Table 5 – revised and updated from (Brayton 2006). Non neoplastic changes; brief definitions or descriptions of some conditions (phenotypes) that may be encountered in mice**.** This is not a complete list and glossary of all non neoplastic conditions that may occur spontaneously or be induced in mice. The information is derived primarily from resources used in the chapter. It is provided to facilitate understanding of terminology in the chapter, and is not an officially sanctioned glossary, dictionary or ontology. Terminology and definitions will continue to change as conditions are characterized further and as new conditions are induced.

SYSTEM Organ, condition; synonyms (historical terms)	
MULTISYSTEM	**i.e. generalized condition that involves multiple systems simultaneously, or condition that may occur in various systems or at various sites**
Amyloidosis Reactive AA Senile AApoAII	Amyloid deposition in mice can occur in many tissues including liver spleen, kidney, lung, heart, parotid, gland, adrenal gland, thyroid, esophagus, skin, stomach small and large intestines. With H&E, amyloid is homogeneous eosinophilic amorphous extracellular material. It stains positively with crystal violet, Congo red and thioflavine T stains. In Congo red – stained section exposed to polarized light, amyloid should demonstrate green birefringence. Intestinal amyloid deposition is in lamina propria and submucosa, with ileum usually affected earliest most severely. Renal amyloid occurs primarily in glomerular mesangium, but may be interstitial especially around collecting tubules in papilla. Splenic amyloid occurs primarily in marginal zones around follicles. Lymph node involvement is primarily of mesenteric nodes with amyloid deposits at periphery in subcapsular sinuses. Hepatic amyloid occurs first around portal veins and then in perisinusoidal spaces of Disse. Cardiac amyloid spreads from around capillaries. Pulmonary amyloid deposition is in septa. Adrenal amyloid deposits are primarily in the inner cortex surrounding the medulla. Parotid gland interstitial amyloid deposition may separate acini Thyroid and parathyroid glands can have interstitial amyloid deposition. (Frith et al. 1991; Higuchi et al. 1991; Hogen-Esch et al. 1996) *Nasal 'amyloid' probably is not amyloid (usually).* (Haines et al. 2001; Doi et al. 2007)
Amyloidosis, reactive AA	AA-amyloid has a predilection for spleen, liver, gut and kidney, and often is associated with chronic inflammatory conditions.(Frith et al. 1991; Higuchi et al. 1991; Hogen-Esch et al. 1996)
Amyloidosis, senile AApoAII	Masses of amyloid in lung, heart and ileum suggest AApoAII. Senile amyloid exclusively is likely to be found in gonads, papillary dermis, epineurium, and lung.(Frith et al. 1991; Higuchi et al. 1991; Hogen-Esch et al. 1996)
Amyloidosis, systemic	Maita et al. 1998 defined the term for their study as amyloidosis involving 3 or more different organs or tissues. Thyroid, adrenal,

	kidney small, intestine, ovary were predilection sites in this study.
Arteritis; polyarteritis; systemic arteritis; (periarteritis)	Inflammation of arteries. See above (MULTISYSTEM) Small-medium muscular arteries, usually in multiple sites, have medial thickening with variable deposition of eosinophilic material, and have mild-marked perivascular fibrosis and predominantly lymphocytic, mononuclear infiltration. There may be early fibrinoid necrosis or thrombi. Common sites include heart, thymus, tongue, uterus, testes, mesentery, kidney and urinary bladder. (Frith et al. 1988; Faccini et al. 1990; Plendl et al. 1996; Elwell et al. 1999) Maita et al. 1988 defined systemic arteritis as arteritis involving 3 or more different organs or tissues. Thymus ovary, uterus, kidney, heart, were predilection sites in this study, and thrombosis frequently was associated with the lesions.
Angiectasis	Marked dilatation of vascular channels (veins, sinusoids or lymphatics). The lesion can occur in any organ but most commonly involves the spleen, ovary, liver or lymph nodes. It may be difficult to distinguish from hemangioma with angiectatic areas, but the lining endothelial cells should be normal in size and morphology. (Frith et al. 1988; Plendl et al. 1996; Elwell et al. 1999; Harada et al. 1999)
Choristoma, lipomatous hamartoma	Similar to hamartoma, including the mass lesion requirement, but unlike hamartoma, includes heterotopic tissue of an adult or embryonic nature (topographical and developmental anomaly) Pathbase 2004 They are soft, raised masses on the dorsal midline, primarily above the sutures of the skull. They may be noticed because of abnormally long hair, change in direction of the hairs, or change in hair color compared. Microscopically, the masses consist of normal adipose tissue in the reticular dermis and subcutis that sometimes extends through the cranial sutures, entering the brain, or expanding into the ventricles. Large masses may contain normal appearing thyroid, intestine, respiratory epithelium lined cysts, squamous epithelial cysts, bone and marrow, cartilage, glands, and angiomatous anomalies. Overlying epidermis is intact.. This condition resembles "lipomatous" hamartomas, a congenital defect in human beings. (Adkison et al. 1991)
Hyalinosis	Epithelial cytoplasmic eosinophilic change. It may be especially common in in 129-related mice including B6;129 mice, but similar changes have been recognized in B6 and other strains. The material, which may be intracytoplasmic or extracellular as hyaline acidophilic material or as needle shaped, rectangular or square crystals, has been identified as a chitinase. Affected tissues can include **lung**, in which the condition is known as acidophilic macrophage or acidophilic crystalline pneumonia, **nasal mucosa, trachea, lung, stomach, gall bladder, bile ducts**. (Ward et al. 2000; Ward et al. 2001) See additional details in discussion above or listed by organ below.
Inflammation; lymphocytic infiltrates	Mild inflammatory cell infiltrates, especially lymphocytic foci, may occur in various tissues in aging mice, in the absence of discernible inciting agents. Frequently these are interstitial, perivascular or periductal depending on the tissue. Affected tissues may include: Harderian glands, salivary glands, nasal cavity, trachea, lung, gall bladder, hepatic portal areas, glandular stomach, thyroid, kidney, urinary bladder, prostate gland. (Radovsky et al. 1999; Ward et al. 2000; Haines et al. 2001)
Melanosis	Melanin pigment can be found in various tissues, other than skin, hair follicles and retinal pigmented epithelium. Because it is considered to be a normal finding, it is not reported in some studies. Commonly affected tissues include; spleen, heart valves, meninges, choroid plexus, parathyroid. (Ward et al. 2000; Haines et al. 2001)
Mineralization	Especially in **DBA –**related mice, dystrophic calcification or mineralization is likely to occur in various tissues especially in the heart but also in aorta, testes, tongue, skeletal muscle, cornea, kidney, stomach, small intestine, ovary with incidence and severity increasing with age and without apparent sex differences (in non-gonadal tissues). (Rings et al. 1972; Maeda et al. 1986; Yamate et al. 1987; Yamate et al. 1990) In **BALB/c** and **C3H**-related mice mineralization is most common in the heart and cornea.(Van

	Winkle et al. 1986) (Frith et al. 1983; Everitt et al. 1988; Vargas et al. 1996) Extracardiac soft tissue mineralization also may occur in C3H mice.(Highman et al. 1951) In most other strains, soft tissue mineralization is unusual.(Elwell et al. 1999)
ALIMENTARY	
Esophagus, dilatation; megaesophagus	Dilatation of the esophagus. Dilatation usually is of the thoracic esophagus, visible at necropsy, with apparent impaction by ingested material. The condition may be a contributory cause of death in some cases. (Ward et al. 2000; Haines et al. 2001) In some strains (ICRC) megaesophagus has been associated with the presence of smooth muscle instead of (normal) skeletal muscle in the distal esophagus. (Randelia et al. 1988; Randelia et al. 1990)
Gall bladder; inflammation	See above (MULTISYSTEM)
Gall bladder; hyalinosis	See above (MULTISYSTEM) Gall bladders with hyalinosis may be grossly enlarged with thickened opaque walls. Extracellular crystals (identified as chitinase), when present, tend to be large and rectangular to square. Affected bile ducts had associated mucoid metaplasia and fibrosis. The acidophilic hyaline or crystalline material has been identified as a chitinase. (Ward et al. 2000; Ward et al. 2001)
Intestine, amyloidosis	See above (MULTISYSTEM) Amyloid deposition is in the lamina propria of the small intestine, especially in the ileum. (Frith et al. 1991; Higuchi et al. 1991; Hogen-Esch et al. 1996)
Liver, amyloidosis	See above (MULTISYSTEM) Amyloid deposition is in sinusoids beneath the sinusoidal-lining cells, is distinctly homogeneous and eosinophilic. (Frith et al. 1991; Higuchi et al. 1991; Hogen-Esch et al. 1996)
Liver, angiectasis; telangiectasis, peliosis hepatis	See above (MULTISYSTEM) Hepatic angiectasis involves dilatation of the vascular sinusoids and may be either focal or diffuse. Angiectasis may be difficult to distinguish from hemangioma. In angiectasis, the vascular spaces are dilated and prominent and their lining endothelial cells are normal in appearance, number and size. (Frith et al. 1988; Harada et al. 1999)
Liver, centrilobular hypertrophy	Enlargement of centrilobular hepatocytes, with increased amount and variable staining characteristics of cytoplasm, with gradual decrease in cell size closer to portal areas. It is especially likely in studies of toxicants that induce proliferation of peroxisomes or of smooth endoplasmic reticulum. (Harada et al. 1999)
Liver, centrilobular necrosis hepatocyte	Centrilobular hepatocellular necrosis can occur with ischemia or chronic passive congestion, and is seen in FVB mice believed to have died after severe or prolonged seizures. (Goelz et al. 1998)
Liver, extramedullary hematopoiesis (EMH)	EMH occurs normally in fetal and neonatal mouse liver. In the adult mouse it may be secondary to infectious disease or neoplasia. Small foci or nests of immature granulocytes, nucleated erythrocytes or megakaryocytes are scattered in sinusoids. Granulopoietic foci may be primarily periportal. Megakaryocytes and nucleated erythrocytes help to distinguish EMH from inflammation and leukemia or lymphoma. (Frith et al. 1988; Harada et al. 1999)
Liver, foci of cellular alteration; altered hepatocellular foci	Altered staining qualities and textural appearance of the cytoplasm and size of hepatocytes, compared to adjacent normal hepatocytes. There is no obvious disruption of the liver architecture, nor compression of adjacent normal parenchyma. They may be classified as eosinophilic, basophilic, clear cell, or mixed. They are much more common in carcinogen treated than in control mice, and are more common in male than in female mice. Clear cell foci consist of cells with pale or sometimes lacy cytoplasm that stain with PAS stain prior to but not after diastase digestion, suggesting the presence of glycogen. Their nuclei tend to be central rather than flattened against the cell membrane as

	in lipid-vacuolated cells. Eosinophilic foci consist of cells that tend to be larger than adjacent normal hepatocytes with eosinophilia due to increased cytoplasmic mitochondria and/or smooth endoplasmic reticulum. Basophilic foci consist of cells that tend to be smaller than adjacent normal hepatocytes with basophilia due to relatively increased cytoplasmic free ribosomes and rough endoplasmic reticulum. Mixed cell foci contain varying proportions of 2 or more of any of the cell types. (Frith et al. 1979; Harada et al. 1996; Harada et al. 1999)
Liver; inflammation	See above (MULTISYSTEM:) Foci of acute and or chronic inflammatory cells (primarily lymphocytes) distributed randomly and sporadically. Mild chronic inflammation characterized by random and or portal or perivascular primarily lymphocytic infiltrates. Some of these cases may be attributable to helicobacter or other infections. (Harada et al. 1996; Harada et al. 1999; Ward et al. 2000)
Liver, necrosis hepatocytes	Focal necrosis may be an incidental finding of unknown etiology, or may be related to infections (MHV, Clostridium piliforme, helicobacters), toxicants. It may involve single cells, single or multiple lobules, and it may vary in distribution. Coagulation necrosis with hypereosinophilic cytoplasm and pyknotic or absent nuclei is the typical morphologic feature, and can be common in some studies. (Harada et al. 1996; Harada et al. 1999; Ward et al. 2000)
Liver, hepatocellular inclusions	Distinctive round eosinophilic intranuclear inclusions in hepatocytes may nearly fill the nucleus. Their incidence increases with age and they are considered to be invaginations of the cytoplasm into the nucleus. Intracytoplasmic inclusions are less common and may occur near neoplasms, and may consist of condensed secretory proteins in dilated cisternae of rough endoplasmic reticulum. (Frith et al. 1979; Harada et al. 1996; Harada et al. 1999)
Liver, hepatocellular vacuolization, steatosis, (fatty change, fatty metamorphosis)	Hepatocellular vacuolization due to fatty change is especially common in old obese controls and is more common in male than in female mice. It also may occur in response to a toxicant. Initially there is usually a centrilobular distribution. The empty clear vacuoles peripherally compress nuclei, and represent lipid that was removed during tissue processing. The lipid nature can be confirmed by staining frozen sections with Oil Red O or Sudan Black B. Frith and Ward, 1988; Harada et al. 1996)
Liver, hepatocyte karyomegaly, cytomegaly; polyploidy	Hepatocellular anisocytosis and anisokaryosis, with enlarged cells and nuclei increase with age, and in response to various agents. There may be binucleate or multinucleate hepatocytes. The increase in nucleus size or number is associated with polyploidy.(Frith et al. 1988; Lu et al. 1993; Styles 1993) Premature polyploidy occurs in some mutant mice with defective DNA repair mechanisms. (Chipchase et al. 2003)
Pancreas, exocrine atrophy	Focal or lobular change resulting in complete absence of acini, or only few small acini with pale exocrine cells due to reduced zymogen granules, and normal islets of Langerhan suspended in fatty stroma. Its occurrence only in aged mice suggests that it is a true atrophy and not a hypoplasia. (Frith et al. 1988; Faccini et al. 1990; Boorman et al. 1991)
Pancreas, inflammation, chronic	See above (MULTISYSTEM) Mild chronic lymphocytic interstitial infiltrates in the exocrine pancreas.
Salivary gland, amyloidosis	See above (MULTISYSTEM) Salivary glands may develop amyloidosis. The parotid glands are serous glands that extend from the base of the ears ventrally and posteriorly. With severe amyloidosis acini may be widely separated by amorphous acidophilic

