Non-proliferative Lesions of the Endocrine System in Rats


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INTRODUCTION

The terminology used to describe non-proliferative lesions of the endocrine system in the rat is quite varied. Since the rat is utilized in both research and testing, proper diagnosis and characterization of non-proliferative endocrine lesions in this species is important. This guide presents a biologically accurate morphologic classification of non-proliferative lesions of the adrenal gland, pituitary gland, thyroid gland, parathyroid gland, and endocrine pancreas in the rat. The lesions have each been divided into one of the following categories: congenital, disturbances of growth, degenerative, inflammatory, vascular, and miscellaneous.

MORPHOLOGY

ADRENAL GLAND

CONGENITAL LESIONS

Accessory (Adreno) Cortical Tissue (Figure 1)
(Synonyms: ectopic adrenal, adrenal cortical nodule, hamartoma, adrenocortical rest)

Accessory (adreno) cortical tissue is characterized by the presence of concomitant adrenocortical tissue outside the adrenal capsule or in the periadrenal tissue. It may be found at any location within the abdominal cavity although it is most commonly found in the retroperitoneal fat adjacent to the adrenal gland or kidney (4). It is composed of normal cortex either detached from the adrenal gland, or attached to the gland but separated from it by a complete fibrous capsule. No medullary tissue is present (19). Accessory (adreno) cortical tissue must be distinguished from cortical neoplasms.

Histologically, accessory (adreno) cortical tissue lacks the distinct zonal arrangement of the adrenal cortex, as there are no cells which are compatible with the zona
glomerulosa and the distinctive anastomosing columns of the zona fasciculata are not apparent. The central portion of the nodule may contain dilated capillaries. Although a capsule is generally present, it may be incomplete. This makes differentiation from a cortical neoplasm difficult, as the cortical tissue may extend past the capsular borders. However, features of cellular atypia and vascular or capsular invasion are not present in accessory (adrenocortical) tissue as they would be in an adrenal cortical carcinoma.

Electron microscopic examination indicates that the cells at the periphery of the nodules exhibit ultrastructural characteristics between those of the zona glomerulosa and zona fasciculata, whereas the cells at the mid- and central-portion exhibit ultrastructural characteristics of the zona fasciculata and zona reticularis, respectively (4). The outer cells have some ultrastructural similarity to zona glomerulosa cells but are not considered to be functional. This lack of functionality may be associated with the lack of chromaffin tissue, as data indicate that production of catecholamines and dopamine exerts a paracrine effect on the control of zona glomerulosa function (36).

**DISRUPTIONS OF GROWTH**

**Atrophy (Figure 2)**

(Synonym: cortical atrophy)

Adrenal atrophy may be bilateral or unilateral and generally affects only the cortex. It is characterized by a reduction in the thickness of the various cortical zones. In most cases, the primary effect is on the zona fasciculata and reticularis. Histologically, the cortex is markedly diminished in area, reflecting actual cell loss and reduction in cytoplasmic volume of the remaining cells. There may also be a variable disruption of the normal architectural cortical arrangement, pyknosis, and lipofuscin deposition (40).

**Hypertrophy (Figure 3)**

Hypertrophy of the adrenal cortex cells may be unilateral or bilateral, and focal, multifocal, or diffuse. Diffuse hypertrophy results in an increased thickness of the cortex and may also result in increased adrenal weight. Focal hypertrophy is characterized by focal areas of enlarged cells, usually within the zona glomerulosa or fasciculata. The focus is usually well-circumscribed but compression is usually not evident. In the F344 rat, some large foci may cause some slight compression. The cytoplasm of the hypertrophic cells may be basophilic or eosinophilic.

**DEGENERATIVE CHANGES**

**Cortical Vacuolation (Figure 4)**

(Synonym: fatty change)

Cortical vacuolation is characterized by the presence of small spaces or cavities in the cytoplasm of cortical cells and usually involves the zona fasciculata (19). The lesion may be focal, multifocal, or diffuse and may be unilateral or bilateral. The distribution of the vacuolation aids in the determination of etiology. Spontaneous cortical vacuolar change, a relatively common change in aged rats, is most often focal. In comparison, physiologic cortical vacuolation is generally present in a diffuse pattern (19), and may be an indirect response to a drug or a reflection of some other stress upon the animal.

The histologic appearance of cortical vacuolation varies from multiple small vacuoles to single, large, clear cytoplasmic vacuoles. Because of the expansion of the cytoplasm, focal lesions may result in minimal to mild compression of the adjacent parenchyma, thus bearing some resemblance to a cortical neoplasm. However, the actual number of cells within the vacuolated area is not increased (it may actually appear hypocellular due to cytoplasmic expansion), and there is no indication of cellular atypia.

The three zones of the adrenal cortex normally have some degree of vacuolation, with the extent of the vacuolar appearance varying between zones and as a state of cellular activity. In the normal rat, the zona fasciculata contains the most prominent vacuoles. These vacuoles consist of large or small, clear, round intracytoplasmic structures which contain neutral lipids and cholesterol. In comparison, cells of the zona reticularis are smaller and generally contain fewer vacuoles. The normal vacuolation of the zona glomerulosa varies, with the presence of numerous fine vacuoles being associated with the highest cellular activity (19).

