Overview of Structural and Functional Lesions in Endocrine Organs of Animals

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ABSTRACT

The objective of this review is to summarize the major pathogenic mechanisms responsible for perturbations of endocrine function that result in important diseases in domestic and laboratory animals. For each major category, several specific disease problems have been selected to illustrate the functional and morphologic lesions that are characteristic for either a naturally occurring endocrinopathy or endocrine disturbances induced by the administration of large doses of xenobiotic chemicals. Disorders of the endocrine system are encountered in a wide variety of domestic and laboratory animal species and often present challenging diagnostic problems. The development of proliferative lesions, usually hyperplasia and benign tumors, in endocrine organs and hormone-responsive tissues are common findings in chronic studies with high doses of many nongenotoxic xenobiotic chemicals administered to sensitive rodent species and may have limited significance for human safety assessment.

Keywords. Endocrine lesions; hormonal imbalances; hyperthyroidism; hyperparathyroidism; congenital goiter; hypothyroidism; panhypopituitarism; testicular Leydig cell adenomas; tubulostromal tumors of ovary; humoral hypercalcemia of malignancy; parathyroid hormone–related protein; prolonged gestation; hormone degradation; iatrogenic syndromes of hormone excess

INTRODUCTION

The objective of this review is to summarize the major pathogenic mechanisms responsible for perturbations of endocrine function that result in important diseases in domestic and laboratory animals. For each major category, several specific disease problems have been selected to illustrate the functional and morphologic lesions that are characteristic for either a naturally occurring endocrinopathy or endocrine disturbances induced by the administration of xenobiotic chemicals. Disorders of the endocrine system are encountered in a wide variety of domestic and laboratory animal species and, as in human patients, often present challenging diagnostic problems. The development of proliferative lesions (usually hyperplasia and benign tumors) in endocrine organs and hormone-responsive tissues are common findings in chronic studies with high doses of many nongenotoxic xenobiotic chemicals administered to sensitive rodent species and may have limited significance for human safety assessment (3, 60). The examples to be discussed, by necessity, will be highly selective and include disease problems investigated by my laboratory as well as data from the literature.

PRIMARY HYPERFUNCTION

One of the most important mechanisms of endocrine disease is primary hyperfunction. A lesion, usually a neoplasm derived from a specific population of endocrine cells, synthesizes and secretes a hormone at an autonomous rate in excess of the body’s ability to utilize and subsequently degrade the hormone, thereby resulting in functional disturbances of hormone excess. A number of specific examples occur in different animal species (Figure 1).

Hyperthyroidism

There has been a dramatic increase in the incidence of thyroid neoplasms and other focal proliferative lesions in cats resulting in hyperthyroidism since the late 1970s, and at present it is one of the two most common endocrine diseases in adult-age cats (diabetes mellitus being the other). Prior to 1980, clinical hyperthyroidism was diagnosed infrequently in cats. The reason(s) for the apparent increased incidence is (are) uncertain but appear(s)
### PRIMARY HYPERFUNCTION OF AN ENDOCRINE GLAND

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Figure 1.—Selected examples of primary hyperfunction of endocrine glands in animals.

To be related, in part, to (a) a larger population of older cats seeking veterinary medical care, (b) improved assays for thyroid hormones, and (c) detailed characterization of the clinical syndrome and increased awareness of its common occurrence in adult to aged cats by veterinary clinicians. In addition, there does appear to be a “real” increase in the incidence of feline hyperthyroidism over the last 30 years. Potential risk factors have been reported to include a predominantly indoor environment, regular treatment with flea powders, exposures to herbicides and fertilizers, a diet primarily of canned food, and non-Siamese breeds (10 times greater occurrence) (102). It has been suggested that wide variations (excessive to inadequate) in dietary iodine intake over prolonged periods may play a role in the pathogenesis of thyroid disorders in cats (51).

The disease in cats is mechanistically different from Grave’s disease in human patients, as hyperthyroid cats do not have elevated circulating levels of thyroid-stimulating immunoglobulins comparable to long-acting thyroid stimulator (LATS) (an autoantibody that binds to the thyroid-stimulating hormone (TSH) receptor and activates follicular cells) (85). Purified immunoglobulin G (IgG) preparations from hyperthyroid cats significantly increased H-thymidine into DNA and stimulated cell proliferation 15-fold but did not stimulate intracellular cAMP (10). The former could be inhibited completely by a specific TSH receptor-blocking antibody. These data suggest that elevated titers of thyroid growth IgGs are present in cats with hyperthyroidism and most likely act by the TSH receptor. This important thyroid disease in cats most closely resembles toxic nodular goiter in human patients (43, 82). Hyperplastic and neoplastic thyroid tissue from cats is transplantable into athymic (nude) mice and continues to overproduce T4 and T3 in a subcuticular location.

Studies utilizing primary cultures of enzymatically dissociated follicles from thyroid proliferative lesions from cats with hyperthyroidism have reported that organification and H-thymidine labeling continue in the absence of TSH in contrast to follicles from normal cat thyroids (81). These findings suggest that an intrinsic alteration in follicular cell function occurs in thyroids of cats with multinodular goiter, leading to autonomy of cell growth and persistent overproduction of thyroid hormones. A recent study reported an overexpression of the c-ras oncogene in areas of nodular hyperplasia and adenomas derived from follicular cells in cats with hyperthyroidism, suggesting that mutations in this oncogene may play a role in the pathogenesis of these proliferative lesions (64).

Point mutations in the thyrotropin receptor (TSHR) gene cause 2 forms of thyrotoxicosis in humans, namely, autonomously functioning toxic follicular adenomas and hereditary (autosomal dominant) toxic thyroid hyperplasia. The normal feline TSHR sequence between codons 480 and 640 is highly homologous to that of other mammalian TSHRs with 95%, 92%, and 90% amino acid identity between the canine, human, and bovine TSHRs, respectively (79). Analysis of single-stranded conformational polymorphisms in thyroid DNA from sporadic cases of feline thyrotoxicosis and leukocyte DNA from 2 cases of familial hyperthyroidism in cats failed to identify mutations between codons 480 and 640 of the TSHR gene. These interesting findings suggest that TSHR gene mutations are not a common cause of the focal proliferative lesions of thyroid follicular cells that result in feline thyrotoxicosis (79). A number of reports have described a syndrome of hyperthyroidism in aged cats associated with multinodular goiter, adenomas, and occasionally adenosarcomas derived from follicular cells of the thyroid (47, 59, 73, 83). Large adenomas and carcinomas may be detected by palpation of swellings in the cranioventral cervical region; however, thyroid tumors in cats occasionally are displaced caudally to the level of the first rib and anterior mediastinum. One or both thyroid lobes are enlarged in hyperthyroid cats. Solitary adenomas derived from thyroid follicular cells are the most common lesions associated with hyperthyroidism in cats. The affected thyroid lobe is partially or completely incorporated by the adenoma. The adenomas often develop in thyroid glands with areas of multinodular hyperplasia of follicular cells. They appear as solitary, soft, lobulated nodules that enlarge and distort the contour of the affected lobe. A thin, fibrous connective tissue capsule separates the adenoma from the adjacent, often compressed, thyroid parenchyma (Figures 2 and 3). The neoplastic cells form irregularly shaped follicles with occasional papillary in-foldings of epithelium and variable amounts of colloid. Focal areas of necrosis, mineralization, and cystic degeneration are present in larger adenomas. Multiple sections of adenomas fail to reveal histological evidence of either vascular or capsular invasion by tumor cells.

Functional thyroid adenomas in cats associated with a clinical syndrome of hyperthyroidism are composed of cuboidal to columnar follicular cells that form follicles of varying sizes and shapes (Figure 3). The follicles usually are partially collapsed and contain little colloid because of the intense endocytotic activity of neoplastic follicular cells. Long cytoplasmic projections often extend from the follicular cells into the lumen to phagocytize colloid. As a result of the marked endocytotic activity, numerous colloid droplets are present in the apical cy-
toplam of follicular cells in close proximity to the many
electron-dense lysosomal bodies. The neoplastic follicu-
lar cells are considerably larger (2–4 times) the size of the
atrophic cells lining the follicles in the rim of normal
thyroid. Follicles in the rim of “normal” thyroid around
a functional adenoma are enlarged and distended by an
accumulation of colloid (ie, colloid involution) (Figure
3). The follicular cells are low cuboidal and atrophied,
with little evidence of endocytotic activity in response to
the elevated levels of thyroid hormones and decreased
circulating levels of TSH.

Thyroid adenomas must be differentiated from multi-
nodular (“adomatous”) hyperplasia (“goiter”) that oc-
curs frequently in old cats. These multiple areas of thy-
roid hyperplasia usually are microscopic and do not en-
large the affected lobe of thyroid unless they are numer-
ous. In contrast to adenomas, the areas of nodular
hyperplasia are not encapsulated, and the adjacent thyroid
parenchyma is not compressed (105). Histopathologi-

cally, the hyperplastic nodules are composed of irregularly
shaped follicles lined by cuboidal follicular cells and con-
tain variable amounts of colloid. Follicles between the
nodules of hyperplasia often have undergone colloid in-
volution, suggesting that these focal proliferative lesions
of follicular cells are producing thyroid hormones at an
autonomous rate, resulting in decreased circulating TSH
concentrations.