	material, with histochemical (staining) properties of amyloid. (West et al. 1965; Sashima et al. 1990)
Salivary gland, ductal hyperplasia	Ductal hyperplasia usually is associated with lobular acinar atrophy and is more common in the submaxillary and parotid salivary glands than in the sublingual gland. The lesion typically involves a single lobule in which some acini are atrophied and replaced by hyperplastic ducts, and there may be associated inflammatory infiltrates. (Frith et al. 1988; Botts et al. 1999; Seely 1999; Ward et al. 2000)
Salivary, gland inflammation	See above (MULTISYSTEM) This typically is chronic lymphocytic or lymphoplasmacytic interstitial, perivascular or periductular inflammation, and may be more common in male than in female mice. (Frith et al. 1988; Faccini et al. 1990; Botts et al. 1999)
Stomach, forestomach; squamous epithelial hyperplasia	Increased thickness of squamous mucosa due to hyperplasia of stratified squamous epithelium, usually with hyperkeratosis, and likely to occur after administration of irritants. (Frith et al. 1988; Leininger et al. 1999)
Stomach, fundic mucosal hyperplasia, gastric hyperplasia; adenomatous hyperplasia	Increased thickness of glandular mucosa due to hyperplasia with increased pit and gland length. Pits become elongated and more basophilic. There may be mucosal folding but gland architecture is retained. Epithelial cells may be enlarged, hypertrophied. Severe cases may have herniation of glands into muscularis mucosae, but basement membrane is not penetrated. (Betton et al. 2001)
Stomach, glandular hyperplasia, plaque	Gastric plaque has been used to refer to foci of glandular hyperplasia associated with gastric hyalinosis in 129S4/SvJae and related mice. They are most common in the cardiac glandular stomach at or near the limiting ridge. Grossly discernible areas of plaque like thickening, sometimes with hemorrhage are periesophageal. Histologically glands are elongated, hyperplastic, and may be focally disorganized with loss of normal differentiation patterns. The plaques contain foci of hyalinized epithelial cells that seemed to arise from chief cells in the mid-region of the glands. Some epithelial cells contain only a few intracytoplasmic droplets, or cells may be distended with nuclei displaced peripherally by brightly eosinophilic material. Glandular lumina may contain abundant extracellular rectangular eosinophilic crystals, as opposed to needle-shaped or square crystals. They are metachromatic with Dominici stain as are the hyaline granules within epithelial cells. The eosinophilic hyaline and crystalline material has been identified as a chitinase. (Haines et al. 2001; Ward et al. 2001)
Stomach, gastric hyalinosis	Eosinophilic cytoplasmic degenerative change, termed hyalinosis, is most common in the cardiac glandular stomach at or near the limiting ridge, and frequently is associated with plaque like thickening. See above. Haines, Chattopadhyay et al. 2001; Ward, Yoon et al. 2001)
Teeth, alveolitis, periodontitis, periodontal disease	Inflammation in the dental alveolus (tooth socket) or around the tooth. In mice the disease is most sever in the maxillary arch. It can begin as gingivitis initiated by hair impaction, plaque or calculus, and can progress to severe inflammatory changes with resorption of tooth and alveolar bone. (Losco 1995; Long et al. 1999)
Teeth, dental dysplasia	Abnormal development or malformations of injured and or displaced odontogenic tissues; may be used to refer to the spectrum of non-neoplastic incisor malformations involving the tooth and periodontal structures. Histologically there can be mild cystic changes in the developing portions of the incisors or the tooth may be replaced and socket filled and expanded irregular masses of dentin-like material with fragments of tooth and bone. . (Losco 1995; Long et al. 1999; Ward et al. 2000)
Teeth, malocclusion	Malocclusion in mice ultimately manifests as long maxillary incisors that grow out from and curl back into the maxilla, and long mandibular incisors that tend to grow upwards from the mandible. Mice with this condition cannot eat hard pelleted chow.

	Trauma and genetics have been implicated in this condition. (Losco 1995; Long et al. 1999; JaxNotes 2003)
CARDIOVASCULAR	
Heart, cardiomyopathy	Foci of myocardial necrosis or myocyte degeneration (myocytolysis) with minimal to mild mononuclear infiltration by, with or without fibrosis, which may be more common in the left ventricle. (Plendl et al. 1996; Price et al. 1996) Some authors include mineralization in this definition, e.g. in BALB/c mice. Some authors may use 'myocardial necrosis, inflammation, fibrosis'. (Frith et al. 1988; Faccini et al. 1990)
Heart, coronary arteritis	Arteritis/polyarteritis involving coronary arteries. See above, MULTISYSTEM.
Heart, melanosis valves	See above, MULTISYSTEM.
Heart, mineralization (dystrophic cardiac calcinosis, epicardial mineralization)	See above, MULTISYSTEM. In BALB/c and related mice mineralization is epicardial, on the right ventricular free wall.(Frith et al. 1983) Mineralization, may be associated with degenerative changes especially in female C3H mice, and involves myocardium. (Frith et al. 1983; Everitt et al. 1988; Vargas et al. 1996) In DBA mice mineralization is myocardial and epicardial and there may be mineralization of other soft tissues, e.g. tongue, testes, aorta. (Yamate et al. 1987; Brunnert et al. 1999) Mineralized foci are basophilic with hematoxylin and eosin (H & E), black with von Kossa, and red with Alizarin Red staining. (Frith et al. 1988; Maita et al. 1988)
Heart, thrombi	Thrombi are usually in the left atrium, which may be enlarged and red. The degree of organization depends on the age of the thrombus. Some thrombi may contain foci of cartilaginous metaplasia. With large thrombi there may be secondary chronic passive congestion. Thrombosis may be associated with uremia and kidney disease, including amyloidosis, may not be associated with arteritis, and may be more common in males. (Frith et al. 1983; Frith et al. 1988; Maita et al. 1988; Faccini et al. 1990; Elwell et al. 1999) In some cases both atria may be involved or there may be ventricular thrombi. (Hagiwara et al. 1996)
Vessels, angiectasis	Marked dilatation of small vessels. See above (MULTISYSTEM).
Vessels, arteritis;	Inflammation of arteries. See above (MULTISYSTEM) Also called polyarteritis; systemic arteritis; periarteritis
ENDOCRINE	
Adrenal cortex, accessory cortical nodule	Small nodules of adrenal cortical cells surrounded by a connective tissue capsule are sometimes associated with the adrenal capsule, and may contain cell of zona glomerulosa and/or zona fasciculata. (Yarrington 1996; Nyska et al. 1999)
Adrenal cortex, atrophy	Especially in male mice, small adrenals may be difficult to find. Histologically the capsular surface is irregular, cortical thickness is reduced and/or variable, and there may be 1 or more foci of cortical cell hypertrophy or hyperplasia. (Hall et al. 1992) (Yarrington 1996; Nyska et al. 1999)
Adrenal cortex, hyperplasia subcapsular cell	Hyperplasia of adrenal subcapsular cells that may represent adrenal subcapsular reserve cells. They may be spindled type A cells or polygonal lipid-laden type B cells that more closely resemble normal cortical cells. Aged mice, especially females in some strains, commonly have subcapsular accumulations or proliferations of basophilic spindle (Type A) cells, with sparse cytoplasm and indistinct cytoplasmic borders, which may be associated with mast cell infiltration. The lesion may be focal or diffuse, involving the entire subcapsular cortex. Hyperplastic foci may slightly bulge the capsule but exhibit no-minimal compression, and should not be larger than the regular width of the cortex in a young mouse, but the distinction between hyperplasia and adenoma may be arbitrary and

	difficult. (Frith et al. 1988; Faccini et al. 1990; Yarrington 1996; Kim et al. 1997; Nyska et al. 1999)
Adrenal cortex, hypertrophy	Enlargement of adrenal cortical cells due to increased cytoplasm with zona fasciculata principally affected. (Yarrington 1996; Nyska et al. 1999; NTP 2000)
Adrenal gland, amyloidosis	See above (MULTISYSTEM) The inner most cortex is the first predilection site for amyloid deposition, and deposits can progress peripherally to involve zona fasciculate, but usually spare zona glomerulosa. (Hogen-Esch et al. 1996; Yarrington 1996; Nyska et al. 1999)
Adrenal gland, pigment ceroid; (Lipogenic pigmentation; Lipoid pigment; Brown degeneration)	Aged mice may develop deposition of ceroid (lipogenic) pigment initially in cortical cells and macrophages near the corticomedullary junction that can progress to surround the medulla. Small amounts of the cytoplasmic pigment are granular to amorphous yellow-brown. Affected cells become enlarged and distended with brown material. Their nuclei may become pyknotic and there may be multinucleated cells. Ceroid deposits in the ovary are mainly in interstitial cells. Ceroid pigments are yellow brown lipid-derived pigments that autofluoresce, are PAS positive, acid fast, stain blue with the Schmoll reaction, are positive with Sudan black, and are negative for iron. (Yarrington 1996; Nyska et al. 1999)
Pancreatic islet hyperplasia	Increased size of islets of Langerhan to hyperplasia (increased number) of cells, which morphologically are similar to those in smaller normal islets. Hyperplasia may be difficult to distinguish from the normal size variation of islets and hyperplasia of beta cells occurs normally during pregnancy. Hyperplasia usually involves more than one islet (multifocal), and may involve all islets in a section. (Sass et al. 1978; Frith et al. 1988; Faccini et al. 1990; Boorman et al. 1999)
Parathyroid melanosis	See above (MULTISYSTEM)
Pituitary cysts	Single or multiple small cysts occur primarily in pars distalis or pars tuberalis. They may be lined by ciliated epithelium and sometimes contain eosinophilic colloid-like secretion. Some may represent craniopharyngeal duct (Rathke's pouch) remnants. Cystic or cyst-like degeneration of pars distalis occurs occasionally in aging untreated control mice, but occurs earlier and with higher incidence with increasing doses of estrogenic compounds. Focal degeneration and loss of cells in pars distalis results in small irregular spaces often containing some eosinophilic material and cell debris. (Frith et al. 1988; Mahler et al. 1999)
Pituitary Pars distalis; hyperplasia	Hyperplastic foci have indistinct edges and are not compressive, they are distinguished from adjacent tissue by slightly different staining properties (usually paler) with increased number or density of cells. They may be composed of chromophobe or acidophil cells. Chromophobe cells may secrete prolactin. (Frith et al. 1988; Mahler et al. 1999; Capen et al. 2001)
Pituitary pars intermedia hyperplasia	Diffuse or nodular thickening of the pars intermedia due to hyperplasia. The cells are large and pale compared to pars distalis cells, and may be larger and more basophilic than typical pars intermedia cells. Tumors of pars intermedia are rare. (Frith et al. 1988; Mahler et al. 1999; Ward et al. 2000; Capen et al. 2001)
Thyroid gland, ectopic tissue	Ectopic thyroid tissue, typically consisting of a few colloid containing follicles may occur in the mediastinum or thymus. Small cysts in or around the thyroid gland, lined by ciliated cuboidal cells or squamous epithelial cells are considered to be remnants of the pharyngobrachialis duct or of the ultimobranchial duct respectively. Thymic rests (small accumulations of thymic tissue) may occur in or near the thyroid glands.
Thyroid gland, cysts	Ultimobranchial cysts, lined by ciliated, cuboidal or squamous epithelial cells occasionally occur in or near the thyroid gland. (Faccini et al. 1990; Hardisty et al. 1999)