**Cystic Degeneration (Figure 5)**

(Synonyms: cystic change, peliosis of the adrenal cortex)

Cystic degeneration is considered to be a continuum of cortical vacuolation, particularly severe forms in which there is cell loss with the resultant formation of cystic (and sometimes blood-filled) spaces. The lesion occurs predominantly in aging female rats, particularly the Sprague-Dawley strain (19). Histologically, the change is variable. It can range from the more common focal areas in which small aggregates of cells feature cytoplasmic vacuolation with coalescence of cells, to the more rarely encountered lesion typified by extensive cell loss involving the majority of the adrenal cortex. Although compression of the adjacent parenchyma may occur, foci of cystic degeneration can be differentiated from neoplasms by the lack of atypia and by the actual decrease, rather than increase, in the number of cells in the lesion. However, the zone adjacent to a region of cystic degeneration should be carefully scrutinized since cystic degeneration can occur within hyperplastic or neoplastic lesions (19). Cystic degeneration can be distinguished from proliferative lesions by the fact that the total number of cells is decreased, as
compared to the surrounding parenchyma, and mitoses are absent.

Mineralization (Figure 6)

Mineralization is the term used for deposition of a non-organic mineral substance which is homogenous and bluish/purple. It may be intracellular or extracellular. Dystrophic mineralization is observed in the adrenal cortex usually following necrosis or hemorrhage. This lesion may be multifocal or diffuse and may not be associated with inflammation. Experimentally, adrenal medullary mineralization has been induced in rats following chronic exposure to chlorodibromomethane.

Lipofuscin Pigmentation (Figure 7)
(Synonyms: lipofuscinosis, ceroid, brown atrophy, brown degeneration, wear-tear pigment)

Lipofuscin pigmentation is characterized by the deposition of yellow to brown granular pigment usually in the cells of the zona reticularis. It may be associated with severe hormone-induced atrophy and must be distinguished from hemosiderin-laden macrophages which also occur frequently in the same region. Special stains may be required to distinguish between hemosiderin and lipofuscin. Iron stains such as Prussian blue will confirm hemosiderin. Lipofuscin may exhibit auto fluorescence. Chemically, it is usually PAS positive, sudanophilic, and acid fast.

Small amounts of lipofuscin are commonly observed in aged rats. However, its presence in young rats is an indication of excessive cellular organelle turnover or defective cell metabolism.

Necrosis (Figure 8)

Foci of necrosis in the adrenal gland may be associated with diverse conditions, such as hemorrhage, cystic degeneration, inflammation, and, in F344 rats, with mononuclear cell leukemia. Foci of coagulative necrosis are well-defined and usually observed in the zona fasciculata and/or reticularis. This lesion can also be induced by some chemical agents.

Vascular Changes

Extramedullary Hematopoiesis (Figure 9)

Extramedullary hematopoiesis is occasionally observed in the adrenal gland. Foci are most often present in the adrenal cortex, are usually multiple, and may consist of either erythrocytic or granulocytic components. When such foci are present in the adrenal gland, the spleen is usually enlarged as a result of increased extramedullary hematopoiesis. This lesion must be distinguished from inflammation.

Hemangiectasis (Figure 10)
(Synonym: peliosis)

Hemangiectasis (capillary dilatation) may be observed in the adrenal cortex or medulla. This lesion is characterized by blood-filled spaces lined by endothelium. It may be associated with inflammatory, degenerative, and/or neoplastic disease processes. Hyperemia with hemangiectasis and dilatation of intercellular spaces may be related to stress and/or exogenous administration of adrenocorticotrophic hormone (ACTH). Hemangiectasis may be difficult to differentiate from cystic degeneration with hemorrhage, as the two lesions may occur together.

Thrombosis (Figure 11)

Thrombosis is observed infrequently in the adrenal gland of rats. It is characterized by the formation of a solid mass of fibrin and platelets within the lumen of a blood vessel. A small number of trapped erythrocytes may also be found.

Inflammatory Changes

Inflammation (Figure 12)

Inflammation of the adrenal gland is rarely observed. It is usually associated with generalized systemic disease or an extension of peritonitis. Inflammatory cells are predominantly neutrophils in acute cases, and plasma cells and lymphocytes in more chronic cases. Epithelial cell degeneration or loss is apparent.

PITUITARY GLAND

Congenital Changes

Persistence of Rathke’s Pouch (Figures 13 & 14)

Portions of Rathke’s pouch, the embryologic structure which ultimately gives rise to the pituitary, may persist in the pituitary of the adult rat. Although they may be located in the pars distalis, pars intermedia, or pars nervosa (28), remnants of Rathke’s pouch often are closely associated with Rathke’s cleft, which separates the pars distalis from the pars intermedia (12). Rathke’s pouch remnants appear as variably-sized tubular or glandular structures. The epithelium lining of these structures is generally ciliated but can be squamous, cuboidal, or columnar. If tubular or glandular structures are not present, the lesion should be referred to simply as a cyst. Some of the cysts seen in aged rats may actually have their origins in Rathke’s pouch remnants (28).