Cats with hyperthyroidism usually have markedly el-
evated serum thyroxine ($T_4$) and tri-iodothyronine ($T_3$) levels (Figure 4) (84). The serum thyroxine ($T_4$) levels in
cats with hyperthyroidism range from 3.4 to 30 μg/dl
(normal range 1.5–5.0 μg/dl), and serum tri-iodothyron-
ine ($T_3$) levels range from 179 to 470 ng/dl (normal 60–
200 ng/dl). Moderately increased liver-derived serum en-
zyme levels, including AST, ALT, SGPT, SGOT, and es-
pecially alkaline phosphatase, occur in hyperthyroid cats. The likelihood of developing clinical hyperthyroidism as-
associated with thyroid neoplasms in animals depends on
(a) the capability of tumor cells to synthesize T4 and T3
(eg, well-differentiated thyroid tumors that form follicles
and produce colloid are more likely to synthesize thyroid

Figure 2.—Follicular cell adenoma (A) in a cat with hyperthyroid-

ism. The adenoma is lobulated reflecting its likely origin from a coa-

lescence of multifocal areas of adenomatous hyperplasia. The tumor is

sharply demarcated from a rim of normal thyroid (arrow). H&E.

Figure 3.—Follicular cell adenoma (A) composed of follicles with

little stored colloid as a result of the autonomous secretion of thyroid

hormones. Follicles in the rim of normal thyroid have undergone colloid

involution (C) and are distended with colloid as a morphologic response
to suppressed TSH levels. A thin fibrous capsule (arrow) separates the

adenoma from the peripheral rim of thyroid. H&E.

Figure 4.—Serum thyroid hormone levels in cats with hyperthyroid-

ism. There is a marked elevation of serum thyroxine [$T_4$] (mean 15 μg/
dl) and triiodothyronine [$T_3$] (mean 300 μg/dl) in cats with hyperthy-
roidism. From Peterson et al (84).
hormones than poorly differentiated solid neoplasms) and (b) the degree of elevation of circulating levels of T4 and T3, which depends on a balance between the rate of secretion of thyroid hormones by the tumor and the rate of degradation of thyroid hormones. For example, dogs have a much more efficient enterohepatic excretory mechanism for thyroid hormones than cats and infrequently have clinical signs associated with functional thyroid tumors. Cats are very sensitive to phenol and phenol derivatives (50) and have a poor ability to conjugate phenolic compounds (such as T4) with glucuronic acid and excrete the T4-glucuronide conjugate into the bile. The capacity of conjugation of T3 with sulfate is limited and easily overloaded. Therefore, cats with relatively small functional proliferative lesions of thyroid follicular cells often have considerable elevations in circulating levels of T4 and T3 with clinical signs of hyperthyroidism.

Primary Hyperparathyroidism

Functional adenomas and carcinomas of parathyroid glands develop in older dogs and cats and often secrete parathyroid hormone (PTH) in excess of normal, resulting in a syndrome of primary hyperparathyroidism (15). The normal control mechanism of the parathyroid gland by the concentration of blood calcium ion is lost in functional parathyroid tumors. Parathyroid hormone secretion by functional tumors is excessive despite an increased level of blood calcium. Cells of the renal tubules are sensitive to alterations in the amount of circulating parathyroid hormone. The hormone acts on cells in the nephron initially to promote the excretion of phosphorus (proximal tubule) and retention of calcium (distal tubule). A prolonged increased secretion of parathyroid hormone also accelerates osteocytic and osteoclastic bone resorption. Mineral is removed from the skeleton and replaced by immature fibrous connective tissue and poorly mineralized osteoid. The bone lesion of fibrous osteodystrophy is generalized throughout the skeleton but is accentuated in local areas of increased bone turnover, such as the maxillae, mandibles, and a subperiosteal location of long bones (17). Tumors of parathyroid chief cells do not appear to be sequelae of long-standing secondary hyperparathyroidism of renal or nutritional origin (19). The incidence of parathyroid adenomas is increased in a dose-dependent manner by both internal (131I) and external (localized X) irradiation in rats (22, 56).

The functional disturbances observed with endocrinologically active parathyroid tumors are the result of the persistent hypercalcemia, increased urinary calcium and phosphorus excretion with the formation of calculi, and weakening of bones by excessive resorption. Lameness due to fractures of long bones may occur after relatively minor physical trauma. In long-standing cases, compression fractures of vertebral bodies may exert pressure on the spinal cord and nerves, resulting in motor or sensory dysfunction or both. Facial hyperostosis with partial obliteration of the nasal cavity and loosening or loss of teeth from alveolar sockets have been observed in dogs with primary hyperparathyroidism due to part of the anabolic effect of PTH on stimulating osteoblasts to form poorly mineralized osteoid (receptor-mediated process). Hypercalcemia results in anorexia, vomiting, constipation, depression, polyuria, polydipsia, and generalized muscular weakness due to decreased neuromuscular excitability. Radiographic evaluation reveals areas of subperiosteal cortical bone resorption, loss of lamina dura dentes around the teeth, soft-tissue mineralization, bone cysts, and a generalized decrease in bone density with multiple fractures in advanced cases.

The laboratory tests most useful in establishing the diagnosis of a primary hyperfunctioning of the parathyroid glands consist of quantitation of total blood calcium and phosphorus plus circulating levels of parathyroid hormone (N-terminal or immunoradiometric assay [IRMA]). Although other laboratory findings may be variable, persistent hypercalcemia (>12 mg/dl) is a consistent finding. Dogs evaluated with primary hyperparathyroidism often have had a greatly elevated (13-20 mg/dl or higher) blood calcium level. The blood phosphorus level is low (4 mg/dl) or in the low to normal range because of inhibition of renal tubular resorption of phosphorus by excess parathyroid hormone. Serum alkaline phosphatase activity may be increased because of increased osteoblastic activity as a response to mechanical stress of bones weakened by excessive resorption or because of direct (receptor-mediated) stimulation of osteoblasts by the elevated PTH level. The urinary excretion of calcium and phosphorus is increased and may predispose to the development of nephrocalcinosis and urolithiasis. Accelerated bone matrix catabolism is reflected by an increased excretion of hydroxyproline in the urine.

Chief cell adenomas result in considerable enlargement usually of a single parathyroid gland. They are located either in the cervical region near the thyroids or rarely within the thoracic cavity near the base of the heart (26, 55). Parathyroid neoplasms in the precordial mediastinum are derived from ectopic parathyroid tissue displaced into the thorax along with the expanding thymus during embryonic development. The adenomas are sharply demarcated and encapsulated from the adjacent thyroid gland (Figure 5). Multiple white foci may be seen in the thyroids of animals with functional parathyroid tumors. These represent areas of C-cell hyperplasia in response to the long-term hypercalcemia (20) (Figures 5 and 6). All parathyroid glands should be evaluated for evidence of primary multinodular chief cell hyperplasia that can result in macroscopic enlargement of multiple glands and persistent hypercalcemia (37).

By comparison, diffuse chief cell hyperplasia is common in animals as part of the compensatory reaction to chronic renal disease and nutritional imbalances. In secondary (compensatory) chief cell hyperplasia, all 4 parathyroid glands are enlarged 2-5 times their normal size. Chief cells undergo organellar hypertrophy initially and cellular hyperplasia later to increase parathyroid hormone synthesis and secretion in response to a hypocalcemic stimulus. A functional parathyroid adenoma enlarges a single gland to a much greater degree, while the remaining parathyroids will be atrophic and smaller than normal. Histopathological demonstration of a compressed rim of parathyroid parenchyma and a fibrous capsule in an enlarged
gland points to the diagnosis of adenoma rather than chief cell hyperplasia (Figure 7).

Parathyroid adenomas are composed of closely packed chief cells subdivided into small groups by fine connective tissue septa with many capillaries (Figure 7). The chief cells are cuboidal or polyhedral, and the abundant cytoplasm stains lightly eosinophilic. Neoplastic chief cells can form follicle-like structures with a lumen containing minimal proteinic material that could (at low power) be confused with a thyroid follicular cell tumor. Adenomas are surrounded by a fine, partial to complete connective tissue capsule and may compress the adjacent thyroid gland. A rim of functionally suppressed parathyroid parenchyma usually is present outside the capsule of small endocrinologically active adenomas (Figure 7). These atrophic chief cells are small, are irregular in shape, and have a densely eosinophilic cytoplasm and a pycnotic nucleus (94). Similar atrophic chief cells are present in the other parathyroid glands in response to the persistent hypercalcemia (Figure 8). Chief cells comprising functional parathyroid adenomas ultrastructurally are in the actively synthesizing stage of the secretory cycle. Multiple large lamellar arrays of rough endoplasmic reticulum and clusters of free ribosomes are present in the cytoplasm. However, few mature secretory (“storage”) granules are present in the cytoplasm, suggesting that parathyroid hormone is secreted at a faster rate than synthesis and storage in autonomous chief cells.

Successful removal of a functional parathyroid adenoma results in a rapid decrease in circulating parathyroid hormone levels because the half-life of the hormone in plasma is less than 10 minutes. The plasma calcium levels in patients with functional chief cell adenomas and overt bone disease may decrease rapidly and be subnormal within 12–24 hours, resulting in life-threatening hypocalcemic tetany (Figure 9). Postoperative hypocalcemia is the result of depressed secretory activity in the remaining atrophic parathyroid tissue (Figure 8), result-
and long-term stimulation of the adrenal cortex, resulting in the syndrome of cortisol excess.