Thyroid gland, inflammation	See above (MULTISYSTEM) Inflammation in the thyroid gland is uncommon in untreated mice. There may be occasional lymphoid infiltrates or arteritis. (Hardisty et al. 1999)
Parathyroid gland, cysts	Parathyroid cysts may be multilocular, are lined by a monolayer of cuboidal to columnar, often ciliated, epithelium and usually contain eosinophilic proteinaceous material. (Faccini et al. 1990; Hardisty et al. 1999)
Parathyroid gland, ectopic tissue	Ectopic parathyroid tissue may occur in the mediastinum or thymus. Thymic rests (small accumulations of thymic tissue) may occur in or near the parathyroid glands. (Faccini et al. 1990; Hardisty et al. 1999)
GENITAL, FEMALE	
Ovary, atrophy	Incidence and severity of ovarian atrophy increases with age in female mice, and may be induced with estrogenic compounds. Atrophic ovaries are smaller than normal ovaries with reduced numbers of follicles and especially of corpora lutea, and relatively increased interstitial tissue. Clusters of large yellow-brown (ceroid) pigmented interstitial cells are common. (Frith et al. 1988; Maekawa et al. 1996; Davis et al. 1999)
Ovary cyst	Ovarian cysts may be single or multiple, may vary in size and most are age-related.(Davis et al. 1999) **Follicular and luteal cysts** derive from anovulatory Graafian follicles and are the most common ovarian lesion in mice on some studies. They may be single or multiple and may essentially replace the ovary. They are lined by 1-4 layers of cuboidal granulosa cells. They should not be confused with cystic corpora lutea that derive from ovulatory follicles and produce progesterone. These have more than 6 layers of hypertrophied luteal cells surrounding a central cavity that may be blood-filled. **Epithelial inclusion** cysts are lined by 1-several layers of columnar epithelial cells that form papillary structures that project into central lumen. They may be precursors of cystadenomas or cystadenocarcinomas. **Epidermoid cysts** are lined by squamous epithelial cells, may be filled with laminated keratin debris, can be found with teratomas. **Paraovarian cysts** arise from mesovarium, are lined by ciliated columnar epithelial cells, and wall contains smooth muscle. **Rete cysts** derive from dilated tubules of rete ovarii. They are lined by columnar epithelial cells with apical nuclei. **Bursal cysts** can be common. The ovary may be compressed within the cystically distended ovarian bursa.
Ovary pigment	**Ceroid** is the most common pigment in mouse ovaries, and there may be a high incidence of deposition of this age related pigment after 1 year of age. Ceroid deposits in the ovary are mainly in interstitial cells. They are yellow brown lipid-derived pigments that autofluoresce, are PAS positive, acid fast, stain blue with the Schmoll reaction, are positive with Sudan black, and are negative for iron . Hemosiderin laden macrophages are likely in sites of earlier follicular hemorrhage. (Frith et al. 1988; Maekawa et al. 1996; Davis et al. 1999)
Uterus, adenomyosis	The presence of endometrial glands in the myometrium is seen with cystic endometrial hyperplasia and can be induced by administration of estrogenic compounds. Glands sometimes extend to the serosa. (Frith et al. 1988; Maekawa et al. 1996; Davis et al. 1999; Davis et al. 2001)
Uterus, angiopathy	Angiectasis in the uterus usually occurs in the myometrium, and arteritis also can occur in the uterus. See above, (MULTISYSTEM).
Uterus, cystic endometrial hyperplasia	Cystic endometrial hyperplasia is the most common uterine change in some studies of aged female mice and the incidence may approach 100%. The condition also can be induced by hormones and agents with estrogenic properties. The uterus may be markedly enlarged by increased numbers of glands plus cystic dilatation of many glands. Endometrial glands are cystic and

	increased in number. There may be adenomyosis (endometrial glands within the myometrium) in severe cases. (Frith et al. 1988; Maekawa et al. 1996; Davis et al. 1999; Davis et al. 2001)
Uterus, hemosiderosis	Hemosiderin deposition is especially likely in aged multiparous females, likely related to involution of placental sites. (Frith et al. 1983; Maekawa et al. 1996)
Uterus, hydrometra, mucometra	Marked dilatation of horns or body of the uterus. One or both horns and the corpus may be involved. The lumen contains serous proteinaceous or mucoid material, and the uterine wall may be thin and atrophic due to prolonged distention. The cause often is not determined, imperforate vagina is a likely cause.(Sheldon et al. 1980; Frith et al. 1988; Sundberg et al. 1994)
Uterus, mineralization	Mineralization is especially likely in aged multiparous females, likely related to involution of placental sites. (Frith et al. 1983; Maekawa et al. 1996)
GENITAL, MALE	
Epididymis, karyomegaly	Karyomegaly frequently with associated cytoplasmic vacuolation in the epithelium of the cauda epididymis causing the enlarged cell to bulge into the lumen, has been a common finding in recent evaluations if 129 and related mice. (Ward et al. 2000; Haines et al. 2001)
Epididymis, sperm granuloma	Granuloma, or pyogranulomatous inflammation resulting from rupture of a duct with release of sperm and duct contents to interstitium. The lesion may include multinucleated giant cells and cholesterol clefts. It may be secondary to ruptured spermatocele, which is a dilated duct segment filled with spermatozoa. (Frith et al. 1988; Radovsky et al. 1999)
Preputial gland, cystic ducts, ectasia	Ductal ectasia and gland atrophy can be common in preputial and clitoral glands, which are composed of modified sebaceous acini and squamous ducts. Associated suppurative and chronic inflammation is common.(Frith et al. 1988; Seely et al. 1999)
Preputial gland, inflammation	Suppurative and chronic inflammation in preputial and clitoral glands can be common, with development of abscesses.(Frith et al. 1988; Seely et al. 1999)
Prostate gland, atypical epithelial hyperplasia	Proliferation of prostate epithelium, without disturbance of acinar architecture or compression of adjacent tissue. (Radovsky et al. 1999; Ward et al. 2000)
Prostate gland, inflammation	See above, MULTISYSTEM. Lymphocytic foci and arteritis can occur in the prostate. (Radovsky et al. 1999; Haines et al. 2001)
Testes, atrophy, degeneration tubular	Degeneration in seminiferous tubules manifests initially as scattered vacuolated or necrotic spermatogenic cells often with multinucleated giant cells and reduced numbers of germinal epithelial cells. More advanced degeneration manifests as severely depleted germ cells, depleted and flattened Sertoli cells, and few remaining spermatogonia. Lipofuscin or ceroid pigment in the testes increases with age and may be associated with degenerative changes. (Radovsky et al. 1999)
Testes, interstitial (Leydig) cell hyperplasia	Increased numbers (hyperplasia) of interstitial (Leydig) cells between seminiferous tubules. These non compressive collections of typical interstitial cells may be focal, multifocal, or diffuse, and range in diameter from about 25% of the diameter of a seminiferous tubule to 3 seminiferous tubules diameter. Interstitial (Leydig) cells have abundant eosinophilic, sometimes vacuolated, cytoplasm, and usually central nucleus with prominent nucleolus. (Gordon et al. 1996; Radovsky et al. 1999; Rehm et al. 2001; Pathbase 2004)
Testes, Mineralization	Focal dystrophic mineralization of the seminiferous tubules may occur occasionally in some strains and commonly in DBA/2 mice.

	It may represent previous areas of injury. Histologically the basophilic concretions may be amorphous or concentrically laminated. (Rings et al. 1972; Frith et al. 1988; Yamate et al. 1990; Radovsky et al. 1999)
Testes, ovo testes & hermaphrodites	Unilateral ovaries and cystic endometrial hyperplasia with contralateral testes and epididymides, or true hermaphrodites with unilateral ovotestes should be expected in ES cell chimeric mice, but are unusual spontaneous findings in most stocks and strains. (Whitten et al. 1979; Eicher et al. 1980; Jankowska-Steifer et al. 1992; McIntyre et al. 2007)
HEMATOPOIETIC	
Bone marrow, fibroosseous change, (myelofibrosis)	Foci of replacement of marrow by fibrous connective tissue, not associated with renal or (Wijnands et al. 1996) parathyroid lesions, can occur in any bones but are commonly reported in sternum, femur, vertebrae especially in aging female mice. In advanced lesions the marrow cavity may be almost replaced by fibrous connective tissue or bony trabeculae. (Sass et al. 1980; Frith et al. 1988; Wijnands et al. 1996; Long et al. 1999; Ward et al. 2000) Intramedullary bone proliferation may be referred to as hyperostosis. See below, MUSCULOSKELETAL.
Bone marrow, hyperplasia myeloid granulocytic	Relative or absolute increase in normal (usually granulopoietic) myeloid elements in the bone marrow usually is a response to infection or necrosis, e.g. tumoral necrosis. Severe granulopoietic hyperplasia may be difficult to distinguish from granulocytic leukemia. (Frith et al. 1985; Kogan et al. 2002)
Lymph node, hyperplasia, lymphoid	Lymphoid hyperplasia of the lymph nodes can be common in especially in females, in some studies of aging mice. Expansion due to hyperplasia occurs in B cell areas (follicles, germinal centers), T cell thymic-dependent areas (paracortex). Marginal sinus is often filled with lymphocytes and medullary cords expanded by plasma cells. The lymphocytes are mature, usually there are few mitotic figures. Lymphoid hyperplasia and plasmacytosis van be a reaction to chronic inflammatory lesions or tumor antigens. (Frith et al. 1985; Frith et al. 1988)
Lymph node, infiltration, macrophages; sinus histiocytosis	Accumulations of macrophages or histiocytes in the subcapsular and medullary sinuses of lymph nodes. The plump macrophages may have abundant distinctly eosinophilic cytoplasm and may contain hemosiderin, other pigments, erythrocytes and other phagocytosed material. (Frith et al. 1985; Frith et al. 1988)
Lymph node, infiltration, plasma cells	Accumulations of plasma cells in the subcapsular and medullary sinuses of lymph nodes.
Spleen, amyloidosis	See above, MULTISYSTEM. Early lesions occur in the white pulp and spread to the red pulp.
Spleen, arteritis	See above, MULTISYSTEM.
Spleen, melanosis	See above, MULTISYSTEM. Both hemosiderin and melanin pigment occur in the spleens of mice. Hemosiderin is golden brown and usually in cytoplasm of macrophages or reticular cells. It stains positively with iron stains such as Prussian blue. Melanin also occurs in the spleen of mice with pigmented skin. It is slightly darker than hemosiderin, maybe in elongate strands rather than clumps (like hemosiderin), is not associated with macrophages and is iron negative. (Frith et al. 1985; Frith et al. 1988)
Spleen, extramedullary hematopoiesis, EMH (myeloid metaplasia)	The spleen is an important hematopoietic organ, and the red pulp expands due to increased, proliferative, normal hematopoietic elements. The increase may be primarily in erythroid or granulopoietic elements. Megakaryocytes also are common in the red pulp and may increase as well. (Frith et al. 1985; Kogan et al. 2002)
Spleen, hyperplasia erythroid	Increased erythropoiesis is characterized by foci of immature erythrocytic precursors with small darkly staining nuclei in the red pulp. Increased erythropoiesis may or may not be associated with an increase in granulopoiesis. (Frith et al. 1985; Frith et al. 1988)

Spleen, hyperplasia myeloid granulocytic	Increased granulopoiesis (e.g. due to infection or abscess) usually occurs in bone marrow as well as in spleen and there may be granulopoietic elements in liver, adrenals and lymph nodes as well. Normal maturation including mature neutrophils should be discerned in granulopoiesis. A primary (inciting) cause such as abscess, ulcerative dermatitis or tumoral necrosis should be sought in cases of marked granulopoiesis. (Frith et al. 1985; Kogan et al. 2002)
Spleen, hyperplasia reticular	This term may be used to refer to apparent increase in monocyte/macrophage or reticuloendothelial cells.(Frith et al. 1985; Wijnands et al. 1996)
Thymus, atrophy cortex or lymphoid depletion or involution	The thymus reaches maximal size at sexual maturity and then undergoes gradual involution. Thymus size and rate of involution varies with mouse strain.(Peleg et al. 1984; Hsu et al. 2003) During involution thymus size decreases due to gradual reduction in cortex and lymphocyte content, and the medulla becomes more prominent, with apparent increase in connective tissue, and in epithelial elements, which may form cysts, cords or tubules. Temporary and reversible involution or atrophy occurs during pregnancy, infection, malnutrition, after surgery or other stressors, and can be caused by toxic insults. Early atrophy may manifest as a starry sky appearance due to phagocytosis of necrotic/apoptotic lymphocytes by phagocytes. (Wijnands et al. 1996; Ward et al. 1999)
Thymus, cysts	Epithelial cysts in the thymus may be come more prominent during involutions. They may be lined by squamous to columnar cells with some ciliated cells. Some cysts may contain cell debris and PAS positive glycoprotein material and may be involved in cell disposal.
Thymus, hyperplasia, lymphoid	Focal or diffuse hyperplastic changes can occur in the cortex or medulla, in 1 or both lobes. There may be focal lymphocytic accumulations in the cortex or medullary, or follicles with germinal center. (Wijnands et al. 1996; Ward et al. 1999)
INTEGUMENT	
Mammary hyperplasia, functional without atypia	Mammary glands may be grossly enlarged and have lobuloalveolar hyperplasia with distended secretory alveoli and ducts that that contain eosinophilic colloid-like secretory material. They resemble glands during pregnancy or delayed involution. The condition may be common in older virgin and multiparous FVB/N mice with or without associated pituitary lesions, and has been associated with mouse mammary tumor virus infection. In FVB/N mice there may be squamous nodules within the hyperplastic gland. (Medina 1982; Frith et al. 1988; Nieto et al. 2003; Wakefield et al. 2003)
Skin ulcer, inflammation, ulcerative dermatitis	The condition can occur in many strains of mice and acariasis should be ruled out. It has been reported most commonly in C7BL related strains. It may begin as a dorsal papular dermatitis, progressing to foci of alopecia and small ulcers, then expansion of the ulcers, with deep necrosis, intense suppurative and chronic inflammatory responses, and secondary changes such as lymphadenopathy, myeloid hyperplasia, amyloidosis.(Sundberg 1996) In outbred Swiss mice the ears and neck may be affected most commonly and severely and has been called progressive necrosing dermatitis of the pinna. (Slattum et al. 1998)
Alopecia areata	Histologically, all species have dystrophic anagen stage hair follicles associated with a peri- and intrafollicular inflammatory cell infiltrate. (McElwee et al. 1998; McElwee et al. 1999)
MUSCULOSKELETAL	
Skeletal, degenerative joint disease; osteoarthritis	Non-inflammatory, progressive loss or destruction of articular cartilage, with thickening of underlying bone, and sometimes subchondral cysts and osteophytes in various strains. Knee and elbow joints may be most severely affected, and vertebrae especially thoracic vertebrae may be affected also. (Long et al. 1999)