Cysts (Figure 15 & 16)

Pituitary cysts most commonly arise either in the periphery of the pars distalis or in close association with the lumen of Rathke’s cleft. The origin of a cyst is rarely
evident and cannot be definitively determined from its structure, position, or contents (5). Cysts may be simple or multilocular, usually contain an eosinophilic to amphophilic mucoproteinaceous material, and may be large enough to be seen macroscopically. The single layer of cuboidal to columnar epithelium lining the cysts is generally ciliated and may or may not contain mucous cells (12). Rathke’s cleft itself may become dilated and cystic and contain a colloid-like proteinaceous material, blood, or blood break-down products.

A clustering of cysts lined by non-ciliated cuboidal to columnar epithelium has been described in the pars nervosa. Lansdown and Grasso (27) postulate that these are derived from a congenital aberration of Rathke’s cleft. In addition, small cysts located around the pituitary stalk, or pars tuberalis, are thought to be derived from remnants of the cranioopharyngeal duct (12). Pseudocysts, which completely lack an epithelial lining, are usually found in the pars distalis and are delimited by normal and degenerate pituitary epithelial cells (28).

**DISTURBANCES OF GROWTH**

**Hypertrophy (Figure 17)**

Hypertrophy, or an increase in size of one or more cell types, is one of the more commonly observed responses of the pituitary in toxicity studies (8, 18, 28, 29, 42). It usually does not reflect a direct effect on the pituitary, but is related to toxicity in other endocrine organs or increased metabolism and/or excretion of the target organ secretion. The resulting reduction in circulating endocrine hormone removes the negative feedback mechanism to the hypothalamic-hypophyseal axis and causes changes in the specific cell type in the pars anterior. Cells first undergo degranulation followed by hypertrophy. If the condition continues, hyperplasia occurs and individual cells may become vacuolated with their nuclei displaced. This gives the cells a signet-ring appearance. The specific cell types affected can be identified using immunocytochemical techniques.

**Vascular Changes**

Vascular changes are occasionally seen in the pars distalis of aging rats.

**Hemangiectasis (Figure 18)**

Hemangiectasis is characterized by the presence of dilated, blood-filled spaces lined by a single layer of well-differentiated endothelium. It is relatively common in the highly vascular pars distalis of older rats. There may be an accompanying accumulation of proteinaceous fluid or hemorrhage (28).

**Hemorrhage (Figure 19)**

Hemorrhage may occur secondary to neoplasia and is sometimes seen in animals with mononuclear cell leukemia. It is characterized by free erythrocytes outside of vascular channels. If the condition is long standing, hemosiderin-laden macrophages, cholesterol clefts, fibrosis, and sometimes infarction may be present (28).

**Thrombosis**

Thrombosis occurs as a solid mass within the lumen of blood vessels. It is composed of fibrin and platelets and may contain trapped erythrocytes.

**INFLAMMATORY CHANGES**

**Inflammation (Figure 20)**

Inflammation in the pituitary gland is uncommon. In the rare instances when inflammation is present, it is generally associated with meningitis secondary to otitis interna, or with sinusitis secondary to periodontitis (12). Inflammatory cells are predominantly neutrophils in acute cases and plasma cells and lymphocytes in more chronic cases. Inflammatory infiltrates in the pituitary gland must be differentiated from the more common neoplastic cell infiltrates seen with leukemia or malignant lymphoma (12).

**THYROID GLAND**

**Congenital Changes**

**Ultimobranchial Cysts (Figure 21)**

Ultimobranchial duct cysts are remnants of the embryonic ultimobranchial bodies, and are common findings in rats. The ultimobranchial bodies arise from the third pharyngeal pouch and contain the precursors of the C-cells, which are thought to migrate to the ultimobranchial bodies from the neural crest. The ultimobranchial bodies lose their attachments to the pharyngeal pouch and become incorporated into the developing lobes of the thyroid gland. Remnants of the ultimobranchial bodies are continuous with the thyroid parenchyma.

Ultimobranchial cysts are commonly located in the central portion of the thyroid lobe and usually appear to be unilateral, although bilateral cysts have been observed. The cysts generally appear as cystic or elongated duct-like structures that may be several times larger than an average thyroid follicle. They are lined by flattened squamous epithelium and usually contain varying amounts of debris. Occasionally, the cysts will take the form of follicular structures that are lined by a mixture of typical flattened ultimobranchial cyst epithelium and normal thyroid follicular epithelial cells. These follicular structures apparently represent areas of continuity between the ultimobranchial cyst and the thyroid parenchyma. It is important to distinguish ultimobranchial cysts from cystic or degenerate follicles.
**Persistent Thyroglossal Ducts**

Persistent thyroglossal ducts are uncommon findings in rats. The embryologic development of the thyroid gland begins as a ventral downgrowth of endoderm from the midline of the floor of the primitive pharynx. As the epithelium continues its downward growth, it remains attached to the epithelium of the pharyngeal floor by way of an epithelial tube known as the thyroglossal duct. The connection between the pharyngeal floor and the thyroglossal duct eventually ruptures and the duct usually regresses. Occasionally, however, remnants of the duct persist within the thyroid gland. They are usually located along the ventral aspect of the larynx on the midline, consistent with the location of the thyroglossal duct during embryonic life. Persistent thyroglossal ducts are small cystic or duct-like structures lined by simple cuboidal to columnar epithelium that may be ciliated. These structures are often filled with mucinous material. As with ultimobranchial cysts, persistent thyroglossal ducts must be differentiated from cystic or degenerate follicles.

