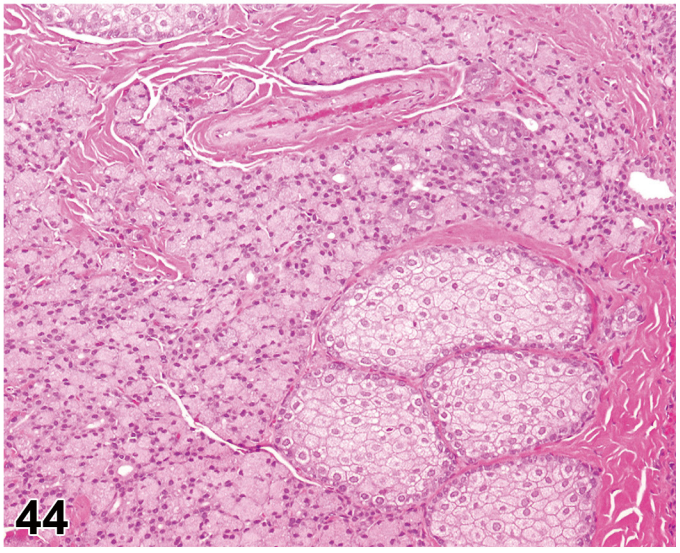


FIGURE 37.—Lung, Metaplasia, osseous, H&E.
FIGURE 38.—Lung, Thrombus, H&E.
FIGURE 39.—Bone, necrosis, H&E.
FIGURE 40.—Bone, Physeal necrosis, H&E.