Bone hyperostosis endosteal	Endosteal bone proliferation. Estrogens may induce this condition in mice. In advanced stages of spontaneous fibroosseous lesions, the medullary cavities may be nearly filled by bone (see bone marrow , above). (Highman et al. 1981; Ward et al. 1999)
NERVOUS	
Brain, hypocallosity	Small or absent corpus callosum connecting cerebral hemispheres occurs especially in 129 and BALB/c strains. (Wahlsten 1982; Livy et al. 1991; Livy et al. 1997)
Brain, lipofuscin	Brown tinged cytoplasm of neuronal cell bodies, due to lipofuscin accumulation, increases with age, and may be most prominent in granule cells of the dentate gyrus. (Moore et al. 1995; Moore et al. 1995; Radovsky et al. 1999)
Brain, melanosis meninges	See above, MULTISYSTEM.
Brain, mineralization thalamus	Small foci (up to 100um diameter) of basophilic mineralized, material, occurs usually bilaterally in the thalamus of old mice, with an incidence of about 5% in CD-1® and B6C3F1 mice. (Faccini et al. 1990) They usually are associated with blood vessels and concentric lamination may be evident with H&E. They stain negative for amyloid and iron, and are weakly positive with Alcian blue, primarily at the periphery of the deposits. They are dark brown or black with distinct lamination by Verhoeff's method, and have a red core and dark periphery with Alizarin Red. (Morgan et al. 1982; Frith et al. 1988; Radovsky et al. 1999)
RESPIRATORY	
Lung, acidophilic Macrophage pneumonia	Acidophilic macrophage pneumonia, also referred to as acidophilic crystalline pneumonia is characterized by abundant macrophages distended with eosinophilic (acidophilic) granular or crystalline material in airways. Intracellular or extracellular eosinophilic needle like crystals in airways may or may not be conspicuous and may stain blue with Perl's reaction (for iron). (Ward et al. 2000; Ward et al. 2001)
Lung, acidophilic crystals	Intracellular or extracellular, non-birefringent, acidophilic crystals, identified as a chitinase, can be striking or dominant feature of acidophilic macrophage pneumonia (acidophilic crystalline pneumonia) in some cases. (Ward et al. 2000; Ward et al. 2001)
Lung, alveolar epithelial hyperplasia bronchoalveolar hyperplasia (Type II cell hyperplasia)	Hyperplasia (increased numbers) of alveolar type II cells or bronchiolar secretory cells. These typically are poorly demarcated foci of hypercellularity with septal thickening due to increased numbers of plump type II cells or bronchiolar type cells with preservation of alveolar septal architecture. Atypia and mitoses are unusual. These may be precursors of adenoma or carcinoma. (Dixon et al. 1999; Dungworth et al. 2001)
Lung, inflammation, perivascular peribronchiolar	See above, MULTISYSTEM. These usually consist of small perivascular lymphocyte aggregates, or mild increase bronchiole associated lymphoid tissue (BALT). They should be minimal in untreated mice not exposed to respiratory pathogens. (Ernst et al. 1996)
Nose, 'amyloidosis', nasal 'amyloidosis'	Expansion of nasal septum by submucosal deposition of amorphous acellular eosinophilic material also has been referred to as septal amyloidosis. The submucosal amorphous eosinophilic material in nasal septa commonly stains better with PAS or trichrome than with Congo red. Probably it usually is not amyloid. (Monticello et al. 1990; Hogen-Esch et al. 1996; Haines et al. 2001; Doi et al. 2007)
Nose; olfactory	Nasal olfactory epithelial hyalinosis is primarily near the olfactory/respiratory transition areas, with foci of hyalinosis characterized by

epithelium hyalinosis	eosinophilic intracytoplasmic inclusions, identified as a chitinase, originating at the basal aspects of lining cells. (Ward et al. 2000; Ward et al. 2001)
Nose; respiratory epithelium hyalinosis	Nasal respiratory epithelium tends to be more affected than olfactory epithelium, particularly in the regions of the nasal glands, Affected respiratory epithelial cells may be distended with peripheral displacement of nuclei by eosinophilic hyaline material. Inflammation usually is not associated with epithelial changes. Extracellular crystals were variably needle-like, rectangular, or square. The acidophilic hyaline material and crystals have been identified as a chitinase. Inflammation usually is not associated with epithelial changes. (Ward et al. 2000; Ward et al. 2001)
Trachea inflammation	See above, MULTISYSTEM. These usually consist of small submucosal lymphocytic aggregates.
Trachea hyalinosis	Tracheal epithelial cytoplasm contains and may be distended by amorphous or spicular hyaline eosinophilic material that has been identified as a YM1 chitinase. (Ward et al. 2000; Ward et al. 2001)
Trachea mucosal gland acidophilic crystals	Epithelial cytoplasm contains and may be distended by amorphous or spicular hyaline eosinophilic material that has been identified as a YM1 chitinase. (Ward et al. 2000; Ward et al. 2001)
SPECIAL SENSES	
Ear, otitis media	Inflammation of the middle ear. There may be intense suppurative exudates in the lumen, with inflammatory and proliferative changes in the lining epithelium, or the chamber may be filled with eosinophilic serous material with few inflammatory cells and little change in the lining epithelium. Some lesions have fibrosis and lipid-like material with cholesterol clefts resembling cholesteatoma or cholesterolinic granuloma. Organisms may be difficult to discern.(Haines et al. 2001)
Eye, Blepharo-conjunctivitis	Inflammation of eyelid and conjunctiva. This condition may be quite common in several pigmented and non-pigmented mouse strains. Initially there is suppurative conjunctivitis and/or ulceration at the mucocutaneous junction, progressing to suppurative inflammation involving meibomian ducts, with conjunctival ulceration. Various bacterial species can be isolated, but their role as pathogens or opportunists is unclear. (Smith et al. 1996)
Eye, cataract gross	Opacification of the lens, resulting in a white or gray lens.(Smith et al. 1994; Hubert et al. 1999)
Eye, cataract microscopic	Changes in lens fibers include fiber swelling, Vacuolation, liquefaction and formation of Morgagnian globules. Damage to lens epithelium can result in epithelial flattening, proliferation, layering and formation of bladder cells. Later changes may include mineralization, cholesterol/lipid deposition, or complete liquefactive necrosis. With hypermature cataracts, leakage of lens material may provoke an inflammatory response.(Frame et al. 1996) Smith, Roderick et al. 1994; Hubert, Gerin et al. 1999)
Eye, keratitis, neovascularization	Inflammation of the cornea with vascularization of the normally avascular cornea. There may be ulceration, corneal thickening due to edema, erosion or ulceration of the anterior surface. (Frame et al. 1996; Hubert et al. 1999)
Eye, corneal opacity, Corneal dystrophy, Corneal mineralization, Band keratopathy	Grossly evident white area on anterior cornea due to mineralization. Histologically there is mineralization of the basement membrane and stroma with varying degrees of edema, inflammation, vascularization of the stroma, and erosion or ulceration. **[DBA/2 (29.1%), C3H (16.2%), CF1 (16.2%) BALB/c (10.0%) >** CD-1 (4.3%) and C57BL/6 (4.1%)] – diet ? NH3 etc factors? (Van Winkle et al. 1986; Frame et al. 1996)
Eye, retinal degeneration	Homozygosity for rd1 mutation in Pde6b locus (gene) results in bilateral complete loss of outer nuclear layer (rod and cone nuclei) and of the outer granular layer (inner and outer segments of rod and cone photoreceptors), so that the inner nuclear layer

	appears to abut the retina pigmented epithelium (RPE). As the disease progresses there is loss of retinal vasculature and pigment in RPE (in pigmented mice), foci of thinning of the inner nuclear layer, and loss of ganglion cells and nerve fibers. (Smith et al. 1996; Chang et al. 2002; Serfilippi et al. 2004; Zeiss et al. 2004)
Eye, retinal atrophy	Age related or light-related degenerative changes in the retina with reduction of the outer layers due to loss of photoreceptor cells. Normally the outer nuclear layer is 10-12 nuclei thick. (Smith et al. 1996) Some studies may use the term for rd1 associated retinal degeneration.(Hall et al. 1992)
Harderian gland, chronic inflammation	See above (MULTISYSTEM) These usually consist of discrete interstitial mononuclear infiltrates. (Frith et al. 1988; Faccini et al. 1990; Botts et al. 1999)
URINARY	
Kidney, amyloidosis	See above (MULTISYSTEM) This lesion can resemble glomerulonephritis and should be distinguished by special stains. Glomeruli are enlarged with mesangium expanded by nodular or diffuse accumulations of acellular eosinophilic homogeneous material. Renal papillary necrosis is usually associated with renal amyloidosis or toxins. (Frith et al. 1988; Wolf et al. 1996)
Kidney, glomerulonephritis (GN)	Membranoproliferative glomerulonephritis characterized by deposition of eosinophilic hyaline material in glomerular basement membranes with proliferation of mesangial cells and inflammatory cell infiltration seems to be the most common GN in most chronic studies. Early changes of focal mesangial thickening with increased numbers of epithelial cells, progress to increased lobular separation of glomeruli, thickening of glomerular capillary walls and increased mesangial matrix. Basement membrane thickening with PAS positive material, usually attributed to immunoglobulin, is expected. Congo red and trichrome stains should distinguish GN from glomerular amyloid and collagen deposition respectively. (Faccini et al. 1990; Montgomery 1998; Son 2003; Pathbase 2004)
Kidney, glomerulosclerosis	The term implies scarring or fibrosis and related late changes in the glomerular tuft in progressive glomerular disease. It may include small, fibrotic tufts and adhesions to the glomerular capsule (synechiae). (Faccini et al. 1990) The term also may be used to include a wide range of glomerular changes (including very little sclerosis) with various tubular changes and interstitial inflammation. (Maita et al. 1988)
Kidney, hydronephrosis	Distention of the renal pelvis may be mild with little change in kidney size, or the dilated pelvis and kidney may cause abdominal distention with compression atrophy of kidney remnants. Possible causes include urinary obstruction due to calculi, tumors or inflammation. It may be unilateral or bilateral. There may be hydroureter if obstruction is chronic and distal in the urinary tract. (Frith et al. 1988; Seely 1999) It should not be confused with genetically determined polycystic kidney syndromes that usually involve bilateral progressive development of multiple cysts of tubules and/or collecting ducts, culminating in renal failure, and sometimes associated with extrarenal cysts and other abnormalities. (Werder et al. 1984; Trudel et al. 1991; Nakayama et al. 1994; Ricker et al. 2000)
Kidney inflammation	See interstitial nephritis.
Kidney, interstitial nephritis	In diffuse chronic interstitial nephritis, kidneys are reduced in size with granular or nodular surfaces. In the subacute stage cellular infiltrate includes lymphocytes, plasma cells, and fewer neutrophils or macrophages. Tubules are dilated with varying degrees of degeneration and regeneration. The chronic stage is characterized by focal or diffuse fibrosis, with lymphocytic or lymphohistiocytic infiltration; tubules may be cystic with proteinaceous casts or be atrophic, there may be areas of tubular

	regeneration or hyperplasia. Glomeruli usually are spared if primary insult is interstitial, or the condition may be secondary to glomerulonephritis. (Faccini et al. 1990; Montgomery 1998) – not very common in contemporary colonies.
Kidney, nephropathy	The term usually includes tubular changes: tubular regeneration, occasionally with tubular casts, thickened basement membrane, crowding of nuclei and inflammatory cell infiltration. (Son 2003) Some authors may include or glomerulonephritis in this term. Some authors refer to the condition as chronic progressive nephropathy, similar to the condition in rats. (Wolf et al. 1996) Interstitial nephritis and nephropathy have been used to refer to similar or identical conditions. (Faccini et al. 1990)
Kidney tubule, hyaline droplets	Hyaline droplets that contain lysozyme from tumor cells can be found in proximal tubules in some mice that have histiocytic sarcoma. The brightly eosinophilic cytoplasmic droplets can be striking in affected kidneys. (Hard et al. 1991; Lacroix-Triki et al. 2003)
Kidney tubule, mineralization (nephrocalcinosis)	Foci of mineralization are granular, faintly basophilic and fill tubular lumina, usually at the corticomedullary junction, or in the loops of Henle in the medulla. It may occur as part of the spectrum of changes in nephropathy or interstitial nephritis, and not diagnosed as a separate entity. (Frith et al. 1988; Faccini et al. 1990; Seely 1999)
Urinary obstruction, 'dysuria'	Maita et al. 1988 Son 2003. uses the term dysuria to refer to urinary obstruction, with urinary bladder severely dilated and urethra near isthmus plugged by gelatinous plug with sperm, or the obstruction may not be identified, and there may be hydroureter or hydronephrosis. Other authors refer to condition as obstructive uropathy (Faccini et al. 1990)or MUS (Mouse urologic syndrome). (Faccini et al. 1990; Bendele 1998)
Urinary obstruction, MUS	MUS has one or more of the following features: bladder distension; peripreputial urine staining, alopecia, and edema; paraphimosis; urethral blockage; ulcerative balanoposthitis; hydronephrosis; pyelonephritis; rectal prolapse; and perineal ulcerative dermatitis. (Everitt et al. 1988) In acute MUS mice are found dead with no prior clinical signs. In the chronic form, there may be ventral wetting, dermatitis, paraphimosis, penile trauma, urinary calculi, pyelonephritis or hydronephrosis. (Bendele 1998)
Urinary bladder, arteritis	See above (MULTISYSTEM)
Urinary bladder, inflammation	See above (MULTISYSTEM)

Table 6. – revised and updated from (Brayton 2006). Neoplasms, brief definitions or descriptions of some neoplasms that may be encountered in mice. This is not a complete list and glossary of all neoplasms that may occur spontaneously or be induced in mice. The information is derived primarily from resources used in the chapter. It is provided to facilitate understanding of terminology in the chapter, and is not an officially sanctioned glossary, dictionary or ontology. Terminology and definitions will continue to change as neoplasms are characterized further and as new neoplasms are induced.