**Ectopic Thymus (Figure 22)**

Foci of ectopic thymic tissue are sometimes found within the connective tissue adjacent to the thyroid or are partially to completely surrounded by thyroid tissue. Some foci, particularly larger ones, have the typical appearance of thymus, with a distinct cortex and medulla. Other foci, particularly smaller ones, may consist mainly of lymphocytes and may be difficult to recognize as thymic tissue. It is necessary to identify the presence of pale staining clusters of thymic epithelial cells and/or Hassall’s corpuscles within these foci in order to be certain they represent ectopic thymic tissue. Ectopic thymic tissue must be differentiated from simple lymphoid aggregates.

**Degenerative Changes**

**Mineralization (Figure 23)**

Irregular, basophilic clumps of mineral are occasionally seen within the lumen of one to a few individual scattered follicles. Some affected follicles may contain pale colloid, but commonly the follicles appear normal except for the presence of the mineral. Mineralization generally occurs in adult animals and appears to be a normal aging change.

**Pigmentation (Figure 24)**

Brown granular pigment is sometimes seen within follicular epithelial cells or within follicular lumina of older animals and is apparently a normal aging change. Thyroid gland pigment has been reported to stain positive with iron and periodic acid-Schiff (PAS) stains and sometimes with acid-fast stain (46). Pigmentation has also been reported to occur as a result of treatment (43, 45), the degree of pigmentation being greater than that normally seen in aging animals.

**Dilated Follicles (Figure 25)**

Thyroid follicles normally accumulate colloid and become enlarged as an animal ages. This enlargement is most apparent in the follicles at the periphery of the gland. Dilated follicles may be enlarged to several times normal diameter, are lined by low cuboidal to flattened epithelium, and generally contain either pale or inapparent colloid. Some dilated follicles may also contain sloughed cells, debris, and a few macrophages. Dilated follicles are also sometimes seen in stimulated thyroid glands, and apparently are the result of excess accumulation of colloid in the affected follicles.

**Cystic Follicles (Figure 26)**

*Synonyms: follicular cyst, colloid cyst*

Cystic follicles are occasionally observed as a spontaneous change in untreated animals, and may also be seen in stimulated thyroid glands. Cystic follicles appear to represent a progression from dilated follicles. They are many times larger than normal and usually displace, and may compress, the adjacent thyroid parenchyma. The follicles are lined by a single layer of low cuboidal to flattened epithelium and are filled with normal staining to somewhat pale colloid. Cystic follicles can be differentiated from cystic hyperplasia by the fact that the epithelium lining cystic follicles is flat and lacks complex papillary projections.

**Inflammatory Changes**

**Inflammation (Figure 27)**

Primary inflammation of the thyroid gland is uncommon in rats. Infiltrates of lymphocytes, sometimes mixed with a few plasma cells, are sometimes seen in older rats and appear to be an incidental aging change. Inflammatory cell infiltrate may sometimes be seen within degenerate follicles and is presumably a part of the degeneration. Inflammatory lesions associated with periarthritis may occur in the thyroid gland. Spontaneous lymphocytic thyroiditis with an apparent autoimmune basis has been described in the BB Wistar diabetic rat (48), and lymphocytic thyroiditis has been induced in Wistar rats by feeding them an immunosuppressive compound (26).

**Parathyroid Gland**

**Congenital Lesions**

**Ectopic Parathyroid/Thymus**

Because of the close association of the parathyroid and the thymus during embryological development (7, 39), ectopic parathyroid is sometimes found in the rat thymus
Ectopic parathyroid lesions are small nodules of parathyroid tissue present in the thymus, while ectopic thymic lesions consist of thymic tissue located within the parathyroid gland. Thymic tissue contains pale staining clusters of epithelial cells and/or Hassall’s corpuscles.

**Cysts (Figure 28)**

Remnants of the connection (Kürsteiner’s duct) between the third and fourth pharyngeal pouches, from which the parathyroid gland and thymus are formed, may form residual cysts within the parathyroid gland (9, 11, 41). The cysts may be lined with flattened cuboidal to columnar epithelium which is variably ciliated. The cysts may be single, multiple, or multiloculated, and may be empty or filled with eosinophilic material. Compression of the adjacent tissue may be evident. This congenital lesion has been correlated with exposure to dihydrotachysterol and calcium acetate administered together in corn oil (41).

**Degenerative Lesions**

**Sycntial Giant Cells (Figure 29)**

(Synonym: multinucleated giant cells)

Sycntial giant cells are uncommonly observed around the periphery of the parathyroid gland. These cells are large and contain brightly eosinophilic cytoplasm with numerous nuclei, which result from the disruption and fusion of the cell membrane of several chief cells (9, 11, 41). Nuclei are darker, smaller, and oval in comparison to the nuclei of chief cells. Organelle ultrastructural studies indicate degenerative changes (11). Infrequently, there may be several giant cells in one parathyroid gland. The significance of these cells is not known.

**Fibrosis (Figure 30)**

Fibrosis is characterized by increased amounts of mature collagen in association with the capsule or within the interstitium of the parathyroid gland. Capsular and interstitial fibrosis of the parathyroid gland are considered to be related to aging (6).

**Vascular Changes**

**Hemangiectasis (Figure 31)**

Hemangiectasis consists of small to large vascular channels that are dilated, blood-filled, and endothelial-lined. This is an uncommon lesion of the parathyroid gland that may be found in hyperplastic glands associated with severe nephropathy.