**Hyperadrenocorticism Associated with an ACTH-Secreting Pituitary Neoplasm**

Functional (endocrinologically active) neoplasms arising in the pituitary gland are derived from corticotroph (ACTH-secreting) cells in either the pars distalis or the pars intermedia of dogs. ACTH-secreting neoplasms result in a clinical syndrome of cortisol excess (Cushing’s disease) by causing secondary hyperfunction of the adrenal cortex. These neoplasms are encountered most frequently in dogs, particularly in adult to aged boxers, Boston terriers, and dachshunds. The pituitary gland is consistently enlarged (Figure 11); however, neither the occurrence nor the severity of functional disturbances appears to be directly related to the size of the ACTH-producing neoplasm. Since the diaphragma sella is incomplete in the dog, the line of least resistance favors dorsal expansion of the gradually enlarging pituitary mass. This results in invagination into the infundibular cavity, dilatation of the infundibular recess and the third ventricle with eventual compression or replacement of the hypothalamus (Figure 11), and possible extension of the neoplasm into the thalamus. Pituitary corticotroph adenomas are composed of well-differentiated, large or small, chromophobic cells supported by connective tissue septa. The cytoplasm of the neoplastic corticotrophs usually contains few or is devoid of secretory granules but stains immunocytochemically for ACTH and MSH. Hormone-containing small secretory granules can be demonstrated by electron microscopy in functional corticotroph adenomas of dogs.

Bilateral enlargement of the adrenal glands occurs in dogs with functional corticotroph adenomas (Figure 11). This enlargement is due to ACTH-mediated cortical hypertrophy and hyperplasia, primarily of the zonae fasciculata and zona reticularis (Figure 12). Nodules of yellow-orange cortical tissue often are found outside the capsule as well as extending down into and compressing the adrenal medulla. These hyperplastic zones are sus-
Figure 11.—Secondary hyperfunction of an endocrine gland. Corticotrophic (ACTH-secreting) adenoma (A) in the pituitary gland resulting in bilateral hyperplasia of the adrenal cortices (arrowheads). This is the most common pathogenic mechanism for the syndrome of cortisol excess. The scale represents 1 cm.

Figure 12.—Secondary hyperfunction of adrenal cortex. Note the prominent widening of the inner zona fasciculata (F) and reticularis (R) with compression of the outer zona multiformis (M) in a dog with an ACTH-producing pituitary adenoma. H&E.

Figure 13.—Mechanisms of primary hypofunction of endocrine glands.

In primary hypofunction, hormone secretion either is subnormal because of excessive destruction of secretory cells by a disease process, the failure of an endocrine organ to develop properly (aplasia or hypoplasia), or a specific biochemical defect in the synthetic pathway of a hormone (Figure 13). Immune-mediated injury is an important mechanism resulting in hypofunction of endo-
cric glands in animals, including the thyroid gland, adrenal cortex, pancreatic islets, parathyroid, and hypotalamus. The following are selected examples of primary hypofunction of endocrine organs.

**Immune-Mediated Lymphocytic Thyroiditis and Hypothyroidism**

Lymphocytic thyroiditis in dogs, obese strains of chickens, nonhuman primates, and Buffalo rats closely resembles Hashimoto’s disease in human beings. Although the exact pathogenetic mechanisms in the dog are not completely established, evidence suggests a polygenic pattern of inheritance similar to that observed in human beings. The immunologic basis of the development of chronic lymphocytic thyroiditis in both human beings and dogs appears to be through production of autoantibodies usually directed against thyroglobulin or a microsomal antigen (thyroperoxidase) and infrequently against the TSH receptor protein, nuclear antigen, or a second colloid antigen from thyroid follicular cells. Thyroglobulin autoantibodies have been found in 48% of pet dogs with hypothyroidism (44). Laboratory beagle dogs with naturally occurring lymphocytic thyroiditis also have circulating thyroidal autoantibodies, but the focal thyroiditis usually is not associated with clinical signs of hypothyroidism.

Microscopic lesions consist of multifocal to diffuse infiltrates of lymphocytes, plasma cells, and macrophages and, sometimes, lymphoid nodules (Figure 14). Thyroid follicles are small and lined by columnar epithelial cells; lymphocytes, macrophages, and degenerate follicular cells are often present in vacuolated colloid. Thyroid C-cells are present as small nests or nodules between follicles and often are more prominent than those in normal dogs. Some remaining follicular cells appear to be transformed into large oxyphilic cells with densely eosinophilic granular cytoplasm.

Hypothyroidism is a clinically important disease in dogs following immune-mediated destruction of secretory cells but is encountered only occasionally in other animals. Although the disease occurs in many adult purebred and mixed-breed dogs, certain breeds (golden retriever, Doberman pinscher, dachshund, Shetland sheepdog, Irish setter, miniature schnauzer, cocker spaniel, and Airedale) are more commonly affected. Many functional disturbances associated with hypothyroidism are due to a reduction in basal metabolic rate. A gain in body weight without an associated change in appetite occurs in some hypothyroid dogs. Thinning of the hair coat often is accompanied by a bilaterally symmetrical alopecia. Areas affected initially by hair loss are those receiving frictional wear, such as the tail, cervical area, and over bony prominences. Hyperkeratosis is a consistent finding in hypothyroidism and results in an increased scaliness of the skin and often involves the external root sheath resulting in follicular keratosis. Myxedema occurs in severe and chronic cases from the accumulation of mucins (neutral and acid mucopolysaccharides combined with protein) in the dermis and subcutis. These substances bind considerable amounts of water and result in marked thickening of the skin.

Hypothyroidism in dogs is accompanied by decreased circulating thyroid hormone concentrations and decreased $^{131}$I uptake by the thyroid gland. In dogs with hypothyroidism, the serum $T_4$ concentration usually is below 0.8 µg/dl (normal 1.5–3.4 µg/dl), and that of $T_3$ is below 50 ng/dl (normal 48–150 ng/dl). In the euthyroid dog, the $T_4$ concentrations will at least double 8 hours after intravenous or intramuscular injection of TSH, whereas in dogs with primary hypothyroidism (due to lymphocytic thyroiditis), the $T_4$ concentrations do not change significantly after injection of TSH. The serum cholesterol concentration often is increased greatly (300–900 mg/dl) in hypothyroid dogs (normal serum cholesterol 40–80 mg/dl). The marked hypercholesterolemia in long-standing and severe hypothyroidism results in a variety of secondary lesions, including atherosclerosis, hepatomegaly, and glomerular and corneal lipidosis.

**Pituitary Aplasia and Dwarfism**

Pituitary dwarfism in German shepherd dogs usually is associated with a failure of the oropharyngeal ectoderm of Rathke’s pouch to differentiate into trophic hormone-secreting cells of the pars distalis. This results in a progressively enlarging, multiloculated cyst in the sella turcica and a partial to complete absence of the adenohypophysis (1). The cyst is lined by pseudostratified, often ciliated, columnar epithelium with interspersed mucin-secreting goblet cells. The mucin-filled cysts eventually occupy the entire pituitary area in the sella turcica and severely compress the pars nervosa and infundibular stalk. A few differentiated trophic hormone-secreting chromophils may be present between the pituitary cysts that stain immunocytochemically for 1 or more of the specific trophic hormones. An occasional small nest or rosette of poorly differentiated epithelial cells is interspersed between multiloculated cysts, but the cell cytoplasm is usually devoid of hormone-containing secretory granules. Cysts associated with pituitary dwarfism morphologically
are distinct from the cysts that develop following the abnormal accumulation of colloid in the residual lumen of Rathke’s pouch. In the latter, the normally developed pars distalis and pars nervosa are compressed to varying degrees by the abnormal accumulation of colloid in a preformed normal cavity of the pituitary gland.

Pups with juvenile-onset hypopituitarism appear normal or are indistinguishable from littermates at birth and until about 2 months of age. Subsequently, the slower growth rate than the littermates, retention of puppy hair coat, and lack of primary guard hairs gradually become evident in dwarf pups. German shepherd dogs with pituitary dwarfism appear coyote-like or fox-like because of their diminutive size and soft woolly coat (69). A bilaterally symmetrical alopecia develops gradually and often progresses to complete alopecia except for the head and tufts of hair on the legs. There is progressive hyperpigmentation of the skin until it is uniformly brown-black over most of the body. Adult German shepherd dogs with panhypopituitarism vary in size from as tiny as 4 lb up to nearly half normal size, apparently depending on the degree of penetrance of the inherited defect and whether the failure of formation of the adenohypophysis is nearly complete or only partial.

Panhypopituitarism in German shepherd dogs often occurs in littermates and related litters, suggesting a simple autosomal recessive mode of inheritance (4, 5, 6, 57, 72, 112). The activity of somatomedin, or insulin-like growth factor-1, (a cartilage growth–promoting peptide whose production in the liver and plasma activity are controlled by somatotrophin) is low in dwarf dogs (57). Intermediate somatomedin activity is present in the phenotypically normal ancestors suspected to be heterozygous carriers. Assays for somatomedin (a non–species-specific, somatotropin-dependent peptide) provide an indirect measurement of circulating growth hormone activity in dogs with suspected pituitary dwarfism (108, 112).

**Biochemical Defect in Synthesis of Thyroid Hormones and Congenital Goiter**

Sporadic outbreaks of hyperplastic goiter develop in calves, lambs, kids, and pups as a consequence of an inability to synthesize thyroglobulin or to an enzyme defect in the biosynthesis of the thyroid hormones by follicular cells (40, 87). The more prevalent forms of inherited goiter in human patients include defects in the iodination of tyrosine, deiodination of iodotyrosines, synthesis and proteolysis of thyroglobulin, coupling of iodotyrosines to form iodothyronines, and a disruption in iodide transport.