SYSTEM Organ, neoplasm (historical or obsolete terms)	
ALIMENTARY	
Intestine, polyp	A mass of tissue which projects outward or upward from the normal surface level being macroscopically visible as a hemispheroidal, spheroidal, or irregular mound like structure growing from a relatively broad base or a slender stalk. These may be adenomas but are not specified in some reports. (Maekawa et al. 1996; Shackelford et al. 1999; Pathbase 2004)
Intestine, adenoma	Benign neoplasm of enterocytes of intestinal mucosa. These are uncommon spontaneous neoplasms in mice, and are more likely to occur in the small intestine (especially in the duodenum) than in the large intestine. They are frequently small and may not be detected in the unopened intestine. Typically they are polypoid and project into the lumen. Mucosal architecture may be distorted and there may be branching villi or tubular crypt proliferation. There may be crypt herniation but without penetration of basement membrane. The epithelium is relatively well differentiated, but may be more basophilic than adjacent normal epithelium. There may be associated inflammatory changes especially if there is ulceration, and the neoplasms may arise near a Peyer's patch. .(Frith et al. 1988; Maekawa et al. 1996; Shackelford et al. 1999; Betton et al. 2001)
Intestine, adenocarcinoma	Malignant neoplasm of enterocytes of intestinal mucosa. Large tumors may be recognized grossly when they expand the intestine. There may be single or multiple nodules or polypoid masses that project into the lumen or endophytic, sessile neoplasms may result in a thickened wall with irregular mucosal surface, and present grossly as a diverticulum or bulge of the serosal surface. Distinction between adenoma and adenocarcinoma may be difficult when there is no metastasis or obvious invasion through the basement membrane into the intestine wall. Invasive glands frequently are associated with a marked inflammatory and scirrhous response. Normal architecture is lost and there may be cystic and solid areas. The neoplastic cells usually are basophilic, more anaplastic and pleomorphic than in adenomas, cuboidal to columnar and there may be goblet or 'signet ring', or Paneth cell components. There are increased mitotic figures and nuclei may be pleomorphic. (Frith et al. 1988; Maekawa et al. 1996; Shackelford et al. 1999; Betton et al. 2001)
Intestine, cecum carcinoid	Neoplasm of neuroendocrine (enterochromaffin) cells of the intestinal mucosa. Gastrointestinal carcinoid or neuroendocrine tumors are very rare neoplasms in mice. They may be induced in the stomach by antisecretory agents that cause hypergastrinemia. Malignancy is determined by invasion and/or distant metastasis. Neuroendocrine tumors typically feature a packeted pattern of clusters of polygonal cells supported delicate fibrovascular stroma. Cytologic features may be similar to other endocrine cells with moderate to ample granular cytoplasm, a round nucleus with prominent nucleous/i, and the bulk of the cytoplasm, rather than the nucleus, may appose the vasculature. The cells may be argyrophilic, and stain with chromogranin A or neuron specific enolase. (Maekawa et al. 1996; Betton et al. 2001)

Intestine, fibrous histiocytoma	These neoplasms derive from pluripotential mesenchymal stem cells and also exhibit histiocytoid features. In mice these are rare outside of the subcutis/skin, Histiocytic sarcoma (see below HEMATOPOIETIC) should be considered especially when there is involvement of liver and other organs. Schwannoma (nerve sheath tumor) and fibroma or fibrosarcoma also should be ruled out. (See below INTEGUMENT.) (Ernst et al. 2001) .
Liver tumor	Hepatocellular neoplasm, adenoma vs. adenocarcinoma not distinguished. Usually other types of tumors in the liver (cholangioma, cholangiocarcinoma, hemangioma, hemangiosarcoma, hepatoblastoma, histiocytic sarcoma, metastatic neoplasm) are not included in this category, unless diagnoses were made by gross examination only.
Liver, adenoma hepatocellular; (Type A nodule hepatoma, hyperplastic nodule, carcinoma)	Benign neoplasm derived from hepatocytes. These usually are distinctly demarcated or circumscribed nodules, 1-10 mm diameter, that lack lobular organization, compress adjacent parenchyma and may bulge from the liver surface. They do not invade adjacent parenchyma or vessels and do not metastasize. They consist of a uniform population of well-differentiated cells that resemble normal hepatocytes but may be larger or smaller than adjacent normal hepatocytes, and can have more basophilic, eosinophilic, or vacuolated cytoplasm. Hepatocellular carcinomas may arise within adenomas. (Frith et al. 1994; Harada et al. 1999; Deschl et al. 2001)
Liver, carcinoma hepatocellular (Type B nodule, trabecular carcinoma, malignant hepatoma)	Malignant neoplasm derived from hepatocytes. Carcinomas in mice often have distinct trabecular or adenoid patterns. Moderately-well differentiated hepatocellular carcinomas are composed of larger hepatocytes that vary in size and shape in trabecular or solid patterns. The poorly differentiated tumors are composed of cells with less cytoplasm and more immature nuclei and some have extremely large anaplastic cells. Metastases are typically to the lung, and careful examination may reveal pulmonary metastases in up to 40% of male B6C3F1 or C3H mice with hepatocellular carcinoma that are allowed to live out their lifespan. Metastases usually occur only when tumors are large (> 10 mm). (Frith et al. 1994; Harada et al. 1999; Deschl et al. 2001)
Liver, foci of cellular alteration	See table 5, They may be reported as neoplastic or nonneoplastic findings, depending on the study.
Liver, hemangioma	Hemangioma in liver, see hemangioma below. These neoplasms may be difficult to distinguish from angiectasis (table 5).
Liver, hemangiosarcoma	Hemangiosarcoma in liver, see hemangiosarcoma below.
Liver, hepatoblastoma	These rare spontaneous or induced liver tumors may be an undifferentiated variant of hepatocellular carcinoma, and fetal or ductular origins have been proposed. Histologically similar neoplasms occur in children, but hepatoblastomas only occur in aged mice. They are almost always found within or adjacent to hepatocellular carcinomas and are distinct because of their basophilia relative to adjacent parenchyma. The tumors frequently have distinctive patterns including rosettes, rows or ribbons, organoid or nest-like structures lined by distinct but delicate vascular channels. The channels are surrounded by one -several layers of radially or concentrically arranged neoplastic cells. (Frith et al. 1994; Harada et al. 1999; Deschl et al. 2001)
Salivary gland, myoepithelioma	Neoplasm of myoepithelial cells of glandular structures including salivary gland; mammary gland and preputial/clitoral glands. Relatively rare in mice (84% in BALB/cJ in Sundberg, 1991, 1992) . Typically present as large soft fluctuant masses in ventral neck. When opened, they contain thick, opaque, red-brown fluid (the result of liquefactive necrosis. Mestastases are rare. They may be most likely in the submaxillary or parotid salivary glands. Histologically, they are biphasic tumors, composed of large pleomorphic cells including elongated or spindle-shaped mesenchymal type cells, mixed with areas of

	polyhedral epithelioid cells. Areas of degeneration and necrosis can result in pseudocysts filled with mucus and necrotic cell debris. The neoplastic cells may palisade around blood vessels. Larger tumors may metastasize to the lung. (Sundberg 1992; Botts et al. 1999; Pathbase 2004)
Stomach, forestomach, squamous papilloma	Benign neoplasm of stratified squamous epithelium of the non-glandular stomach (forestomach). These are usually exophytic villous or arborescent outgrowths of fibrovascular stroma covered by neoplastic stratified. There may be acanthosis and hyperkeratosis but maturation is normal and mitotic figures are rare. The incidence in control B6C3F1 mice, Swiss mice and other strains usually is < 2%. (Maekawa et al. 1996; Betton et al. 2001; Pathbase 2004)
Stomach, forestomach, squamous cell carcinoma	Squamous cell carcinoma arising from stratified squamous epithelium of the forestomach. In the stomach these malignant neoplasms tend to be polypoid, with marked cellular pleomorphism, keratin pearls and many mitotic figures. They exhibit invasion, and ulceration, inflammation and fibrosis of submucosa are common features. The incidence in control B6C3F1 mice, Swiss mice and other strains usually is < 2%.
CARDIOVASCULAR	
Heart, hemangioma;	See below hemangioma. (angioma)
Heart, hemangiosarcoma;	See below hemangiosarcoma. (angiosarcoma)
Vessels, hemangioma	Benign neoplasm of endothelial cells can be found at any site in the body. The most common sites are **spleen** and **liver**. Subcutis, skeletal muscle, and female reproductive tract are other common sites. **Cavernous** hemangiomas are dilated cavernous spaces that are lined by endothelial cells and filled with red blood cells. **Capillary** hemangiomas are circumscribed accumulations of small cleft like spaces lined by typically plump endothelial cells and containing red blood cells, or spaces may be vacant or flattened. Mitotic figures are rare in hemangiomas. (Frith et al. 1982; Booth et al. 1995; Peckham et al. 1999; Ernst et al. 2001)
Vessels, hemangiosarcoma	Malignant neoplasms of endothelial cells, consisting of dilated vascular spaces of varying sizes which may or may not be filled with red blood cells, non-circumscribed and locally invasive. . Cells may be very pleomorphic and vessel-like structures may be difficult to appreciate in predominantly solid neoplasms. The cells lining vascular spaces are plump with oval basophilic nuclei, indistinct cell borders, and may have bizarre mitotic figures. There is often piling-up of lining cells. Particularly in the spleen, tumors may be predominantly solid. Necrosis, hemorrhage, and thrombi are frequent. (Frith et al. 1982; Booth et al. 1995; Peckham et al. 1999; Ernst et al. 2001)
Heart, mesothelioma	Neoplasm of mesothelial cells that line pleural & peritoneal cavities. RARE spontaneous tumors in mice but may be induced by intrapleural or aerosol exposure to asbestos or other mineral fibers. Epithelial, mesenchymal or mixed patterns; nodular or diffuse involvement of pleural or peritoneal surfaces. Nodular mesotheliomas are characterized by 1 to several nodules on pleural or peritoneal surfaces, and may be benign or malignant. Diffuse mesotheliomas have many contiguous nodules or thick confluent, creeping, growth over surfaces and tend to be malignant with deep invasion. Epithelial-type neoplasms may be papillary with exophytic fronds of pleomorphic cells supported on fibrous stalks, or tubular with atypical cells forming glandular patterns, or solid with many bizarre atypical cells with karyomegaly or several nuclei. Mesenchymal type areas consist of interlacing bundles of spindle cells with nuclear pleomorphism. (Dixon et al. 1999; Dungworth et al. 2001)
ENDOCRINE	