**Inflammatory Lesions**

**Inflammation**

Inflammation is rarely observed in the parathyroid gland and is similar to that observed in the other endocrine organs. Passive immunization was reported to result in experimental parathyroiditis in rats (2).

**Miscellaneous Changes**

**Melanocytes/Mast Cells**

Melanocytes may be scattered in the interstitium of the parathyroid gland in wild grey Norway rats (1) and Long-Evans rats (16). Mast cells were reported, particularly in hyperplastic lesions, but may be present in the normal parathyroid gland (34).

**Endocrine Pancreas (Islets of Langerhans)**

Spontaneous or treatment-related non-proliferative changes of the pancreatic islets are uncommon findings in rats. Most lesions of the islets reported in the literature have been observed with agents (e.g. alloxan and streptozotocin) used to induce experimental diabetes mellitus, or are lesions seen in rats which develop diabetes spontaneously.

**Disturbances of Growth**

**Atrophy (Figure 32)**

While the endocrine pancreas generally comprises 1-2% of total pancreatic tissue, the range of “normal” observed in routine sections of pancreas is variable. Factors which affect the amount of islet tissue include sampling site, sectioning, strain of rat, nutritional status, and hormonal status. Occasionally the number and/or size of islets are significantly reduced. Under routine study conditions, a treatment-related decrease in islet tissue would probably represent atrophy rather than hypoplasia.

**Degenerative Changes**

**β-Cell Degranulation (Figure 33)**

Degranulation of the β-cells of the islets of Langerhans denotes a morphological alteration, and may be followed by vacuolation. Wolters, et al. (47) described degranulation of the β-cells as a result of the oral administration of tolbutamide to rats. The degranulation occurred in conjunction with a reduction in insulin, zinc, and calcium concentrations. Kast and Ueberberg (24) described cytoplasmic vacuolation of pancreatic β-cells of rats after oral administration of a derivative of isoquinoline. At a dose of 250 mg, β-cell degranulation was present in the islets after one day and vacuolation occurred after two days. Effects were more severe in male rats. The administration of an oral antidiabetic (sulfonyl urea) in dosages exceeding the physiological/pharmacological dose resulted in a dose-dependent degranulation of β-cells which
started predominantly from the center of the islet (3, 20, 25).

**Vacuolation (Figures 34)**

Some agents that produce diabetes experimentally (e.g., cyproheptadine and cyclazine) may cause a diffuse vacuolar change involving the β-cells of the islets. This change is most often the result of dilated rough endoplasmic reticulum and is generally reversible.

**Fibrosis**

Fibrosis is characterized by an increase in mature collagen that may occur secondary to inflammation. Dihydromorphanthidrine is reported to cause focal fibrosis of the islets of Langerhans in rats. Male Wistar rats (WBN/Kob) develop a spontaneous diabetes-like syndrome in which an infiltration of inflammatory cells is observed around islets and among adjacent acinar cells. In these animals, fibrosis first occurs around pancreatic ducts and blood vessels, then involves the exocrine and endocrine pancreas (32).

**Pigmentation**

Brown pigments may be associated with the islets of Langerhans of older rats. Special stains may be required to determine the exact type of pigment (hemosiderin, lipofuscin, etc.). The combination of pigmentation, inflammation, and fibrosis of the islets of Langerhans may result in a lobular appearance in old rats.

**Necrosis**

Chemical agents (especially streptozotocin) can cause cellular necrosis. Apoptosis may also occasionally be observed. Marked vacuolar change may be observed in these islets as well and is presumed to be an early degenerative change in the progression to cell death.

**Vascular Changes**

**Hemangiectasis (Figure 35)**

Occasionally, islets are expanded by variably-sized, blood-filled spaces. Little is known relative to the biology or pathogenesis of this change. Presumably some of these blood-filled spaces represent hemangiectasis. In other cases, there is more of a cystic change with hemorrhage; there may be some degeneration of the islet cells surrounding the “cyst”. Hemosiderin pigment may be observed within these vascular lesions.

**Inflammatory Changes**

**Inflammation**

For most strains of rats, inflammation of the islets is an uncommon, non-specific lesion. In the BB rat (a spontaneous diabetic rat), lymphocytes and macrophages are observed in the periphery and within the islets. Though usually not markedly affected by inflammatory processes involving the exocrine pancreas, islets may be slightly affected.

**Miscellaneous Changes**

**Hepatocyte Metaplasia (Figure 36)**

“Pancreatic hepatocytes” are occasionally observed spontaneously and presumably represent metaplasia of peri-insular parenchymal cells to hepatocyte-like cells. They can also be induced by certain chemicals (30), a methyl-group-deficient diet, and by a copper depletion/repletion technique. These cells have morphological and functional characteristics of hepatocytes. Cells with hepatocyte-specific enzymes and both pancreatic endocrine and exocrine granules have been demonstrated to induce hepatocyte metaplasia after treatment (37). Often there will only be a single islet affected per section. The pattern of these cells about an islet and the percentage of islet occupied is variable. Most commonly, they occur in one to several layers in the periphery of an islet; however, they may appear as focal nests or occupy the entire islet. It is not certain if these cells are invariably associated with islets.