Congenital dyshormonogenetic goiter is inherited by an autosomal recessive gene in sheep (Corriedale, Dorset Horn, Merino, and Romney breeds) (87), Afrikaner cattle (77), and Saanen dwarf goats (90). The subnormal growth rate, absence of normal wool development or a rough sparse hair coat, myxedematous swellings of the subcutis, weakness, and sluggish behavior suggest that the affected young clinically are hypothyroid. Most lambs with congenital goiter either die shortly after birth or are highly sensitive to the effects of adverse environmental conditions. Thyroid glands are symmetrically enlarged at birth (Figure 15) because of an intense diffuse hyperplasia of follicular cells (12). Thyroid follicles are lined by tall columnar cells, but follicles often have collapsed because of lack of colloid resulting from the inability to synthesize thyroglobulin and have slit-like lumens (arrow). Periodic acid–Schiff.

**FIGURE 15.**—Congenital goiter in a lamb with symmetrical diffuse enlargements of thyroid (T) lobes. The primary hypofunction of the thyroid was due to an inability of follicular cells to synthesize thyroglobulin. The thyroid enlargement was due to TSH-mediated hypertrophy and hyperplasia of follicular cells in response to the low blood thyroid hormone levels.

**FIGURE 16.**—Severe diffuse TSH-mediated follicular cell hypertrophy and hyperplasia in a lamb with congenital goiter (refer to Figure 15). Follicles have collapsed due to a lack of colloid from the inability to synthesize thyroglobulin and have slit-like lumens (arrow). Periodic acid–Schiff.
T4 and T3 levels are consistently low. There is a lack of a defect in the iodide transport mechanism, organification, or dehalogenation but an absence of normal 19S thyroglobulin in goitrous thyroids and only minute amounts of thyroglobulin-related antigens (0.01% of normal), suggesting an impairment in thyroglobulin biosynthesis in animals with congenital goiter. Although thyroglobulin mRNA sequences are present in the goitrous tissue, their concentration is markedly reduced (1/10–1/40 that of normal thyroid), and the intracellular distribution is abnormal (nuclear, 42% of normal; cytoplasmic, 7%; membrane fraction, 1–2%). The lack of thyroglobulin in these examples of congenital goiter in animals appears to be due to a defect in thyroglobulin mRNA leading to aberrant processing of primary transcripts and/or transport of the thyroglobulin mRNA from the nucleus to the ribosomes on the endoplasmic reticulum in the cytoplasm of follicular cells.

Genetic Enzyme Deficiency and Vitamin D–Dependent Rickets

Deficiency of vitamin D may result from a lack of the renal 25-hydroxy-cholecalciferol-1α-hydroxylase, an enzyme essential for the metabolic activation of precursor molecules (eg, 25-OH cholecalciferol) to form the active (hormonal) form of vitamin D (eg, 1,25-(OH)2-cholecalciferol) (Figure 17) (111, 113). Vitamin D–dependent rickets in both pigs and humans is a familial disease inherited by an autosomal recessive gene. Newborn pigs appear healthy and have normal concentrations of calcium and phosphorus in the blood; however, blood levels of calcium and phosphorus decrease progressively after 4–6 weeks of age, while alkaline phosphatase activity increases. Clinically detectable rickets develops during the following 3–4 weeks, and affected pigs develop deformities of bone in the axial and abaxial skeleton and evidence severe pain. In response to the hypocalcemia caused by a deficiency of the hormonal form of vitamin D, plasma levels of parathyroid hormone are elevated in pigs with vitamin D–dependent rickets. Serum levels of 25-OH cholecalciferol are elevated in pigs with clinical rickets, whereas the circulating concentration of 1,25-(OH)2-CC is markedly depressed.

SECONDARY HYPOFUNCTION

A destructive lesion in 1 organ (ie, pituitary gland) interferes with the secretion of trophic hormones and results in subnormal function of target endocrine glands in secondary hypofunction. Large, endocrinologically inactive neoplasms may interfere with the secretion of multiple pituitary trophic hormones and result in clinically significant hypofunction of the adrenal cortex, follicular cells of the thyroid, and gonads (Figure 18). The disruption of growth hormone secretion has little effect on body stature because lesions of this type usually develop in adult to aged animals. Hypofunction of an endocrine organ also may be secondary to a lack of raw materials (eg, iodine) necessary for the synthesis of hormone (T4, T3) (Figure 18). Marginal deficiencies often are associated with the presence of goitrogenic chemicals in the diet that interfere with the process of hormone synthesis by thyroid follicular cells.

Lack of Normal Trophic Stimulus and Adult-Onset Panhypopituitarism

Nonfunctional (endocrinologically inactive) pituitary tumors are most common in dogs, cats, and certain strains of laboratory rats and are uncommon in other species (115). Although these adenomas are endocrinologically inactive, they may result in significant functional disturbances by virtue of compression atrophy of the pars nervosa and pars distalis or extension into the overlying brain.
and optic nerves. Animals with nonfunctional pituitary adenomas usually have clinical disturbances related to dysfunction of the central nervous and neurohypophyseal systems as well as a lack of secretion of pituitary trophic hormones with diminished end-organ function (eg, thyroid follicular cells, adrenal cortex, and gonads). The history often includes depression, incoordination and other disturbances of balance, weakness, collapse with exercise, and a marked change in personality. In long-standing cases, there may be evidence of blindness with dilated and fixed pupils due to compression of optic nerves (46). The body condition varies from a progressive loss of weight to obvious obesity. Another common finding with pituitary tumors is the excretion of large volumes of dilute urine with a low specific gravity and a corresponding increase in water intake. The disturbances of water balance are the result of an interference with the synthesis and release of antidiuretic hormone (ADH) (53). The posterior lobe, infundibular stalk, and hypothalamus often are compressed or disrupted by the infiltration of neoplastic cells. This interrupts the nonmyelinated axons that transport ADH from the site of production in the hypothalamus (primarily in the supraoptic nucleus) to the site of release in the capillary plexus of the posterior lobe. Compression of neurosecretory neurons in the hypothalamus by a large dorsally expanding pituitary tumor also may result in decreased ADH synthesis.

Nonfunctional pituitary adenomas usually reach considerable size before they cause obvious clinical signs or kill the animal (Figure 19). The proliferating tumor cells incorporate the remaining structures of the adenohypophysis and infundibular stalk. The neoplasms are firmly attached to the base of the sella turcica, but there usually is no evidence of erosion of the sphenoid bone. In dogs, cats, rats, and horses, the diaphragma sellae is incomplete, so the line of least resistance favors dorsal expansion of the progressively enlarging adenoma, resulting either in a broad-based indentation or extension into the overlying brain (Figure 19). The entire hypothalamus often is compressed and replaced by the tumor, which also may extend into the thalamus. The tumor cells are cuboidal to polyhedral and either arranged in diffuse sheets or subdivided into small packets by a fine connective tissue septa with numerous small capillaries. Special histochimical techniques for pituitary cytology fail to demonstrate specific secretory granules within the cytoplasm of tumor cells. The histogenesis of these nonfunctional tumors is uncertain, but they appear to be derived from pituitary cells that have not differentiated sufficiently to synthesize and secrete a specific trophic hormone.

The target endocrine organs respond dramatically to a lack of normal production of pituitary trophic hormones (Figure 19). The adrenal glands of animals with large nonfunctional pituitary adenomas are small and often difficult to find at necropsy. The adrenals consist primarily of medullary tissue surrounded by a narrow zone of atrophic cortex. The adrenal cortex appears as a thin yellow-brown rim composed of a moderately thickened capsule and secretory cells of the outer layer, zona multiformis (glomerulosa), which is not under primary ACTH control. The zonae fasciculata and reticularis are severely atrophied compared with those in normal adrenal glands, secrete subnormal amounts of glucocorticoid hormones, and have a blunted increase in cortisol or corticosterone following the administration of exogenous ACTH. By comparison, thyroid glands in animals with large pituitary adenomas disrupting normal trophic hormone (eg, TSH) production either are near normal size or only slightly reduced in size to a much lesser degree than is the adrenal cortex (Figure 19). The majority of thyroid follicles are large, lined by flattened (atrophic) cuboidal follicular cells, and distended with a densely stained colloid with little evidence of endocytotic activity because of a lack of TSH (Figure 20). Seminiferous tubules in the testis are small with little evidence of active spermatogenesis and the ovarian cortex is devoid of functional graafian follicles.
OVERVIEW OF ENDOCRINE LESIONS

HYPERFUNCTION OF ENDOCRINE GLAND SECONDARY TO OTHER CONDITIONS

**HYPERPARATHYROIDISM**
- CHRONIC RENAL DISEASE / FAILURE
  - Pi RETENTION; (1) 1,25-(OH)₂ VD
  - HYPOCALCEMIA; (7) PTH
- NUTRITIONAL IMBALANCES
  - HIGH Pi; LOW OR NORMAL CA**
  - VITAMIN D₃ DEFICIENCY

**FIGURE 21.**—Examples of hyperfunction of an endocrine gland (eg, parathyroid) secondary to other conditions (eg, chronic renal disease and nutritional imbalances).