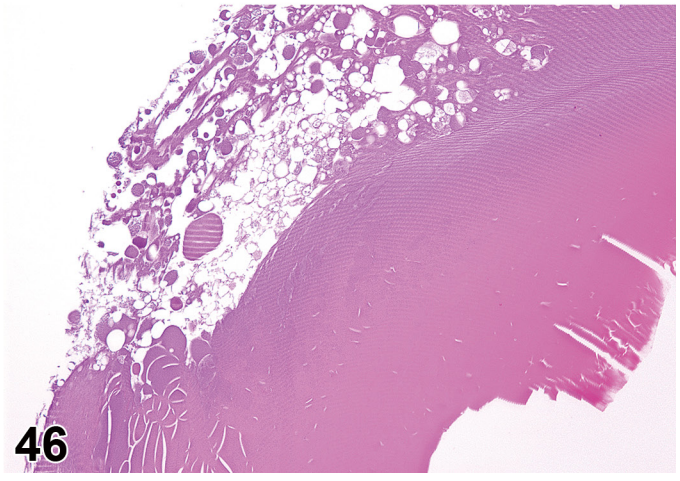
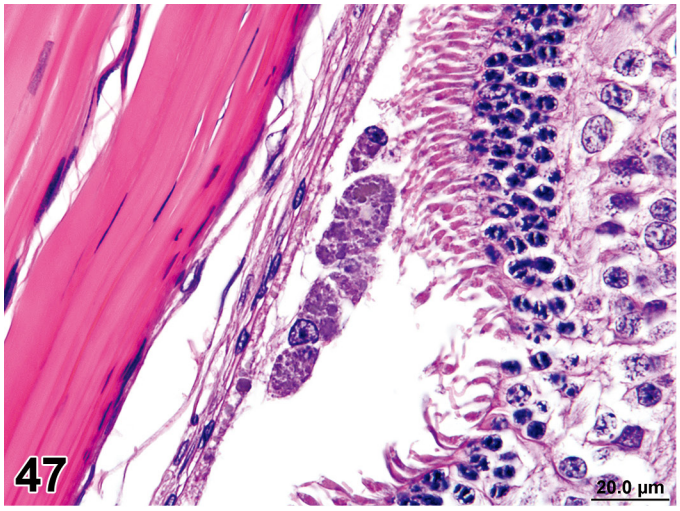
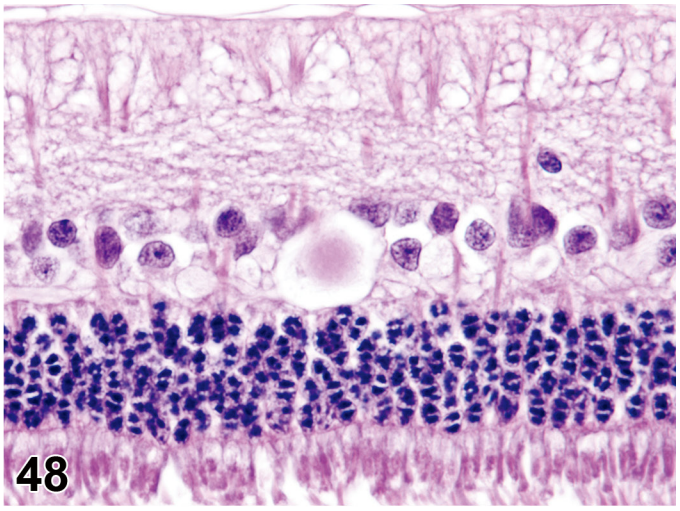
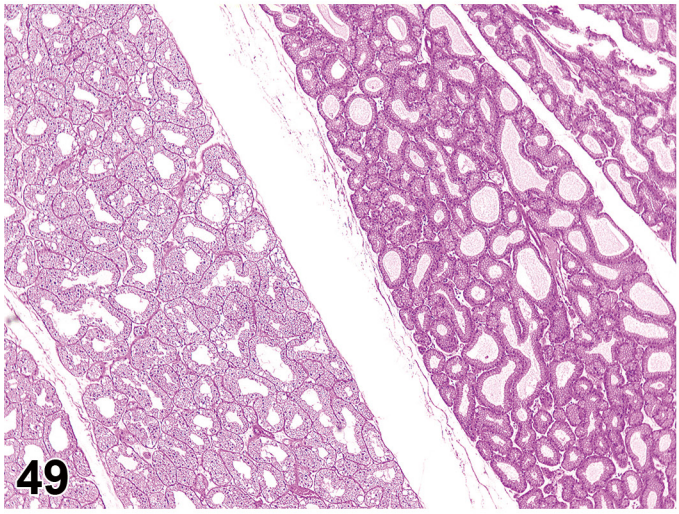
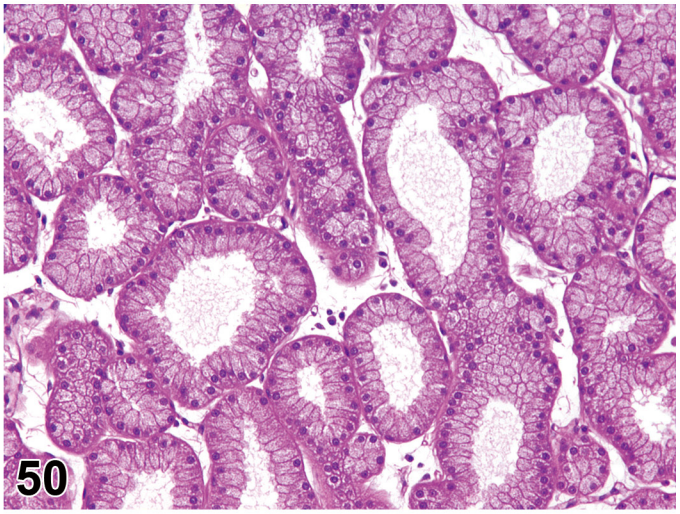