**DISCUSSION**

Of all the endocrine tissues, the adrenal gland is the most susceptible to compound-induced lesions (38). The basic areas that may be affected are the zona glomerulosa, zona fasciculata, and zona reticularis, although some compounds may produce lesions in more than one of these zones. The zona fasciculata and zona reticularis are the most frequently affected by xenobiotic agents (10).

Although the reason for the differential effects is not always clear, certain anatomical or functional characteristics of the different zones may explain the induction of lesions in specific portions of the adrenal gland. For example, the zona glomerulosa has a portion of its vascular supply derived from the capsule. This unique anatomical characteristic may spare this zone from damage associated with disruption of the blood supply from the adrenal artery or arterioles (38). Functional characteristics of the adrenal gland zones which explain differences in lesions include the existence of various metabolic processes, including cholesterol synthesis, hydroxylation, and conversion of cholesterol to pregnenolone, and processes which may be damaged by specific compounds with resultant excessive precursor accumulation (14, 22, 35).

The most common non-proliferative lesion of the adrenal gland is cystic degeneration. Cystic degeneration is a continuum of cortical vacuolation. It may progress to extensive cell loss with numerous, large, blood-filled cystic spaces. It is particularly common in the female Sprague-Dawley rat. Hemangiectasis of the adrenal gland
may be difficult to differentiate from cystic degeneration with hemorrhage, as the two lesions may occur together.

Reports on the incidence of accessory (adreno) cortical tissue vary considerably. Many routine toxicology studies record a very low incidence of this lesion because many pathologists consider it a normal finding and do not record it as a lesion. A thorough visceral examination reveals a relatively low incidence (approximately 8%) (13, 17), whereas accessory cortical tissue has been found in 100% of rats subjected to serial sections of the entire abdomen (4).

Bilateral atrophy of the adrenal gland may be secondary to exogenous administration of glucocorticoids or from destructive lesions in the pituitary that cause a deficiency in adrenocorticotropic hormone (ACTH). Atrophy may also be seen following long term administration of low doses of chemicals which, at high dosages, are known to cause cortical necrosis (49). Unilateral lesions are most frequently associated with a functional cortical neoplasm in the contralateral adrenal gland (23).

One estimate indicates that cortical vacuolation can be found in up to 17% of 24 month old rats and 29% of 33-40 month old rats (44). Aged rats with pituitary neoplasms may have a higher incidence of focal or diffuse vacuolation.

An actual reduction of cortical vacuolation may be seen in stressed animals. Excessive lipid droplets in the adrenal cortex in the form of coalescing vacuoles has been suggested as an indication of a degenerative process. Vacuolation may be a spontaneous age-related change, a physiologic response (via stress and endogenous chronic ACTH stimulation), or directly related to a wide variety of toxic agents. For the purposes of this review, these agents will be classified as non-specific lipodosis-inducing agents and phospholipidosis-inducing agents.

Lipidosis-inducing compounds generally cause a diffuse accumulation of lipid in the zona fasciculata/reticularis. The normal adrenal cortical cell contains a large amount of steroid, but a relatively small amount of neutral lipid (38). With accumulation of large amounts of neutral lipids, there is potential destruction of cell structure and function (38). With high dosages or prolonged administration of lipidosis-inducing agents, cell death with resultant adrenal cortical atrophy may occur.

Phospholipidosis-inducing compounds consist of a number of cationic amphophilic compounds which also induce a diffuse change in the zona fasciculata/reticularis (19). In the adrenal gland, phospholipidosis is manifested by microscopic or submicroscopic cytoplasmic inclusions rich in phospholipid. Electron microscopic evaluation reveals the inclusions to be enlarged lysosomes filled with membranous lamellae or myelin figures.

Non-proliferative lesions are much more rare in the other endocrine tissues. The more commonly found non-proliferative lesions include: cysts in the pituitary gland; dilated follicles and cystic follicles in the thyroid gland; cysts (21, 33) and ectopic thymic tissue in the parathyroid gland; and atrophy in the islets of Langerhans.

**RECOMMENDED NOMENCLATURE AND DIAGNOSTIC CRITERIA**

**ADRENAL GLAND**

**CONGENITAL LESIONS**

Accessory (Adreno) Cortical Tissue
1. Concomitant adrenocortical tissue outside the adrenal capsule
2. Composed of normal cortex
3. Separated from cortex by fibrous capsule
4. Lacks distinct zonal arrangement and contains no medullary tissue

**DISTURBANCES OF GROWTH**

Atrophy
1. May be bilateral or unilateral
2. Primary effect usually on zona fasciculata and reticularis
3. Reduction in thickness of cortical zones

Hyptertrophy
1. May be unilateral or bilateral, and focal, multifocal, or diffuse
2. Diffuse hypertrophy results in increased thickness of the adrenal cortex
3. Focal hypertrophy characterized by focal areas of enlarged cells
4. Focus is well-circumscribed but does not cause compression
5. Cytoplasm of hypertrophic cells may be eosinophilic or basophilic

**DEGENERATIVE CHANGES**

Cortical Vacuolation
1. Small, clear spaces or cavities in cytoplasm of cortical cells
2. Focal, multifocal, or diffuse
3. Unilateral or bilateral
4. Focal lesions may be poorly circumscribed or may cause compression
5. Usually involves the zona fasciculata