Lack of Essential Raw Materials for Hormone Synthesis and Iodine-Deficient Goiter

Secondary hypofunction of an endocrine gland also occurs when insufficient iodide ion is available for thyroid follicular cells to synthesize adequate amounts of thyroid hormones to meet the animal’s daily requirements. The thyroid gland attempts to compensate by increasing the efficiency of iodide trapping (by upregulating expression of the genes for the sodium/iodide symporter in the basolateral membrane of follicular cells) and by preferentially synthesizing more T₃ than T₄, thereby saving a molecule of iodide for every molecule of thyroid hormone produced. Dietary iodine deficiency resulting in diffuse hyperplastic goiter was common in many areas of the world before the widespread addition of iodized salt to animal diets and still occurs worldwide in domestic animals and human beings living in iodine-deficient areas. Marginally iodine-deficient diets that contain goitrogenic compounds may cause severe thyroid follicular cell hyperplasia and goiter. Goitrogenic substances include thioracil, sulfonamides, anions of the Hofmeister series, and a number of plants of the family *Brassicaceae*. Offspring of females fed iodine-deficient diets are likely to develop severe thyroid follicular cell hyperplasia and have clinical signs of hypothyroidism. The affected lobes are firm and dark red because an extensive interfollicular capillary network develops under the influence of long-term TSH stimulation. Follicles are irregular in size and shape in hyperplastic goiter because they contain varying amounts of lightly eosinophilic and vacuolated colloid. Some follicles collapse because of the lack of colloid. Their lining epithelial cells are columnar and have a eosinophilic cytoplasm, partly vacuolated, and small hyperchromatic nuclei that are often situated in the basilar portion of the cell. The follicles are lined by single or multiple layers of hyperplastic follicular cells that form papillary projections into the lumens of some follicles.

ENDOCRINE HYPERACTIVITY SECONDARY TO OTHER CONDITIONS

The classic example of endocrine hyperactivity secondary to diseases of other organs in animals is hyperparathyroidism that develops secondary to either chronic renal failure or nutritional imbalances (Figure 21). In the renal form, the retention of phosphorus early and subsequent progressive destruction of cells in the proximal convoluted tubules interferes with the metabolic activation of vitamin D by the 25-OH Cholecalciferol-1α-hydroxylase in the kidney. This is the rate-limiting step in the metabolic activation of vitamin D and is tightly controlled by parathyroid hormone and several other factors, including the serum phosphorus concentration. The impaired intestinal absorption of calcium results in the development of progressive hypocalcemia that leads to long-term parathyroid stimulation and development of generalized demineralization of the skeleton. Nutritional hyperparathyroidism develops in animals fed abnormal diets that are either low in calcium, high in phosphorus, or deficient in cholecalciferol (Figure 21).

Renal Hyperparathyroidism

In this form of hyperparathyroidism, there is an excessive, but not autonomous, rate of parathyroid hormone (PTH) secretion as part of the body’s compensatory mechanisms to chronic renal failure. This disorder is encountered most frequently in dogs but also occurs in cats, laboratory rats, and many other animal species. The secretion of parathyroid hormone by the diffusely hyperplastic parathyroid glands of animals affected with this disorder usually remains responsive to fluctuations in blood calcium. Chronic renal insufficiency from interstitial nephritis, glomerulonephritis, nephrosclerosis (Figure 22) in older animals, or amyloidosis and congenital anomalies (such as cortical hypoplasia, polycystic kidneys, and bilateral hydronephrosis) in young animals may result in a significant reduction in glomerular filtration rate, leading to the retention of phosphorus and the development of progressive hyperphosphatemia.

Parathyroid stimulation in animals with chronic renal disease can be directly attributed to the hypocalcemia that develops. As the phosphorus concentration increases, blood calcium decreases reciprocally, largely because of the suppressive effects of the hyperphosphatemia on the renal 1α-hydroxylase, resulting in an interference in pro-
Hyperparathyroidism secondary to chronic renal disease resulting in diffuse demineralization of the maxilla and mandibles (“rubber jaw”) due to activation of osteoclasts.

**Figure 23.**

Nutritional Hyperparathyroidism

Nutritional secondary hyperparathyroidism is characterized by the increased secretion of parathyroid hormone, which develops as part of the body’s compensatory mechanisms to disturbances of mineral homeostasis caused by nutritional imbalances. The disease is common in cats, dogs, certain nonhuman primates, and many laboratory and farm animal species (Figure 24). Dietary mineral imbalances of etiologic importance in the pathogenesis of nutritional hyperparathyroidism are (a) a low content of calcium, (b) excessive phosphorus with normal or low levels of calcium, and (c) inadequate amounts of vitamin D₃ in New-World non-human primates. The end result is hypocalcemia, which results in the stimulation of parathyroid chief cells.

A diet low in calcium fails to supply the daily requirement and hypocalcemia develops even though a greater proportion of ingested calcium is absorbed. Ingestion of excessive phosphorus results in the increased intestinal absorption and elevation of blood levels of phosphorus with a reciprocal lowering of the blood calcium. Hyperphosphatemia does not stimulate the parathyroid gland directly but does so indirectly by virtue of its ability to lower blood calcium by decreasing intestinal calcium absorption, similar to that described for the renal form of the disease. Diets containing inadequate amounts of vitamin D₃, even with normal levels of vitamin D₂, cause the diminished absorption of calcium by intestinal cells and results in hypocalcemia in certain New World monkeys because of their relative resistance to vitamin D₂.

In response to nutritionally induced hypocalcemia, the parathyroid glands undergo chief cell hypertrophy and hyperplasia. Active chief cells stimulated by the diet-induced hypocalcemia become larger and more tightly arranged together (Figure 25) compared to chief cells of normal animals (Figure 26). Because kidney function is normal, the increased levels of PTH result in a diminished rate of renal reabsorption of phosphorus and an increased tubular reabsorption of calcium, and blood levels of calcium return toward normal. The continued ingestion of an imbalanced diet sustains the state of compensatory hyperparathyroidism, which eventually leads to the progressive development of metabolic bone disease. Nutritional hyperparathyroidism develops in young animals fed a nonsupplemented all-meat diet. Clinical signs are dominated by disturbances in locomotion manifested by a reluctance of animals to move, incoordinated gait, and posterior lameness.

**Figure 24.** Dietary imbalances in different animal species that result in nutritional secondary hyperparathyroidism. The dietary imbalance most common in a particular species is indicated by the number in parentheses.

**Table:**

<table>
<thead>
<tr>
<th>Etiology: Dietary Imbalances</th>
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<tr>
<td>1. Low Calcium Content</td>
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<td>2. Excess Phosphorus</td>
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<tr>
<td>- Normal Calcium</td>
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<tr>
<td>- Low Calcium</td>
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<tr>
<td>3. Inadequate Vitamin D₃</td>
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<th>Species Affected (Etiology)</th>
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<td>(1) Cat, Dog, Pig, Cattle, Caged Birds, Turtles, Reptiles</td>
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<td>(2) Horse, Monkey, Reptiles</td>
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<tr>
<td>(3) New World Non-Human Primates</td>
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Hormonal Imbalances Induced by Xenobiotic Chemicals

Hyperfunction of an endocrine organ also can be the result of hormonal imbalances induced by xenobiotic chemicals. For example, hyperactivity of the pituitary gland in rodents during chronic toxicity testing often results in an increased development of tumors in the gonads or mammary glands (Figure 27). An excess production of luteinizing hormone (LH), usually due to disruption of negative feedback control by estrogen or testosterone, increases the incidence of tubulostromal adenomas and granulosa cell tumors in the ovary of mice and Leydig (interstitial) cell adenomas of the testes in rats.

Ovarian Tumorigenesis. The tubular (or tubulostromal) adenomas are the most important of the ovarian tumors in mice and are the tumors whose incidence often is increased by various endocrine perturbations associated with chronic exposure to xenobiotic chemicals, senescence, or inherited genic deletion (71). Tubular adenomas are a unique lesion that develops frequently in the mouse ovary, accounting for approximately 25% of naturally occurring ovarian tumors in this species (3, 89). They are uncommon in rats, rare in other animal species, and not recognized in the ovaries of women. In some ovarian tumors of this type in mice, there is an intense proliferation of stromal (interstitial) cells of sex cord origin. These tumors often are designated tubulostromal adenomas or carcinomas to reflect the bimorphic appearance.

The tubulostromal adenomas in mice are composed of numerous tubular profiles derived from the surface epithelium, plus abundant large luteinized stromal cells from the ovarian interstitium (Figure 28). The differences in histological appearance of this type of unique ovarian tumor in mice are interpreted to represent a morphological spectrum with variable contributions from the surface epithelium and sex cord-derived ovarian interstitium rather than being 2 distinct types of ovarian tumors. The

**Figure 25.**—Diffuse chief cell hypertrophy and hyperplasia in a kitten fed a low-calcium (all-meat) diet. Note the expanded cytoplasmic area of chief cells and narrow perivascular spaces (arrow). H&E.

**Figure 26.**—Parathyroid gland from an age-matched control kitten fed a normal diet at similar magnification. The cytoplasmic area is less and the perivascular spaces are wider (arrow) than in the kitten with secondary hyperparathyroidism (refer to Figure 25). H&E.

**Figure 27.**—Hyperfunction of the pituitary gland as a result of disruption of hormonal feedback by xenobiotic chemicals through one of several mechanisms leading to an overproduction of luteinizing hormone (LH) or prolactin. In sensitive rodent species, these hormonal imbalances frequently lead to an increased incidence of ovarian, testicular, or mammary tumors in chronic studies with large doses of the compound.

**Figure 28.**—Tubulostromal adenoma in a mouse ovary following a chronic overproduction of LH subsequent to xenobiotic chemical-induced destruction of ovarian follicles. The tumor is composed of tubular down-growths of the surface epithelium (arrow) and proliferating interstitial cells (C). H&E.
histogenic origin of this unique ovarian tumor in mice has been a controversial topic in the literature, but most investigators currently agree that it is derived from the ovarian surface epithelium, with varying contributions from stromal cells of the ovarian interstitium.