Adrenal cortex, subcapsular cell hyperplasia	See table 5.
Adrenal cortex, adenoma; (adrenal adenoma; adrenal cortical adenoma)	Benign neoplasm of adrenal cortical tissue. Expansile accumulations of neoplastic cells with low mitotic activity that are well delineated from adjacent normal cortex, typically bulge the surface of the gland, compress underlying cortex and exceed the regular width of the cortex in a young mouse. **Type A adenomas are composed of spindled cell**s. **Type B adenomas (solid adenomas) are composed of more polygonal, small or larger lipid-laden cells that resemble normal adrenal cortical cells**. In both types neoplastic cells appear to be packeted by fine vascular stroma. The tumors frequently have both cell types, and usually may be named for the predominant cell type. Mast cells intermingled with the tumor cells often are associated with the Type A tumors. Small 'accessory adrenal cortical nodules', are especially common in BALB/c mice. In ,ost strains/studies cortical adenoma are relatively uncommon, usually <1% incidence even in old populations, but are more common than carcinomas. (Yarrington 1996; Nyska et al. 1999; Capen et al. 2001)
Adrenal medulla, phaeochromocytoma (adrenal medullary (chromaffin) cell tumor)	Neoplasm of the adrenal medulla. These tumors are much less common in mice than they are in rats, and like human pheochromocytomas, spontaneous tumors in mice produce catecholamines. The neoplastic cells are relatively uniform polyhedral cells that resemble normal medullary secretory cells with central nuclei and finely stippled cytoplasm, and are supported or packeted in delicate fibrovascular stroma. As tumors enlarge, the stroma tends to be less conspicuous and capillaries are distended with blood. Cytoplasm of neoplastic cells may be more basophilic with H & E than that of normal medullary cells. Lesions that involve <50% of the medulla and do not compress adjacent tissue may be diagnosed as hyperplasia. Lesions that invade the adrenal capsule or spread beyond the adrenal gland are classified as malignant pheochromocytoma. (Tischler et al. 1996; Nyska et al. 1999; Capen et al. 2001)
Pancreas isle; adenoma insulinoma)	Islet cell adenomas in mice typically involve a single islet in a histologic section, in contrast to hyperplasia which typically affects multiple islets or all islets in a lobule. Islet adenomas are larger than hyperplastic islets and compress adjacent normal pancreas. Adenomas may be more vascular than normal or hyperplastic islets and cells tend to be well differentiated, with few mitotic figures. Usually these are functional beta cell tumors that produce insulin without causing hypoglycemia. Carcinomas are even less common and tend to be larger than adenomas but also composed of well differentiated cells, but demonstrate invasion or distant metastasis usually to the liver. (Boorman et al. 1999; Capen et al. 2001)
Pituitary gland, adenoma	Benign neoplasm of pituitary gland. Adenomas of pars distalis are more common than of pars intermedia. Pars distalis adenomas can be common in aged female mice. Adenomas are distinguished from pituitary hyperplasia by being well-delineated and causing compression of adjacent normal cells, but the distinction may be subtle. They are typically composed of large cells with abundant eosinophilic cytoplasm, and angiectatic or cyst-like spaces are common. **Mammotroph or prolactin secreting adenomas of the pars distalis** may be especially common in female C57BL6/J mice. Carcinomas of the pars distalis are rare and are diagnosed when there is unequivocal invasion into surrounding tissues or distant metastases. (Schechter et al. 1981; Frith et al. 1988; Mahler et al. 1999; Capen et al. 2001)
Pituitary gland, hyperplasia, pars distalis / intermedia	See table 5.
Thyroid, C cell, adenoma	Benign neoplasm derived from calcitonin producing C-cells (parafollicular cells) of thyroid gland. These are much less common than thyroid follicular adenomas in mice (compared to rats). They occur as solid nests (as opposed to papillary or

	follicular structures typical of follicular adenomas) of polygonal pale polyhedral cells with indistinct cytoplasmic borders. They have been (arbitrarily) distinguished from hyperplastic foci by occupying an area larger than 5 average follicles. (Hardisty et al. 1999; Capen et al. 2001)
Thyroid, C cell, carcinoma	Malignant neoplasm derived from the calcitonin producing C-cells (parafollicular cells) of the thyroid gland. The distinction between adenoma and carcinoma is not clearly defined. There may be central necrosis. Invasion of extrathyroidal tissue may be the only useful criterion for malignancy. (Hardisty et al. 1999; Capen et al. 2001)
Thyroid, follicular cell, adenoma	Benign neoplasm of thyroid follicular cells. Thyroid tumors are uncommon in mice, <1% in most studies, and follicular cell adenoma is the most commonly reported spontaneous tumor. Usually ingle well-delineated lesions in otherewise normal thyroid gland. The most common type is a small papillary adenoma, in which a papillary projection of follicular epithelium extends into a cystic lumen. Follicular patterns consisting of small colloid-containing follicles mixed with normal sized follicles, and solid patterns with cells in sheets and densely packed nodules are less common. Follicular epithelium is cuboidal, cytoplasm stains slightly more basophilic than adjacent normal thyroid, and there may be colloid in follicle lumens. Solid pattern adenomas may resemble C- cell tumors (Thomas et al. 1996; Hardisty et al. 1999; Capen et al. 2001)
Thyroid follicular cell, carcinoma	Malignant neoplasm of thyroid follicular cells. These are much less common than follicular cell adenomas, and may be difficult to distinguish from them. The primary pattern is solid, but they may have follicular, papillary or mixed patterns. They are usually larger than adenomas, with more atypia, and evidence of invasion or distant metastases. (Thomas et al. 1996; Hardisty et al. 1999; Capen et al. 2001)
GENITAL, FEMALE	
Ovary, adenoma	Benign tumor of the ovary. The type of adenoma is not specified in some reports. Tubulostromal adenoma or cystadenoma are likely, but with gross examination, the term may refer to any ovarian neoplasm.
Ovary, choriocarcinoma	Malignant neoplasm derived from trophoblasts, and considered to be germ cell neoplasms. Trophoblasts are giant cells with nuclei up to 50u diameter that are found in normal embryonic membranes and produce chorionic gonadotropins. Chroriocarcinomas are rare neoplasms in mice even in carcinogen studies, and usually occur in the uterus. They are composed of sheets of large anaplastic multinucleated syncytioblasts, and smaller basophilic cells that resemble placental cytotophoblasts pleomorphic, as well as more typical giant uninucleated trophoblasts and highly anaplastic trophoblast-like cells. Hemorrhage is a prominent feature. (Davis et al. 1999; Davis et al. 2001)
Ovary, cyst adenoma	Benign neoplasm derived from the surface epithelium of the ovary. It is a common spontaneous ovarian neoplasm in some strains of mice. Anastomosing papillary fronds, lined by non-ciliated cuboidal-columnar cells project into the cyst lumen. The cyst lining typically is cuboidal-columnar epithelium, which may include ciliated cells. The cyst lumen may contain eosinophilic serous fluid or blood. (Frith et al. 1988; Maekawa et al. 1996; Davis et al. 1999; Davis et al. 2001)
Ovary, granulosa cell tumor	Ovarian neoplasm derived from sex cord stromal cells. Granulosa cell tumors are usually unilateral, but may be bilateral or occur in conjunction with another ovarian tumor. They are characterized by a diversity of patterns including solid, tubular, follicular, trabecular. The neoplastic cells resemble normal granulosa cells and have scant to moderate amphophilic vacuolated cytoplasm depending on their degree of luteinization. They tend to have small oval nuclei with stippled chromatin, and there may be few to many mitotic figures. Some tumors have distinctive areas of fusiform theca-like cells. Some large tumors have areas of necrosis and hemorrhage and prominent lipofuscin-laden cells. Mitoses vary in number from few to

	numerous. Call-Exner-like rosettes are rare but may be found in the follicular types. Malignant granulosa cell tumors exhibit more cellular pleomorphism, high mitotic rates, local invasion, frequent necrosis and hemorrhage, and may metastasize to the lungs, kidneys, lymph nodes. (Frith et al. 1988; Maekawa et al. 1996; Davis et al. 1999; Davis et al. 2001)
Ovary, hemangioma.	Hemangioma in the ovary, see above, CARDIOVASCULAR.
Ovary, hemangiosarcoma	Hemangiosarcoma in the ovary, see above, CARDIOVASCULAR.
Ovary, Sex cord stromal tumors	Neoplasms derived from ovarian sex cord stromal cells. They are composed of endocrine-stromal cells of the ovary and include neoplasms of granulosa, theca and lutea cell origin, Sertoli cell tumors, and fibroma or fibrosarcoma of stromal cell origin. Neoplasms may include more than one sex cord stromal cell type and usually are named for the predominant cell type, but some reports may use names that indicate more than one cell type. (Davis et al. 1999; Davis et al. 2001)
Ovary, luteoma	Benign ovarian neoplasm derived from sex cord stromal cells. They may be the most common ovarian tumor in some strains e.g. BALB/c. Luteomas are generally well circumscribed but not encapsulated, and may involve the entire ovary. They consist of large polygonal cells that closely resemble the cells of a normal corpus luteum. They should exceed the size of 3 normal corpora lutea. The neoplastic cells have abundant pale granular eosinophilic, sometimes vacuolated, cytoplasm, and a single round nucleus, usually with few mitotic figures. In some luteomas the cells may be brown tinged due to ceroid, which is PAS-positive and acid fast. Mast cells, scattered or in clusters, may be common in luteomas of BALB/c and C57BL/6 but are less common in those of the C3H strains. (Frith et al. 1988; Maekawa et al. 1996; Davis et al. 1999; Davis et al. 2001)
Ovary, Sertoli cell tumor	Ovarian neoplasm derived from sex cord stromal cells. Sertoli cell tumor is a rare ovarian neoplasm, and histologically resembles testicular Sertoli cell tumors, with a distinctive tubular pattern of elongated epithelial cells with homogeneous faintly eosinophilic cytoplasm and basal, round nuclei, palisading on thin strands of fibrovascular stroma. Mitotic activity is usually low.
Ovary, Sertoli – Leydig cell tumor	This term probably refers to a mixed sex cord stromal tumor.
Ovary, teratoma	Benign or malignant germ cell derived neoplasm containing derivatives from all 3 germ layers (endoderm, mesoderm, ectoderm). Ovarian teratomas are rare but usually seen in young mice, and are frequently cystic with a mixture of epithelial cell types, including prominent areas of cornifying, stratified squamous epithelium, ciliated tall columnar epithelium and intestinal epithelium, sometimes thyroid or pancreas, along with well differentiated cartilage, bone, skeletal or smooth muscle, and variable amounts of well differentiated nervous tissue resembling cerebral cortex. Benign tumors tend to appear more differentiated with easily recognizable mature tissues. Malignant tumors tend to be less differentiated, with large areas of necrosis and hemorrhage, and are highly metastatic. (Frith et al. 1988; Maekawa et al. 1996; Davis et al. 1999; Davis et al. 2001) Extragonadal teratomas are usually in chimeric mice, originating from ES cells. (Blackshear et al. 1999)
Ovary, theca Sertoli cell tumor	Ovarian neoplasm derived from sex cord stromal cells, with theca cell and Sertoli cell-like areas.
Ovary, thecoma	Benign ovarian neoplasm derived from sex cord stromal cells. The nodules are composed of densely packed distinctive fusiform theca cells typically in bundles or whorling patterns, supported on delicate fibrovascular stroma. Paler luteinized cell clusters may be interspersed between strands of fusiform thecal cells. The principle cell type is fusiform, with an oval nucleus and sparse basophilic cytoplasm. Luteinization is characterized by increased cell size, faintly eosinophilic, brownish,

	foamy cytoplasm and a round nucleus with a delicate chromatin pattern. Large tumors may have extensive necrosis with only perivascular persistence of viable tissue. (Frith et al. 1988; Maekawa et al. 1996; Davis et al. 1999; Davis et al. 2001)
Ovary, tubulostromal adenomas; Tubular adenoma (tubular mesothelioma)	Benign neoplasm derived from the surface epithelium of the ovary. It is the most common spontaneous ovarian neoplasm in some strains of mice. Tubulostromal adenomas are at least 2-3 mm diam and compress adjacent ovarian tissue or efface the ovary. They are composed of cords or tubules of non-ciliated cuboidal or columnar cells separated by large round-polygonal cells that resemble stromal interstitial cells and have eosinophilic foamy or vacuolated cytoplasm, sometimes with golden-brown pigment. They have been interpreted as invaginations of mesothelial (or germinal) epithelium into the ovarian stroma, sometimes dividing the ovary into multiple lobules. These invaginations usually present as variably sized tubular structures, lined by simple columnar, cuboidal or occasionally flattened epithelium. Tubulostromal hyperplasia does not form discrete masses, is not compressive, nor invasive, but differentiation of these conditions may be arbitrary. (Frith et al. 1988; Maekawa et al. 1996; Davis et al. 1999; Davis et al. 2001)
Ovary, tubulostromal adenocarcinoma	Malignant neoplasm derived from the surface epithelium of the ovary. Compared to tubulostromal adenoma, these neoplasms are much less common, and feature increased cellular atypia, increased mitotic index, hemorrhage metastasis, and invasion beyond the ovarian bursa. (Maekawa et al. 1996; Davis et al. 1999; Davis et al. 2001)
Uterus, adenoma endometrial	Benign neoplasm of uterine mucosal epithelium. These may be on a broad base or on a stalk (when they may be called polyps). They form well differentiated glandular or tubular papillary structures lined by cuboidal epithelium. Stromal proliferation should not be a feature (see stromal polyp). Maekawa, Maita et al. 1996; Davis, Dixon et al. 1999; Davis, Harleman et al. 2001)
Uterus, adenocarcinoma endometrial	Malignant neoplasm of uterine mucosal epithelium. These are uncommon in mice. They are poorly circumscribed masses that extend into and occlude the uterine lumen, invade deeply into myometrium and beyond, and may metastasize to lungs. The neoplastic epithelial cells may be well differentiated or very pleomorphic. Necrosis and hemorrhage are common. (Maekawa et al. 1996; Davis et al. 1999; Davis et al. 2001)
Uterus, hemangioma	Hemangioma in the uterus, see above, CARDIOVASCULAR.
Uterus, hemangiosarcoma	Hemangiosarcoma in the uterus, see above, CARDIOVASCULAR.
Uterus, leiomyoma	Benign neoplasm of smooth muscle cells of the myometrium. They may be reported in up to 3% of CD-1® or B6C3F1 mice in some studies and are more common than leiomyosarcomas. They are solitary well circumscribed masses that may compress adjacent tissues. They are composed of densely cellular sheets of interlacing bundles and whorls of spindle cells, with eosinophilic cytoplasm similar to adjacent myometrial smooth muscle cells. (Maekawa et al. 1996; Davis et al. 1999)
Uterus, leiomyosarcoma	Malignant neoplasm of smooth muscle cells of the myometrium. They are poorly delineated masses with disorganized and invasive growth patterns, and may have areas of necrosis and hemorrhage. The spindled cells may be more pleomorphic than in leiomyoma.(Maekawa et al. 1996; Davis et al. 1999)
Uterus, polyp stromal	Polypoid mass of uterine stromal tissue that projects into the uterine lumen. It is covered by cuboidal-columnar epithelium that is continuous with and similar to endometrial lining epithelium. There may be endometrial glandular elements as well. Most endometrial polyps have abundant loose stroma composed of stellate or spindle cells and numerous small blood vessels, and may have a few large dilated or pleomorphic endometrial glands. When the polyp is composed primarily of endometrial glandular tissue with little stroma, it may be referred to as a glandular polyp. (Maekawa et al. 1996; Davis et al.