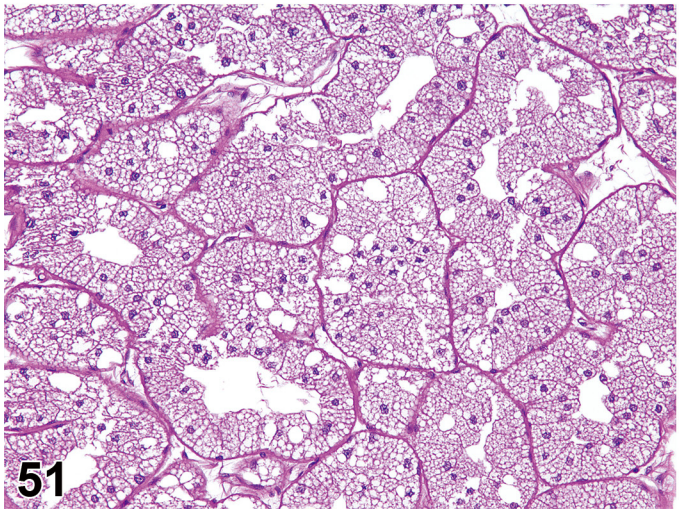
FIGURE 41.—Eyelid with Meibomian gland, H&E.
FIGURE 42.—Eyelid, accessory lacrimal gland (gland of Wolfring), H&E.
FIGURE 43.—Eyelid, accessory lacrimal gland (gland of Wolfring) Meibomian gland, H&E.
FIGURE 44.—Eyelid, accessory lacrimal gland (gland of Wolfring) and Meibomian gland, H&E (high mag).
FIGURE 45.—Eye, Ciliary Body, Ciliary Web, H&E.
FIGURE 46.—Eye, Degeneration lens fibre, H&E.











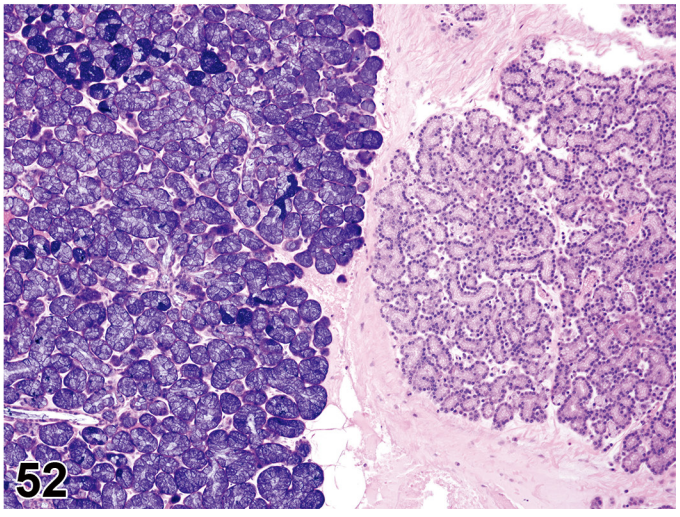
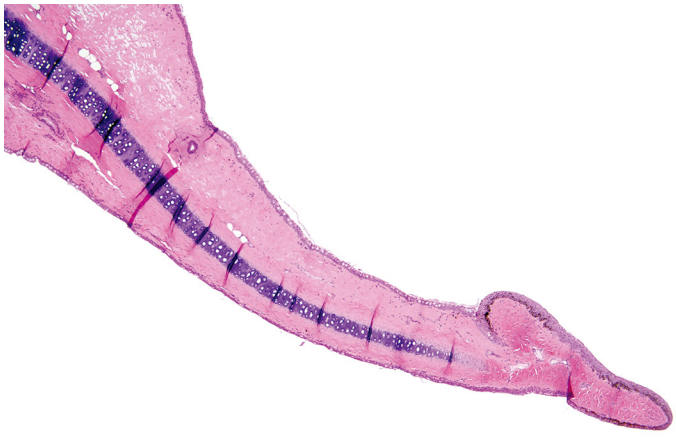
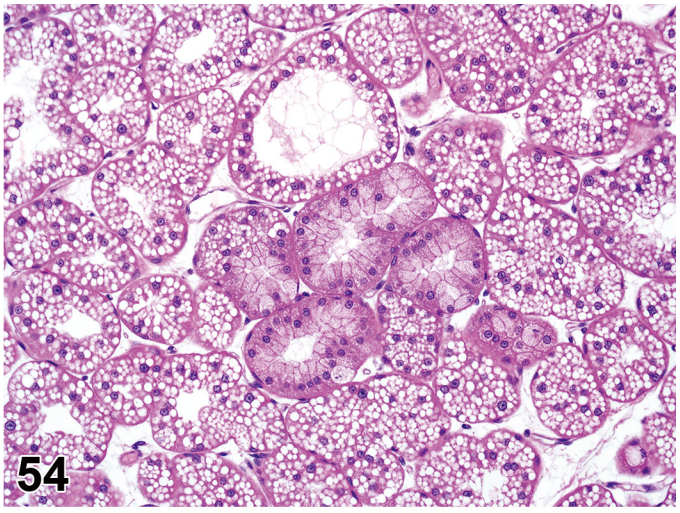
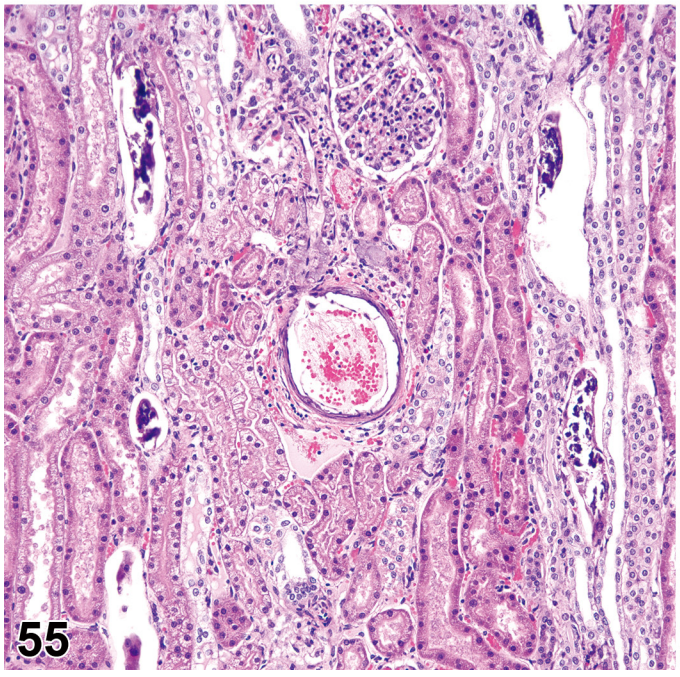