Factors that destroy or greatly diminish the numbers of ovarian follicles, such as senescence, genetic deletion of follicles, X-irradiation, drugs and xenobiologic chemicals such as nitrofurantoïn, and early thymectomy with the development of autoantibodies to oocytes, all diminish sex steroid hormone secretion by the ovary. This results in elevated circulating levels of gonadotrophins, especially LH, because of decreased negative feedback on the hypothalamic-pituitary axis by estrogens and possibly other humoral factors produced by the graafian follicles (25). The long-term stimulation of stromal (interstitial) cells, which have receptors for LH (106), and, indirectly, the ovarian surface epithelium appears to place the mouse ovary at increased risk for developing the unique tubular adenomas and granulosa cell tumors in chronic studies. The intense proliferation of ovarian surface epithelium and stromal (interstitial) cells with the development of unique tubular adenomas in mice as a response to sterility does not have a counterpart in the ovaries of human adult females.

Testicular Tumorigenesis. Leydig (interstitial) cells of the testis frequently undergo proliferative changes with advancing age and following chronic exposure to large doses of xenobiologic chemicals that result in hormonal imbalances in rodents. Pathogenic mechanisms reported to be important in the development of proliferative lesions of Leydig cells include hormonal imbalances, irradiation, species and strain differences, exposure to certain chemicals such as cadmium salts and 2-acetoaminofluorene (86), as well as certain physiological perturbations such as cryptorchidism, a compromised blood supply to the testis, and heterotransplantation into the spleen.

Hormonal imbalances are important factors in the development of focal proliferative lesions of Leydig cells, including increased estrogenic steroids in mice and hamsters and elevated pituitary gonadotrophins in rats resulting from the chronic administration of xenobiologic chemicals (Figure 31) (27, 34). Many xenobiologic chemicals, when administered chronically to rats, disrupt the hypothalamic-pituitary-testes axis at one of several possible sites (eg, androgen receptor antagonists, 5α-reductase inhibitors, testosterone biosynthesis inhibitors, GnRH agonists, and aromatase inhibitors), interfering with negative feedback control, resulting in hyperfunctioning of the pituitary gland and an overproduction of LH that leads to the proliferative changes (hyperplasia and adenoma) in Leydig cells (Figure 32). For example, chronic exposure to chemicals with antiandrogenic activity, such as pro-
cymidone due to binding to the androgen receptor, increases circulating levels of LH and results in stimulation of Leydig cells, leading to an increased incidence of hyperplasia and adenomas in rats (70).

Another important mechanism by which xenobiotic chemicals result in hormonal imbalances that increase the incidence of Leydig cell tumors in rats is by inhibition of testosterone synthesis by cells in the testis. For example, lansoprazole is a substituted benzimidzole that inhibits the hydrogen-potassium ATPase (proton pump) responsible for acid secretion by the parietal cells in the fundic mucosa of the stomach (41). The presence of the imidazole moiety in lansoprazole suggested a possible direct effect on the testis since several imidazole compounds (eg, ketoconazole and miconazole) are known to inhibit testosterone synthesis. Lansoprazole resulted in decreased circulating levels of testosterone, compensatory increased levels of LH, and an increased incidence of Leydig cell hyperplasia and adenomas in chronic studies in rats (41). The most sensitive site for inhibition of testosterone synthesis by lansoprazole was the transport of cholesterol to the cholesterol side chain cleavage enzyme.

Although several hormonal imbalances result in an increased incidence of Leydig cell tumors in rodents, human patients with several disease conditions associated with chronic elevations in serum LH (including Klinefelter's syndrome and gonadotroph adenomas of the pituitary gland) have not been associated with an increased development of this type of rare testicular tumor in men. There are a number of reports of marketed drugs that increased the incidence of proliferative lesions of Leydig cells in chronic toxicology/carcinogenicity studies in rats. These include indomethacin, lactitol, muselergine, cimetidine, gemfibrozil, and flutamide, among many others (27, 34). Although a number of xenobiotic chemicals have been reported to increase the incidence of Leydig cell adenomas in chronic studies in rats, similar compounds (eg, cimetidine, ketoconizole, and certain calcium channel blocking agents) have not resulted in an increased incidence of Leydig cell neoplasia in man. Leydig cell tumors are a frequently occurring tumor in rats, often associated mechanistically with hormonal imbalances; however, they are not an appropriate model for assessing the potential risk to human males of developing this rare testicular tumor following exposure to a xenobiotic chemical.

**HYPERSECRETION OF HORMONES BY NONENDOCRINE TUMORS**

Certain neoplasms of nonendocrine tissues in both animals and human secrete either hormones or humoral substances that share chemical and/or biologic characteristics with the “native” hormones secreted by an endocrine gland. Most of the recently discovered humoral substances secreted by nonendocrine tumors are peptides rather than steroids, iodothyronines, or catecholamines, which require more complex biosynthetic pathways. For example, humoral hypercalcemia of malignancy (“pseudo-hyperparathyroidism”) is a clinical syndrome produced primarily by the autonomous hypersecretion of parathyroid hormone–related peptide (PTH-rP) by cancer cells (Figure 33) (23). PTH-rP is able to interact with the parathyroid hormone receptor in target cells (eg, bone and kidney) and result in persistent, often life-threatening, hypercalcemia.

**Humoral Hypercalcemia of Malignancy**

Humoral hypercalcemia of malignancy (HHM) is a syndrome associated with diverse malignant neoplasms in animal and human patients (95, 96). Characteristic findings in patients with HHM include hypercalcemia, hypophosphatemia, hypercalciuria (often with decreased fractional calcium excretion), increased fractional excretion of phosphorus, increased nephrogenous cAMP, and increased osteoclastic bone resorption. Hypercalcemia is produced by the effects of PTH-rP on bone, kidney (Figure 34), and possibly the intestine. Increased osteoclastic bone resorption is a consistent finding in HHM with increased calcium release from bone. The kidney plays a
critical role in the pathogenesis of hypercalcemia and hypophosphatemia since renal calcium reabsorption is stimulated by PTH-rP and phosphorus reabsorption is inhibited because of binding to and activation of the renal PTH/PTH-rP receptors. PTH-rP binds to the N-terminal PTH/PTH-rP receptor in bone and kidney but does not cross react immunologically with native PTH. PTH-rP stimulates adenylate cyclase and increases intracellular calcium ion in bone and kidney cells by binding to and activating the cell membrane PTH/PTH-rP receptors. This results in a stimulation of osteoclastic bone resorption, increased renal tubular calcium reabsorption, and decreased renal tubular phosphorus reabsorption. In some forms of HHM, there are increased serum 1,25-dihydroxyvitamin D levels that may increase calcium absorption from the intestine (100). Although excessive secretion of biologically active PTH-rP plays a central role in the pathogenesis of hypercalcemia in most forms of HHM cytokines such as interleukin-1, tumor necrosis factor-alpha, transforming growth factors, and 1,25-dihydroxyvitamin D may have synergistic or cooperative actions with PTH-rP (45, 65, 66).

A well-characterized example of this disease mechanism in animals is the adenocarcinoma derived from the apocrine glands of the anal sac in dogs. Serum PTH levels are lower in dogs with apocrine carcinomas than in controls, and PTH levels are undetectable in tumor tissue (67, 100). The parathyroid glands are small and difficult to locate or not visible macroscopically in dogs with persistent cancer-associated hypercalcemia (67). Atrophic parathyroid glands are characterized by narrow cords of inactive chief cells with an abundant fibrous connective tissue stroma and widened perivascular spaces. The inactive chief cells have a markedly reduced cytoplasmic area, prominent hyperchromatic nuclei, and relatively straight cell membranes with uncomplicated interdigitations and are closely packed together. These morphologic findings indicate that the malignant neoplasms are not producing a substance that stimulates parathyroid hormone secretion by chief cells but rather that the parathyroid glands are responding to the persistent hypercalcemia by undergoing trophic atrophy. Thyroid parafollicular cells (C-cells) often respond to the persistent elevation in blood calcium by undergoing diffuse or nodular hyperplasia (67). Most dogs with HHM with different types of cancer have increased circulating concentrations of PTH-rP. Plasma concentrations of PTH-rP were greatest (10-100 pM) in dogs with adenocarcinomas derived from apocrine glands of the anal sac and sporadic carcinomas associated with HHM (97, 100). The serum calcium concentrations in these dogs correlated well with circulating PTH-rP concentrations and was consistent with the concept that PTH-rP plays a primary role in the pathogenesis of HHM.

Physiologic Role for Parathyroid Hormone–Related Protein. Parathyroid hormone–related protein (PTH-rP) is a 139-173 amino acid peptide, originally isolated from human and animal tumors associated with humoral hypercalcemia of malignancy (98). The PTH-rP peptide shares 70% sequence homology with the first 13 amino acids of intact PTH. The N-terminal region of PTH-rP (amino acids 1-34) binds and stimulates PTH receptors in bone and kidney cells with equal affinity as PTH. However, PTH-rP is not strictly a calcium-regulating hormone, as it appears to have an important physiologic role in many normal tissues (Figure 35). It has been determined that PTH-rP is widely produced in the body and acts as a paracrine factor in the tissues in which it is produced.

The fetus maintains higher concentrations of serum calcium compared to the dam. Because the fetal parathyroid glands produce low levels of PTH, the mechanism of maintaining increased serum concentrations of calcium was unknown until the finding that PTH-rP maintains calcium balance in the fetus and is the major hormone secreted by the chief cells of the fetal parathyroid glands (24). The PTH-rP produced by the placenta also stimulates the uptake of calcium by the fetus. Parathyroid hormone–related peptide plays a role in the differentiation of many tissues during gestation and is especially im-

**Figure 33.—Examples of hypersecretion of hormones by nonendocrine tumors.**

**Figure 34.—Humoral hypercalcemia of malignancy (HHM) develops in animal and human patients when neoplasms constitutively secrete parathyroid hormone–related protein (PTH-rP). PTH-rP binds to receptors on osteoblasts, which subsequently signal osteoclasts to increase bone resorption and renal epithelial cells in the distal nephron to enhance calcium reabsorption (decreasing fractional (F) calcium (Ca²⁺) excretion), resulting in persistent hypercalcemia. cAMP = cyclic adenosine monophosphate.**
important in the growth and development of bone. Growth of cartilage at the epiphyseal plate is regulated by the actions or PTH-rP, which stimulates chondrocyte proliferation, inhibits apoptosis, and inhibits the maturation of chondrocytes from the proliferative zone to the hypertrophic zone (109).