**Cystic Degeneration**
1. Continuum of cortical vacuolation
2. Cell loss with formation of cystic spaces
3. Cystic spaces may be blood-filled
4. May result in compression of adjacent parenchyma

**Mineralization**
1. Inorganic mineral substance
2. May be intracellular or extracellular
3. May follow necrosis or hemorrhage
4. Homogenous and bluish/purple

**Lipofuscin Pigmentation**
1. Yellow to brown granular pigment
2. Usually in zona reticularis
3. May exhibit autofluorescence
4. Usually PAS positive, sudanophilic, and acid fast

**Necrosis**
1. May be associated with hemorrhage, cystic degeneration, and inflammation
2. Well-defined areas
3. Usually occurs in zona fasciculata and/or reticularis

**Vascular Changes**

**Extramedullary Hematopoiesis**
1. Consists of either erythrocytic or granulocytic components
2. Usually present in adrenal cortex
3. Usually multiple
4. Must be distinguished from inflammation

**Hemangiectasis**
1. Blood-filled spaces lined by endothelium
2. May occur in cortex or medulla

**Thrombosis**
1. Solid mass within the lumen of a blood vessel
2. Composed of fibrin and platelets, and may contain trapped erythrocytes

**Inflammatory Changes**

**Inflammation**
1. Inflammatory cellular infiltrate
2. In acute cases, inflammatory cells are predominantly neutrophils
3. In chronic cases, inflammatory cells are plasma cells and lymphocytes
4. Epithelial cell degeneration or loss

**PITUITARY GLAND**

**Congenital Changes**

**Persistence of Rathke’s Pouch**
1. May be located in pars distalis, pars intermedia, or pars nervosa

2. Often associated with Rathke’s cleft
3. Variably-sized tubular or glandular structures
4. Epithelial lining is usually ciliated but can be squamous, cuboidal, or columnar

**Disturbances of Growth**

**Hypertrophy**
1. Enlargement of individual cells in pars anterior
2. Common response to toxicity of other related endocrine organs
3. Specific cell type can be identified by immunocytochemistry
4. May precede hyperplasia

**Vascular Changes**

**Hemangiectasis**
1. Dilated, blood-filled spaces lined by endothelium
2. Usually present in pars distalis
3. May be accompanied by proteinaceous fluid or hemorrhage

**Hemorrhage**
1. Free erythrocytes outside of vascular channels
2. May be accompanied by hemosiderin-laden macrophages, cholesterol clefts, and fibrosis if long-standing

**Thrombosis**
1. Solid mass within lumen of blood vessels
2. Composed of fibrin and platelets, and may contain trapped erythrocytes

**Inflammatory Changes**

**Inflammation**
1. Inflammatory cellular infiltrate
2. In acute cases, inflammatory cells are predominantly neutrophils
3. In chronic cases, inflammatory cells are plasma cells and lymphocytes
4. Epithelial cell degeneration or loss

**Miscellaneous Changes**

**Cysts**
1. Simple or multilocular
2. Common in pars distalis
3. Usually contain eosinophilic to amphophilic mucoproteinaceous material
4. Single layer of cuboidal to columnar epithelium
5. Epithelial lining is generally ciliated and may contain mucous cells
THYROID GLAND

CONGENITAL LESIONS

Ultimobranchial Cysts
1. Remnants of embryonic ultimobranchial ducts
2. May be single or multiple
3. Commonly located in central portion of thyroid lobe
4. Cystic or elongated duct-like structures lined by flattened squamous epithelium
5. Usually contain varying amounts of debris

Persistent Thyroglossal Ducts
1. Small cystic or duct-like structures lined by simple cuboidal to columnar epithelium that may be ciliated
2. Often filled with mucinous material

Ectopic Thymus
1. Thymic tissue located adjacent to thyroid or completely surrounded by thyroid tissue
2. Contains pale staining clusters of epithelial cells and/or Hassall’s corpuscles

DEGENERATIVE CHANGES

Mineralization
1. Irregular, basophilic clumps of mineral present within lumen of thyroid follicles

Pigmentation
1. Brown granular pigment within follicular epithelial cells or within follicular lumina
2. Considered an aging change
3. Increased amounts of pigmentation may be due to deposition of test material within thyroid follicular cells

Dilated Follicles
1. Follicles dilated to several times normal diameter
2. Usually located at periphery of gland
3. Lined by low cuboidal or flattened epithelium
4. Generally contain pale or inapparent colloid

Cystic Follicles
1. Many times larger than normal follicles
2. Usually displace and may compress adjacent thyroid parenchyma
3. Follicles lined by a single layer of low cuboidal to flattened epithelium
4. Flattened epithelium does not contain papillary projections
5. Follicles are filled with normal staining to pale colloid

INFLAMMATORY CHANGES

Inflammation
1. Inflammatory cellular infiltrate
2. In acute cases, inflammatory cells are predominantly neutrophils
3. In chronic cases, inflammatory cells are plasma cells and lymphocytes
4. Epithelial cell degeneration or loss

PARATHYROID GLAND

CONGENITAL LESIONS

Ectopic Parathyroid/Thymus
1. Small nodules of parathyroid tissue present in the thymus
2. Thymic tissue located within parathyroid gland
3. Thymic tissue contains pale staining clusters of epithelial cells and/or Hassall’s corpuscles