FIGURE 47.—Eye, Retina pigment epithelium, hypertrophy H&E.
FIGURE 48.—Eye, Eosinophilic bodies, retina, H&E.
FIGURE 49.—Harderian Gland, pink lobe (left) and white lobe (right), H&E.
FIGURE 50.—Harderian Gland, white lobe, H&E (high mag).
FIGURE 51.—Harderian Gland, pink lobe, H&E (high mag).
FIGURE 52.—Zygomatic salivary gland (left) and Lacrimal gland (right), H&E.







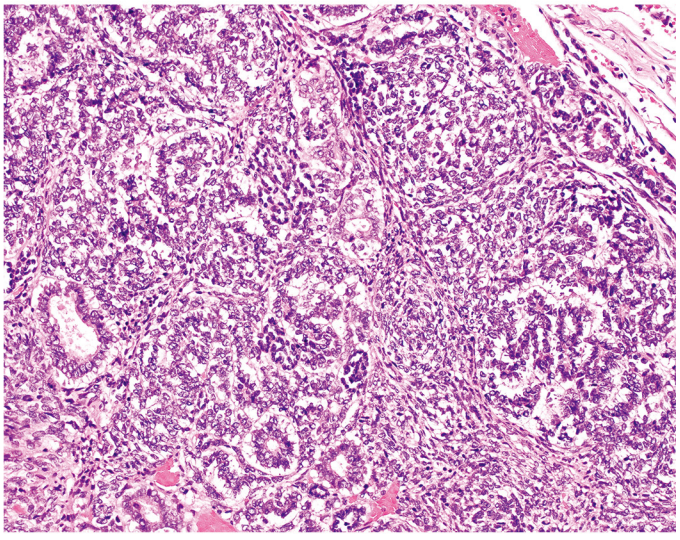


FIGURE 53.—Nictitating membrane, H&E.
FIGURE 54.—Harderian gland, Cytoplasmic alteration, H&E.
FIGURE 55.—Kidney, Renal mineralisation, H&E.
FIGURE 56.—Kidney, Nephroblastoma, H&E.

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