Many tissues in adult animals, including endocrine glands; smooth, skeletal, and cardiac muscles; brain; lymphocytes; lactating mammary gland; kidney; prostate gland; lung; skin; and bone produce PTH-rP. The function of PTH-rP in most of these tissues is poorly understood but likely is an autocrine or paracrine regulatory factor. Circulating concentrations of PTH-rP in normal animals and humans are low (<1 pM) (11, 98), and the PTH/PTH-rP receptor is often expressed on the same or adjacent cells in tissues that synthesize PTH-rP. Epidermal keratinocytes produce PTH-rP, which plays a role in their proliferation or differentiation.

The greatest concentration of PTH-rP is found in milk (10–100 nmol/L) and is 10,000- to 100,000-fold greater than in the serum (88). The function of PTH-rP in the mammary gland and in milk is poorly understood at present. However, overexpression of PTH-rP in the mammary gland during glandular development prior to lactation results in glandular hypoplasia due to a reduction in the morphogenesis and branching of the mammary ducts. Biologically active PTH-rP produced by alveolar epithelial cells during lactation results in the high concentration of PTH-rP in milk, and this PTH-rP may play a role in stimulating the transport of calcium by alveolar epithelial cells from serum to milk (7, 78). Synthesis of PTH-rP by the mammary gland abruptly ceases when suckling stops and the gland undergoes involution. The PTH-rP peptide is enzymatically cleaved in milk, but the N-terminal PTH-rP fragment retains biologic activity. Smooth muscle, including blood vessels, uterus, urinary bladder, gastrointestinal tract, and the oviduct of the hen, produce PTH-rP. In general, PTH-rP expression is increased when smooth muscle is stretched and PTH-rP induces relaxation of smooth muscle and attenuation of contraction. With progressive distension of the uterus during pregnancy or during descent of the ovum in the hen’s oviduct, PTH-rP likely functions as a paracrine regulator of vascular tone, causing vasodilation and modulating vasoconstriction by other vasoactive compounds.

**Failure of Target Cells to Respond to Hormone**

This mechanism of endocrine disease has been appreciated coincident with the more complete understanding of how hormones interact with target cells to convey their biologic message. A failure of target cells to respond to hormone may be due either to a lack of adenylate cyclase activity or to an alteration in hormone receptors (Figure 36). Hormone is secreted in normal or increased amounts by the cells of the endocrine gland.

Insulin resistance associated with obesity in both animals and humans can result from a decrease or “down-regulation” of receptors on the surface of target cells. This develops in response to the chronic increased insulin secretion stimulated by the hyperglycemia resulting from the excessive food intake. For example, animals with large pituitary neoplasms that extend dorsally out of the sella turcica often destroy critical hypothalamic nuclei that regulate the intake of food (Figure 37). They often develop insulin-resistant hyperglycemia and glycosuria as a result of a down-regulation of insulin receptors on target cells induced by the chronic excessive intake of food and hyperinsulinemia (Figure 38). Secretory cells in the corresponding endocrine gland (ie, pancreatic islets) undergo compensatory hypertrophy and hyperplasia in an attempt to secrete additional hormone and lower the blood glucose concentration.

An interesting form of hypoparathyroidism has been reported in human patients in which the inability of target cells to respond is due to a defect in the cAMP-mediated signal transduction resulting from a lack of specific nucleotide regulatory protein in the cell membrane. Patients with “pseudohypoparathyroidism” develop hypocalcemia and hyperphosphatemia despite hyperplastic parathyroids and elevated blood levels of PTH. Similarly, animals and humans with nephrogenic diabetes have defects

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**Table: Evolving Physiologic Roles for Parathyroid Hormone-Related Protein**

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<thead>
<tr>
<th>Role</th>
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<tr>
<td>Development of cartilage and bone</td>
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<td>Development of skin and appendages</td>
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<td>Regulation of growth and differentiation of mammary gland</td>
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<td>Maintenance of calcium homeostasis in fetus</td>
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<td>Stimulation of placental calcium transport</td>
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**Table: Failure of Target Cells to Respond to Hormone**

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<th>Condition</th>
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<td>Lack of adenylate cyclase activity</td>
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<tr>
<td>Pseudohypoparathyroidism (PHT)</td>
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<tr>
<td>Alterations in hormone receptors</td>
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<td>Numbers or affinity (H-R)</td>
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<td>Insulin-resistance with obesity</td>
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in the vasopressin receptor on cells of the distal nephron and collecting ducts in the kidney, resulting in a lack of adenylylate cyclase stimulation and generation of cyclic AMP after vasopressin binding to its receptor on target cells.

Failure of Fetal Endocrine Function

Subnormal function of the fetal endocrine system, especially in ruminants, may disrupt normal fetal development and result in prolongation of the gestation period (Figure 39). In Guernsey and Jersey cattle, a genetically determined failure of development (aplasia) of the adenohypophysis results in a lack of fetal pituitary trophic hormone secretion during the last trimester and hypoplastic development of target endocrine organs (eg, adrenal cortex, thyroid follicular cells, and gonads). Fetal development is normal up to approximately 7 months gestation, but subsequently fetal growth ceases, regardless of how long the viable fetus is retained in utero. Prolongation of the gestation period also occurs in ewes that ingest the plant *Veratrum californicum* early in gestation. Toxins in the plant cause extensive malformations of the central nervous system (CNS) and hypothalamus in lambs. Although the adenohypophysis is present, it is unable to secrete normal amounts of trophic hormones (eg, adrenocorticotropic [ACTH]) because it lacks the necessary fine control derived from the releasing hormones of the hypothalamus. Target endocrine organs in the fetus are hypoplastic, and the adrenal cortex does not differentiate completely into the 3 distinctive zones that secrete corticosteroid hormones. The plant contains potent steroidal alkaloids that inhibit neural tube development when ingested by the ewe between the 9th and 14th day of gestation. Cyclopia and extensive CNS malformations are found in lambs. Arrhinencephalia and lack of development of nasal bones accompany the formation of a proboscis-like structure. The lambs retained in the uterus continue to grow beyond the normal gestation period.

The concepts that have emerged from the study of these naturally occurring diseases are, first, that fetal hormones are necessary for final growth and development in utero in certain animals and, second, that normal parturition at term requires an intact fetal hypothalamic-adenohypophyseal-adrenal cortical axis in these species working in concert with trophoblasts of the placenta. Although the presence or absence of functional adenohypophyseal tissue determines whether the fetus continues to grow in utero, the pathogenesis of prolongation of the gestational interval is similar in these examples. The subnormal development of the fetal adrenal cortex results in an inadequate secretion of cortisol and a failure to induce the 17α-hydroxylase in the placenta that converts precursor molecules (eg, progesterone) to estrogen. The fetal adrenal gland is small, and there is incomplete development of the 3 distinct zones of the cortex (Figure 40). The dam’s circulating progesterone is maintained near midgestational concentrations, and there is a lack of the

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**Figure 37.**—Dorsal extension of pituitary adenoma (A) (pars intermedia origin) with compression and destruction of autonomic centers in ventral-medial region of hypothalamus (H) that regulate the intake of food resulting in insulin-resistant hyperglycemia (see Figure 38). The optic nerve (O) also is compressed. Scale represents 1 cm. Equine pituitary.

**Figure 38.**—Down-regulation of insulin receptors on target cells in response to chronic increased food intake resulting in decreased insulin sensitivity (resistance) and hyperglycemia.

**Figure 39.**—Examples of failure of fetal endocrine function resulting in prolongation of the gestation period. B = bovine; O = ovine; A.C. = adrenal cortex.

**Figure 40.**—Failure of induction placental 17α-OHase.

**Failure of Fetal Endocrine Function**

- **Examples:**
  - Adenohypophyseal aplasia (B)
  - Synthesis defect in adrenal cortex (B)
  - Hypothalamic-pituitary malformations (O)

- **Pathogenesis:**
  - A.C. hypoplasia, (↑) blood cortisol
  - Failure of induction placental 17α-OHase
  - Lack of estrogen peak at term
FIGURE 40.—Failure of fetal endocrine function. Adrenal cortical hypoplasia in calf with prolongation of the gestation period. The adrenal cortex (C) is markedly reduced in thickness, and the adrenal medulla (M) is relatively more prominent. The scale represents 1 cm.

marked increase in estrogens that normally occurs near term and results in parturition by stimulating the local synthesis of prostaglandins in the uterus. This normally results in the smooth muscle contractions and biochemical changes in collagen along the birth canal that permits delivery of the fetus.

ABNORMAL DEGRADATION OF HORMONE

Increased Degradation of Hormone

In laboratory rodents, the long-term administration of various xenobiotics (ie, phenobarbital and others) results in the induction of liver enzymes (eg, \( T_4 \)-uridine diphosphate [UDP]-glucuronyl transferase) that increases the degradation of thyroxine. Endocrine gland and target cell function are normal (Figure 41) (16, 17). The chronic disruption of the thyroid-pituitary axis and augmented TSH secretion in rodents, especially male rats, often increases the development of thyroid follicular cell tumors in chronic toxicity and oncogenicity studies with certain drugs and chemicals (14).