	1999; Davis et al. 2001)
Uterus, stromal sarcoma	Malignant neoplasm of uterine fibrovascular stroma. Uncommon, reported in < 1% of CD-1® or B6C3F1 mice on chronic studies. Some may arise in stroma of uterine polyps. Composed of sheets of poorly differentiated spindle cells, may be pleomorphic and with giant cell and many mitoses. **Rule out Histiocytic sarcoma**, involving uterus. Variable amounts of fibrillar or collagenous matrix, and endothelium-lined vascular spaces. Rule out Hemangiosarcoma. There may be necrosis, hemorrhage and infiltration of myometrium, cervix and adjacent structures. Metastasis is rare. Differential diagnoses include histiocytic sarcoma, leiomyosarcoma, fibrosarcoma and Schwannoma. (Maekawa et al. 1996; Davis et al. 1999; Davis et al. 2001)
GENITAL, MALE	
Testes, interstitial cell tumor, Leydig cell tumor	Tumor derived from testicular Leydig cells (interstitial cells). Both benign and malignant spontaneous interstitial cell tumors are rare in mice, but can be induced with synthetic or natural estrogens in certain strains, especially in BALB/c mice. Unilateral, with no right or left predilection. 'Tumors' may be difficult to distinguish from interstitial hyperplasia. Hyperplastic foci may be distinguished by size (<3 seminiferous tubules diameter) and non-compression, compared to adenomas (> 3 seminiferous tubules diameter), compress surrounding tissue and exhibit some cellular pleomorphism. Spontaneous Leydig cell tumors tend to be well differentiated & of solid, diffuse type, composed of round homogeneous cells with eosinophilic granular cytoplasm. Small, well circumscribed tumors are adenomas, and large tumors which are invasive or metastasize are referred to as carcinomas. Larger carcinomas may metastasize to lungs. (Frith et al. 1988; Prahalada et al. 1994; Gordon et al. 1996; Mahler et al. 1997; Radovsky et al. 1999; Pathbase 2004)
Testes, teratoma; Testicular germ cell tumor (TGCT)	Benign or malignant germ cell derived tumors of the testes containing tissues from all 3 germ cell layers (endoderm, mesoderm, ectoderm). Testicular teratomas are rare but usually seen in young mice, especially of 129 strains. Should contain a variety of epithelial types, including cornifying, stratified squamous epithelium, ciliated tall columnar epithelium and intestinal epithelium, sometimes thyroid or pancreas, along with well differentiated cartilage, bone, skeletal or smooth muscle, and variable amounts of well differentiated nervous tissue resembling cerebral cortex. Benign tumors tend to appear more differentiated with easily recognizable mature tissues. Malignant tumors tend to be less differentiated, with large areas of necrosis and hemorrhage, and may metastasize. (Gordon et al. 1996; Rehm et al. 2001; Pathbase 2004) Extragonadal teratomas are usually in chimeric mice, originating from ES cells. (Blackshear et al. 1999)
Testes, seminoma	Testicular germ cell tumor derived from spermatogenic cells resembling spermatogonia or spermatocytes. These are very rare in mice, composed of fairly uniform large cells with clear (glycogen containing) cytoplasm and well defined cell borders, resembling primitive germ cells. (Gordon et al. 1996; Rehm et al. 2001; Pathbase 2004)
Testes, Sertoli cell tumor	Testicular germ cell tumor derived from sex cord/stromal cells (Sertoli cells). These are very rare in mice, composed of elongate cells typically arranged in distinctive palisades on delicate fibrovascular stroma (picket fence pattern), forming tortuous tubular structures without distinct lumina. A poorly organized diffuse pattern with few or indistinct tubular structures is less common. Neoplastic cells tend to have indistinct borders, pale vacuolated cytoplasm and many mitotic figures. (Rehm et al. 2001; Pathbase 2004)
HEMATOPOIETIC	
Histiocytic sarcoma	Solid tumor mass composed predominantly of histiocytic cells (Kogan et al. 2002) These can be common hematopoietic

(reticulum cell sarcoma or reticulum cell neoplasm, type A; endometrial sarcoma)	neoplasms in some strains, and usually are more common in female mice. Usuallydiagnosed after 12 months of age. Liver and uterus or vagina are commonly involved. Spleen, lymph node, bone marrow, lung, kidney and ovaries also may be involved. Non circumscribed, highly infiltrative accumulations of usually large histiocytoid cells with ample eosinophilic cytoplasm. There may be areas of primarily elongate cells in sarcomatous patterns, multinucleated cells, and erythrophagocytosis. There may be areas of necrosis surrounded by palisading cells. Liver sinusoids may be filled and expanded by neoplastic cells, and (metastatic) neoplastic cells may be prominent in pulmonary vasculature. The cells should be immunocytochemically positive for histiocytic markers including lysozyme. Eosinophilic hyaline droplets (of lysozyme) are reported in kidney tubules. Liver hematopoiesis may be increased. (Ward et al. 1999; Frith et al. 2001; Lacroix-Triki et al. 2003)
Leukemia, lymphoid	The majority of lymphoid leukemias in mice, as defined by involvement of the blood, represent “spillover" of lymphoma cells into the blood, i.e. not primary leukemias but rather lymphomas with leukemic phases. (Morse et al. 2002)
Leukemia, non lymphoid	Nonlymphoid leukemias, myeloid dysplasias, and myeloid proliferations (non reactive) include diseases that arise primarily as increased numbers of nonlymphoid hematopoietic cells in the spleen and/or bone marrow. Leukemias are disseminated diseases that are rapidly fatal. Many leukemias are characterized by impaired differentiation, but myeloproliferative-disease–like (MPD-like) myeloid leukemias retain differentiation to mature forms. Myeloid dysplasias are characterized by cytopenias and abnormal differentiation. Nonlymphoid hematopoietic sarcomas are cellular proliferations that arise primarily as solid tumors e.g. histiocytic sarcoma. Myelogenous leukemias or erythroleukemias are uncommon in mice and can be induced by some murine leukemia viruses and by genetic manipulations.(Kogan et al. 2002)
Lymphoma (any type)	Malignant neoplasm of lymphoid cells. This term usually designates solid neoplasms. Some studies do not distinguish hematopoietic neoplasms, or it is not clear what the correct current nomenclature should be based on the nomenclature used. Immunohistochemistry and/or molecular techniques should be used to determine accurate diagnoses and subclassifications. Only a few of more common spontaneous lymphomas are listed here. (Ward et al. 1999; Frith et al. 2001; Morse et al. 2002)
Lymphoma, diffuse large B cell lymphoma; follicular center cell lymphoma	Neoplasm of mature B lymphocytes. This has been reported as a spontaneous tumor in some congenic and recombinant inbred mice. There usually is splenic involvement with little or late lymph node involvement, sometimes liver and blood involvement. The cells are uniformly small B cells.(Morse et al. 2002)
Lymphoma, follicular B cell lymphoma; follicular center cell lymphoma; reticulum cell sarcoma or reticulum cell neoplasm, type B	Neoplasm of mature B lymphocytes, although infiltrating (polyclonal) T cells may be numerous. These are the most common spontaneous hematopoietic neoplasm in many mouse strains. Usually they are diagnosed after 12 months of age. There is progressive enlargement of the spleen with mottling on cut section due to neoplastic enlargement of follicles in white pulp. Advanced cases have massively enlarged mesenteric lymph nodes and spleen, and prominent GALT. Histologically there is diffuse involvement of splenic white pulp and cells are small or large, with cleaved or non-cleaved nuclei with clumped or vesicular chromatin of apparently mixed-cell types, although early tumors may be more plasmacytoid. (Ward et al. 1999; Frith et al. 2001; Morse et al. 2002)
Lymphoma, precursor T cell lymphoblastic lymphoma; (thymic	Neoplasm of immature T cells that arises in the thymus. Lymphomas of T cell origin usually arise in the thymus. Clinically mice with thymic lymphoma may be dyspneic due to massive enlargement of the thymus. Necropsy findings commonly also include enlarged spleen and lymph nodes. Involvement of liver, kidneys and bone marrow may occur in advanced

leukemia)	stages, or may represent an additional neoplastic process. Histologically neoplastic cells are monomorphic and medium sized with scant cytoplasm, and the starry sky pattern is attributed to scattered larger paler (tingible body) macrophages, which are engulfing apoptotic or necrotic cells and debris, in sheets of homogeneous neoplastic lymphoid cells. This is the most common lymphoma affecting the thymus, is very common in AKR mice and is the most commonly induced tumor by viruses and carcinogens. (Ward et al. 1999; Frith et al. 2001; Karpova et al. 2002; Morse et al. 2002)
Plasmacytoma	Neoplasm of mature secretory B cells. It is an uncommon spontaneous neoplasms in mice but can be induced by induced by pristane and mineral oil, especially in BALB/c mice. The spontaneous tumor presents with splenomegaly and lymphadenopathy. The pristane induced tumor arises in peritoneal granulomas. Histologically it is characterized by mature plasmacytoid cells with ample amphophilic cytoplasm, frequently with paranuclear pallor due to golgi material, and round clock-face nuclei with central nucleoli. They should be immunocytochemically positive for cytoplasmic immunoglobulins. (Ward et al. 1999; Frith et al. 2001; Morse et al. 2002)
Spleen, hemangioma	See above, CARDIOVASCULAR.
INTEGUMENT	
Mammary hyperplasia functional without atypia	See table 5
Mammary hyperplastic alveolar nodule; HAN	**HAN** are common preneoplastic findings in MMTV-infected and MMTV-free mice & in carcinogen-treated mice. Grossly HAN are 1-5 mm nodules, frequently outlined by yellow pigment. Histology: foci of lobuloalveolar hyperplasia, characterized by closely crowded acini lined by a single layer of epithelium, lacking significant dysplasia, in a background of normal fatty stroma. This hyperplastic mammary tissue is **immortal and can be serially transplanted**, with development into focal proliferations and neoplastic lesions. (Medina 1982; Rehm et al. 1996; Cardiff et al. 1999; Cardiff et al. 2000)
Mammary plaques	Mammary plaques are epithelial proliferations that occur in mouse mammary glands during pregnancy or after hormone induction, but **regress** after withdrawal of the stimulus. These were formerly known as type P or pregnancy dependent tumors. Histologically they consist of radiating ducts surrounded by dense connective tissue. (Medina 1982; Rehm et al. 1996; Cardiff et al. 1999)
Mammary gland, tumor	Mammary neoplasm, adenoma vs. adenocarcinoma vs. other not specified
Mammary gland, adenoma	Benign neoplasm of the mammary gland. These are rare in mice, but well differentiated acinar pattern carcinomas may be referred to as adenomas in some studies. These are well differentiated, circumscribed or encapsulated nodules composed of closely packed, small, uniform, acinar structures. (Seely et al. 1999; Bruner et al. 2001)
Mammary gland, adenocarcinoma	Malignant neoplasm of the mammary gland. Most spontaneous or MMTV-induced mammary tumors in mice have been classified as type A, B or C adenocarcinomas according to Thelma Dunn's original 1959 classification. **Type A (acinar) or microacinar** adenocarcinomas are composed of small acini lined by a single layer of cuboidal cells. These also have been referred to as adenoma and tubular carcinoma. **Type B (bizarre) or ductal tumors** are most common, have more variable histologic features, with well- and poorly-differentiated regions of neoplastic cells in cords or sheets or papilloma-like configurations. They can rise from carcinogen-