Cysts
1. Cysts may be single or multilocular
2. Lined by flattened cuboidal to columnar epithelium
3. May be empty or contain eosinophilic material
4. May cause compression of adjacent tissue

DEGENERATIVE CHANGES

Synecytial Giant Cells
1. Multinucleated giant cells around periphery of gland
2. Prominent eosinophilic cytoplasm and numerous nuclei

Fibrosis
1. Increased amounts of mature collagen
2. May be associated with the capsule or within the interstitium of the gland

VASCULAR CHANGES

Hemangiectasis
1. Small to large vascular channels
2. Blood-filled and endothelial-lined

INFLAMMATORY CHANGES

Inflammation
1. Inflammatory cellular infiltrate
2. In acute cases, inflammatory cells are predominantly neutrophils
3. In chronic cases, inflammatory cells are plasma cells and lymphocytes
4. Epithelial cell degeneration or loss
MISCELLANEOUS CHANGES

Melanocytes/Mast Cells
1. Presence of melanocytes scattered in interstitium
2. Presence of mast cells scattered in interstitium

ENDOCRINE PANCREAS
(ISLETS OF LANGERHANS)

DISTURBANCES OF GROWTH

Atrophy
1. Decrease in the number and size of islets

DEGENERATIVE CHANGES

β-Cell Degranulation
1. Degranulation of the β-cells of the islets
2. May be followed by vacuolation

Vacuolation
1. Vacuolar change of islets
2. Change is usually diffuse
3. β-cells usually involved

Fibrosis
1. Increase of mature collagen
2. May be secondary to inflammation
3. May be extension from around pancreatic ducts involving both exocrine and endocrine pancreas

Pigmentation
1. Brown granular pigment associated with the islets
2. Special stains may be need to determine the type of pigment

Necrosis
1. May be preceded by vacuolar change
2. Cellular degeneration and death

VASCULAR CHANGES

Hemangiectasis
1. Expansion of islets by blood-filled, endothelial-lined spaces
2. May progress to cystic change with hemorrhage

Inflammatory Changes
1. Uncommon finding

MISCELLANEOUS CHANGES

Hepatocyte Metaplasia
1. Presence of hepatocyte-like cells at periphery of islet
2. May involve entire islet or occur as focal nest
3. May involve single or multiple islets

REFERENCES


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Fig. 1 - Accessory (adreno) cortical tissue. Note that no medullary tissue is present (H&E).

Fig. 2 - Diffuse atrophy, adrenal cortex (H&E).

Fig. 3 - Focal hypertrophy, adrenal cortex (H&E).

Fig. 4 - Focal cortical vacuolation, adrenal cortex (H&E).
Fig. 5 - Cystic degeneration, adrenal cortex (H&E).

Fig. 6 - Focal mineralization, adrenal cortex (H&E).

Fig. 7 - Lipofuscin pigmentation, adrenal cortex (H&E).

Fig. 8 - Focal necrosis, adrenal cortex (H&E).
Fig. 9 - Extramedullary hematopoiesis, adrenal cortex (H&E).

Fig. 10 - Top: focal hemangiectasis, adrenal cortex (H&E); Bottom: more advanced hemangiectasis, adrenal cortex (H&E).

Fig. 11 - Thrombosis, adrenal cortex (H&E).

Fig. 12 - Top: fibrosis and pigmentation, adrenal cortex (H&E); Bottom: fibrosis and hemosiderin pigmentation, adrenal cortex (Prussian Blue).
Fig. 13 - Persistence of Rathke’s pouch, pituitary (H&E).

Fig. 14 - Higher magnification of Fig. 13 (H&E).

Fig. 15 - Cyst, anterior pituitary (H&E).

Fig. 16 - Cysts, anterior pituitary (H&E).
Fig. 17 - Hypertrophy, anterior pituitary (H&E).

Fig. 18 - Hemangiectasis, pituitary (H&E).

Fig. 19 - Hemorrhage, pars distalis of pituitary (H&E).

Fig. 20 - Inflammation, pars nervosa of pituitary (H&E).
Fig. 21 - Ultimobranchial cyst, thyroid gland (H&E).

Fig. 22 - Ectopic thymic tissue adjacent to thyroid gland (H&E).

Fig. 23 - Mineralization, thyroid gland (H&E).

Fig. 24 - Pigmentation, thyroid gland (H&E).
Fig. 25 - Dilated follicle, thyroid gland (H&E).

Fig. 26 - Cystic follicle, thyroid gland (H&E).

Fig. 27 - Focal lymphoplasmocytic inflammation, thyroid gland (H&E).

Fig. 28 - Cyst, parathyroid gland (H&E).
Fig. 29 - Syncytial giant cell, parathyroid (H&E).

Fig. 30 - Fibrosis, parathyroid gland (H&E).

Fig. 31 - Hemangiectasis, parathyroid gland (H&E).

Fig. 32 - Atrophy, islets of Langerhans (H&E).
Fig. 33 - Top: normal islet of Langerhans (Gomori); Bottom: β-cell degranulation, islet of Langerhans (Gomori).

Fig. 34 - Vacuolation, islets of Langerhans (H&E).

Fig. 35 - Hemangiectasis and hemorrhage, islets of Langerhans (H&E).

Fig. 36 - Hepatocyte metaplasia, islets of Langerhans (H&E).