	induced ductal hyperplasias. **Type C (cystic)** tumors are less common than A or B tumors, and feature cystic epithelial structures in more abundant stroma. (Medina 1982; Rehm et al. 1996; Cardiff et al. 1999; Cardiff et al. 2000)
Mammary gland, carcinoma with squamous differentiation, adenoacanthoma, adenosquamous carcinoma	The term adenoacanthoma has been used to refer to benign and malignant adenomatous epithelial tumors with some squamous differentiation. In mice mammary adenoacanthoma usually refers to a malignant mammary neoplasm with squamous cell areas covering > 25% of the lesion. When squamous component is < 25%, it is 'adenocarcinoma'. (Bruner et al. 2001) Adenoacanthomas are more likely to occur in old retired breeders than in young animals, are more common in BALB/c (and maybe FVB/N mice) than in other common strains, and they can have a high incidence with some carcinogenesis protocols. (Rehm 1990; Rehm et al. 1996; Cardiff et al. 1999; Cardiff et al. 2000; Nieto et al. 2003)
Mammary gland, fibroadenoma	Benign neoplasm of mammary epithelium plus fibrocollagenous connective tissue. Common in rats, but unusual in mice. It is composed of proliferating ducts within a dense fibrous stroma. (Seely et al. 1999; Bruner et al. 2001)
Skin subcutis, fibroma	Benign neoplasm of fibroblasts or fibrocytes, characterized by production of collagen. Present as firm rounded skin masses or elevations. . Circumscribed masses of collagenous connective tissue that can compress or distort surrounding tissues. Spindle cells are enmeshed in collagen fibers in interlacing bundles. (Sundberg 1996; Peckham et al. 1999; Ernst et al. 2001)
Skin subcutis, fibrosarcoma	Malignant neoplasm of fibroblasts or fibrocytes. Tend to have more irregular patterns, higher cellularity, more cellular pleomorphism or atypia, and may have less collagen than fibromas. May have herring bone patterns, necrosis, hemorrhage, inflammation, and alopecia and ulceration of overlying skin. Local invasion can be extensive but metastasis late and infrequent. (Peckham et al. 1999; Ernst et al. 2001)
Skin subcutis, fibrous histiocytoma	Neoplasm of pluripotential mesenchymal stem cells. Should exhibit storiform patterns and have histiocytoid features to be diagnosed. They may be positive for histiocytic enzymes such as lysozyme, cathepsin B, alpha 1 antitrypsin, alspha1 antichymotrypsin as well as mesenchymal markers. They have been reported as the most common skin/subcutaneous neoplasm in CD-1® mice. Histologically benign fibrous histiocytoma are composed of primarily well differentiated spindled fibroblast-like cells in storiform and cartwheel patterns, and may have abundant collagen, but also have a histiocytoid component of plumper cells that may exhibit phagocytosis. There may be inflammatory cells scattered in and around the neoplasm. Malignant neoplasms have more variable patterns, fibrous, myxoid, pleomorphic, and mixed. These neoplasms may be difficult to distinguish from poorly differentiated fibrosarcomas, and may be diagnosed as fibrosarcoma or undifferentiated sarcoma in some reports. (Peckham et al. 1999; Ernst et al. 2001)
Skin subcutis, hemangioma (angioma)	Hemangiomas in skin or subcutis are dark red or purple raised lesions that bleed profusely when cut. See above Hemangioma. (Booth et al. 1995; Booth et al. 1996) also see above CARDIOVASCULAR.
Skin subcutis, lipoma, liposarcoma	Lipoma and liposarcoma are rare in mice. Lipomas are well circumscribed accumulations mature unilocular adipocytes with peripherally compressed nuclei. Liposarcomas tend to be firmer, poorly circumscribed, more cellular with more poorly differentiated spindle cells, and fewer typical adipocytes. (Peckham et al. 1999; Ernst et al. 2001)
Skin subcutis, neural crest tumor	Subcutaneous spindle cell tumors occurring on the pinna and tail of FVB/N mice were diagnosed as neural crest tumors. They resemble the amelanotic melanomas of the pinnae of Fischer 344 rats. (Mahler et al. 1996)
Skin subcutis, neurofibroma, neurofibrosarcoma	See below, NERVOUS.

Skin subcutis, Schwannoma, nerve sheath tumor	See below, NERVOUS.
Skin, papilloma; Squamous papilloma	A benign neoplasm consisting of villous or arborescent outgrowths of fibrovascular stroma covered by neoplastic squamous epithelial cells. These are uncommon spontaneous neoplasms, but are induce in various carcinogen protocols. They are usually exophytic or papillary, but may be pedunculated (on a thin stalk) or sessile (flat). The basal cell layer or borderline should be distinct. Acanthosis, and hyperkeratosis or parakeratosis are typical. (Bruner et al. 2001; Pathbase 2004)
MUSCULOSKELETAL	
Rhabdomyosarcoma	Malignant neoplasm of striated skeletal muscle. These neoplasms arise as nodules in skeletal muscle. Neoplastic cells are pleomorphic, with elongate, strap-like cells with multiple nuclei in tandem array, and smaller plump to spindled haphazardly oriented cells. Cross striations in neoplastic cells distinguishes this from other sarcomas, but can be very difficult to discern. They may be enhanced by phosphotungstic acid hematoxylin (PTAH) stains. (Sundberg et al. 1991; Sundberg et al. 1996)
NERVOUS	
Brain, astrocytoma	Neoplasm of astrocytic glial cells. Astrocytomas is even less common than oligodendrogliomas in mice. Should be confined to one area of brain but margins are indistinct and there may be edema, hemorrhage. Cells tend to be monomorphic but with indistinct cytoplasmic border, and large, oval or slightly folded nuclei. Hemorrhage and necrosis may be more typical of astrocytomas than of oligodendrogliomas. Malignant neoplasms may be multicentric with invasion of perivascular spaces and meninges. Morgan, Frith et al. 1984; Frith and Ward 1988; Radovsky and Mahler 1999; Krinke, Fix et al. 2001)
Brain, meningioma	Neoplasm of meningeal cells. These usually present as discrete nodules on the surface of the brain or spinal cord. They are expansile and compress adjacent soft tissue, and rarely exhibit invasion (malignancy). The fibrous type has a regular pattern of loosely interwoven bundles of delicate spindle cells, with single small hyperchromatic oval nuclei. The neoplasms may appear myxomatous when there is abundant faintly basophilic finely granular ground substance. Meningothelial types are less common and have larger, more epithelioid cells with abundant eosinophilic cytoplasm forming sheets or lobules. (Morgan et al. 1984; Frith et al. 1988; Radovsky et al. 1999; Krinke et al. 2001)
Brain, oligodendroglioma	Neoplasm of oligodendrocytes that normally form myelin sheaths in the CNS. Brain tumors are uncommon in spontaneous or induced tumors in mice but these are the most commonly diagnosed CNS neoplasms. It occurs in the cerebrum and/or diencephalon, usually is ventro-lateral and involves much of the thalamus, hypothalamus and amygdaloid. It is poorly demarcated mass but expansile and distorts surrounding tissues. It is distinct from adjacent neuropil due to distinctive monomorphic cell population of small cell with small dark round nuclei, and a typical perinuclear clear halo, that may result in a honeycomb pattern. Blood vessels within the neoplasm may have hyperplastic endothelium.. There may be necrosis and hemorrhage. (Morgan et al. 1984; Frith et al. 1988; Radovsky et al. 1999; Krinke et al. 2001)
Neurofibroma, neurofibrosarcoma	Neoplasm derived from fibroblasts of perineural connective tissue (perineurium), distinct from schwannoma. Histologically they resemble fibroma or fibrosarcoma, with neoplastic spindle cells arranged in bundles of eosinophilic fibers. (Peckham et al. 1999)
Schwannoma, nerve sheath tumor	Neoplasm derived from nerve sheath cells (Schwann cells), which normally produce the neurilemma and myelin layers surrounding axons in the peripheral nervous system (PNS), and are of ectodermal, neural crest, origin. These are

	uncommon neoplasms in mice but most likely to be diagnosed in the subcutis and heart. Benign neoplasms are discrete, expansile, compressive. Malignant neoplasms are invasive, usually with more atypia and mitotic figures. These spindle cell tumors have 2 typical growth patterns. Antoni type A pattern features elongate cells in whirls and bundles with their nuclei palisading in parallel array. These areas may be called Verocay bodies. Antoni B pattern is a looser pattern with sparser cells more haphazardly arranged in a clear or edematous matrix. Ultrastructurally these cells should have basal laminae, and immunohistochemical staining for S 100 indicating neural crest origin. (Peckham et al. 1999; Ernst et al. 2001)
RESPIRATORY	
Nasal cavity hemangioma	Hemangioma in the nasal cavity, see above, cardiovascular
Nasal cavity; schwannoma, neurilemmoma	Schwannoma of the nasal cavity. See above, NERVOUS
Lung tumors	Pulmonary neoplasm, adenoma vs. adenocarcinoma not distinguished. Usually other types of tumors or metastases in the lung are not included in this category, unless diagnoses were made by gross examination only.
Lung, bronchoalveolar hyperplasia; Type II cell hyperplasia	See table 5.
Lung, adenoma (BAA, bronchioloalveolar adenoma)	Benign neoplasm of airway epithelium supported on fibrovascular stroma in acinar or papillary patterns. right lobes are involved more frequently than the left. The most common tumor type, previously called bronchoalveolar or bronchioloalveolar adenoma, currently is classified simply as adenoma of the lung, and they may have acinar (solid) papillary or mixed patterns.(Nikitin AY 2004) Grossly, these tumors are yellow-white, discrete nodules ranging in size from 1.0-10 mm. Adenomas are usually less than 4 mm in diameter with solid > papillary > mixed patterns. (Dixon et al. 1991; Festing et al. 1994; Dixon et al. 1999; Dungworth et al. 2001)
Lung, carcinoma (bronchioloalveolar carcinoma)	Malignant neoplasm of airway epithelium. Carcinomas usually are irregular nodules larger than 4 mm in diameter with papillary >> mixed patterns. Carcinomas are less common than adenomas and may metastasize to liver. They may be difficult to distinguish from large adenomas when there is not obvious destruction of parenchyma, invasion of bronchiolar walls, interstitial tissue or pleura, lymphatic dissemination or distant metastasis. (Dixon et al. 1991; Festing et al. 1994; Dixon et al. 1999; Dungworth et al. 2001)
SPECIAL SENSES	
Harderian gland, tumor	Neoplasm of the Harderian gland adenoma vs. carcinoma not specified.
Harderian gland, adenoma	Benign neoplasm of acinar epithelium of Harderian gland. Especially common in BALB/c females. Adenomas are much more common than carcinomas. They may be under-reported because the gland may not be examined unless there is a grossly obvious lesion. Usually well demarcated or encapsulated nodules, with compression of surrounding gland. Patterns may be papillary, cystic, cystic-papillary or acinar, and the neoplastic cells usually are well differentiated and in a single layer. (Sheldon et al. 1983; Botts et al. 1999; Krinke et al. 2001)
Harderian gland, carcinoma or adenocarcinoma	Malignant tumor of acinar epithelium of the Harderian gland. These usually are larger than adenomas and may cause facial selling and/or exophthalmos. They are highly cellular, and disorganized compared to adenomas, with piling up of

	pleomorphic cells. Areas of medullary or solid growth patterns are common. There may be necrosis and hemorrhage, invasion beyond the orbit and distant metastasis to lungs, local lymph nodes, thymus, or liver. (Botts et al. 1999; Krinke et al. 2001)
URINARY	
Kidney, renal tubular hyperplasia	Hyperplasia or proliferation of renal tubule epithelium. By convention foci of hyperplasia are < 3 times the diameter of a normal tubule. They may be precursors of adenomas or carcinomas. The tubule may be expanded by several layers of slightly pleomorphic epithelial cells, or the tubule may be dilated with an expanded lumen and lined by an irregular and crowded pleomorphic epithelial cells. Crowded cells with nuclear crowding usually is apparent. Tubule structure is essentially maintained and there is no compression of adjacent parenchyma. (Seely 1999; Hard et al. 2001)
Kidney, adenoma (renal tubular cell adenoma)	Benign neoplasm of renal tubule epithelium. These are uncommon spontaneous neoplasms in mice, with adenoma and carcinoma incidence usually < 1%. They usually are solitary, and classified morphologically as cystic, papillary, or solid, with papillary being most common type. The neoplastic cells are uniformly cuboidal with eosinophilic cytoplasm and relatively small nuclei. Mitotic figures are rare. Cystic and papillary adenomas usually are encapsulated. Solid adenomas usually are well demarcated from adjacent parenchyma, but not encapsulated. (Frith et al. 1988; Seely 1999; Hard et al. 2001)
Kidney adenocarcinoma; (renal tubular cell carcinoma, renal cell carcinoma)	Malignant neoplasm of renal tubule epithelium. These are uncommon spontaneous neoplasms in mice, with adenoma and carcinoma incidence usually < 1%. They may have solid, papillary or tubular, or anaplastic patterns. They are compressive and may have necrosis or hemorrhage, or cystic areas with intraluminal pale eosinophilic material. Neoplastic cells vary from small and uniform to large and pleomorphic, with granular eosinophilic, clear or basophilic cytoplasm. Their nuclei may be uniformly small and round or oval, or large and pleomorphic, and the mitotic index is variable. Metastasis is rare and usually to the lungs. (Frith et al. 1988; Seely 1999; Hard et al. 2001)

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