Thyroid Tumorigenesis. Hepatic microsomal enzymes play an important role in thyroid hormone economy because glucuronidation is the rate-limiting step in the biliary excretion of \( T_4 \) and sulfation primarily by phenol sulfotransferase for the excretion of \( T_3 \). Long-term exposure of rats to a wide variety of different chemicals induces these enzyme pathways and results in chronic stimulation of the thyroid by disrupting the hypothalamic-pituitary-thyroid axis (36). The resulting chronic stimulation of the thyroid by increased circulating levels of TSH often results in a greater risk of developing tumors derived from follicular cells in chronic (2-year or lifetime) toxicity/carcinogenicity studies with these compounds in rats (Figure 42). The activation of the thyroid gland during the treatment of rodents with substances that stimulate thyroxine catabolism is a well-known phenomenon and has been investigated extensively with many compounds (36). It occurs particularly in rats, first because UDP-glucuronyl transferase can easily be induced in rodent species and second because thyroxine metabolism takes place very rapidly in rats in the absence of thyroxine-binding globulin in the circulation. In humans, a lowering of the circulating \( T_3 \) level but no change in TSH and \( T_3 \) concentrations has been observed only with high doses of very powerful enzyme-inducing compounds, such as rifampicin with and without antipyrine.

Xenobiotic chemicals that induce liver microsomal enzymes and disrupt thyroid function in rats include CNS-acting drugs (eg, phenobarbital and benzodiazepines), calcium channel blockers (eg, nicardipine and bepridil), steroids (spironolactone), retinoids, chlorinated hydrocarbons (eg, chlordane, DDT, and TCDD), and polychlorinated biphenyls (PCB and PBB), among others (36). Most of the hepatic microsomal enzyme inducers have no apparent intrinsic carcinogenic activity and produce little or no mutagenicity or DNA damage. Their promot-
ing effect on thyroid tumors usually is greater in rats than in mice, with males more often developing a higher incidence of tumors than females. In certain strains of mice, these compounds alter liver cell turnover and promote the development of hepatic tumors from spontaneously initiated hepatocytes.

Phenobarbital has been studied extensively as the prototype for hepatic microsomal inducers that increase a spectrum of cytochrome P-450 isoenzymes (62, 63). McClain et al. reported that the activity of UDP-GT, the rate-limiting enzyme in \( T_4 \) metabolism, is increased in purified hepatic microsomes of male rats when expressed as picomoles per minute per milligram of microsomal protein (1.3-fold) or as total hepatic activity (3-fold) (Figure 43). This resulted in a significantly higher cumulative (4-hour) biliary excretion of \( ^{125}I\)-\( T_4 \) and bile flow than in controls. Most of the increase in bile excretion was accounted for by an increase in \( T_4 \)-glucuronide due to an increased metabolism of \( T_4 \) in phenobarbital-treated rats. This is consistent with enzymatic activity measurements that result in increased hepatic \( T_4 \)-UDP-glucuronyl transferase activity in phenobarbital-treated rats. These results are consistent with the hypothesis that the promotion of thyroid tumors in rats by phenobarbital was not a direct effect of the compound on the thyroid gland but rather an indirect effect mediated by TSH secretion from the pituitary secondary to the hepatic microsomal enzyme-induced increase of \( T_4 \) excretion in the bile.

There is no convincing evidence that humans treated with drugs or exposed to chemicals that induce hepatic microsomal enzymes are at increased risk for the development of thyroid cancer (36). In a study on the effects of microsomal enzyme-inducing compounds on thyroid hormone metabolism in normal healthy adults, phenobarbital (100 mg daily for 14 days) did not affect the serum \( T_4 \), \( T_3 \), or TSH levels (74). A decrease in serum \( T_4 \) levels was observed after treatment with either a combination of phenobarbital plus rifampicin or a combination of phenobarbital plus antipyrine; however, these treatments had no effect on serum \( T_3 \) or TSH levels (75). Phenobarbital has been used clinically as an anticonvulsant for more than 80 years, and relatively high microsomal enzyme-inducing doses have been used chronically, sometimes for lifetime exposures, to control seizure activity in human beings. Epidemiological studies of patients treated with therapeutic doses of phenobarbital have reported no increase in risk for the development of thyroid neoplasia (29, 30, 31, 32, 42, 76, 104, 110). High-sensitivity assays for thyroid and pituitary hormones are readily available in a clinical setting to monitor circulating hormone levels in patients exposed to chemicals potentially disruptive of pituitary-thyroid axis homeostasis.

Many chemicals and drugs disrupt 1 or more steps in the synthesis, secretion, or metabolism of thyroid hormones, resulting in subnormal levels of \( T_4 \) and \( T_3 \), associated with a compensatory increased secretion of pituitary TSH (49). When tested in highly sensitive species, such as rats and mice, these compounds in acute and subchronic studies result in follicular cell hypertrophy/hyperplasia and increased thyroid weights, and in long-term studies they produce an increased incidence of thyroid tumors (usually adenomas) by a secondary (indirect) mechanism associated with hormonal imbalances. In the secondary mechanism of thyroid oncogenesis in rodents, the specific xenobiotic chemical or physiological perturbation evokes another stimulus (e.g., chronic hypersecretion of TSH) that promotes the development of the proliferative lesions (e.g., adenomas [Figure 44]) derived from follicular cells. Thresholds for “no effect” on the thyroid gland can be established by determining the dose of the
xenobiotic chemical that fails to elicit an elevation in the circulating level of TSH. Compounds acting by this indirect (secondary) mechanism with hormonal imbalances usually have little or no evidence for mutagenicity or for producing DNA damage.

In human patients who have marked changes in thyroid function and elevated TSH levels, as is common in areas with a high incidence of endemic goiter due to iodine deficiency, there is little if any increase in the incidence of thyroid cancer (36, 38). The relative resistance to the development of thyroid cancer in humans with elevated plasma TSH levels is in marked contrast to the response of the thyroid gland to chronic TSH stimulation in rats and mice. The human thyroid is much less sensitive to this pathogenetic phenomenon than rodents. The literature suggests that prolonged stimulation of the human thyroid by TSH will induce neoplasia only in exceptional circumstances, possibly by acting together with some other metabolic or immunologic abnormalities (28, 35, 36, 80).

**Decreased Degradation of Hormone**

The rate of secretion of hormone by an endocrine gland may be normal with this mechanism, but blood hormone levels are persistently elevated, thereby simulating a syndrome of hypersecretion, because of a decreased rate of hormone degradation (Figure 41). The classic example of this pathogenic mechanism is the syndrome of feminization due to hyperestrogenism associated with cirrhosis and decreased hepatic degradation of estrogens. Chronic renal disease in dogs occasionally is associated with persistent hypercalcemia due, in part, to decreased degradation of PTH (along with decreased urinary excretion of calcium) by the diseased kidney.

**IATROGENIC SYNDROMES OF HORMONE EXCESS**

**Direct Effects**

The administration of hormone, either directly or indirectly, influences the activity of target cells with this mechanism of endocrine disease and results in important functional disturbances (Figure 45). It is well recognized that the daily administration of potent preparations of adrenal cortical steroids at inappropriately high daily doses for prolonged intervals in the symptomatic treatment of various diseases can produce most of the functional disturbances associated with an endogenous hypersecretion of cortisol. Similarly, the administration of excessively large doses of insulin can result in hypoglycemia, and an excess $T_4/T_3$ may result in hyperthyroidism, especially in

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**Figure 45.** Examples (direct and indirect) of iatrogenic syndromes of hormone excess.

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**Figure 46.** Elevation of circulating concentrations of growth hormone (GH), insulin-like growth factor (IGF), and insulin by the administration of synthetic progestins to dogs. Data from Selman et al (103).

**Figure 47.** Failure of hypophysectomy to decrease circulating growth hormone (GH) levels in progestin-treated dogs. From Selman et al (103).

**Figure 48.** Rapid reduction in plasma growth hormone (GH) levels in progestin-administered dogs following mammary resection. From Selman et al (103).


10. Capen CC (1997). Mechanistic data and risk assessment of several species (eg, cats) that have limited capacity to conjugate T4 with glucuronic acid and enhance bile excretion.

Indirect Effects

The administration of progestins to dogs indirectly results in a syndrome of growth hormone excess. The injection of medroxyprogesterone acetate for the prevention of estrus in dogs appears to stimulate expression of the growth hormone gene in the mammary gland, leading to an elevation in circulating growth hormone levels, and results in the classic clinical manifestations and lesions of acromegaly (eg, excessive skin folds, respiratory stridor due to increased soft tissue in oropharyngeal region, expansion of interdental spaces, and hyperglycemia).

It was assumed initially that the reversibly elevated circulating levels of growth hormone (GH) in response to the administration of synthetic progestins in dogs was from stimulation of somatotrophs in the pituitary gland (91); however, somatotroph hyperplasia and adenomas have not been found in the adenohypophysis of progestin-treated dogs. The elevated GH levels were associated with progressively increasing circulating concentrations of insulin-like growth factor-1 (IGF-1) and insulin (Figure 46) (68). The progestin-induced excessive GH secretion in dogs was characterized by a disappearance of the pulsatile secretion pattern and insensitivity to stimulation of GH secretion by both growth hormone-releasing hormone and clonidine as well as inhibition of GH release with a somatostatin analogue. Transphenoidal hypophysectomy 4–6 weeks after the last progestin injection in dogs with markedly elevated plasma GH concentrations did not change the circulating levels of GH (92, 103) (Figure 47). Subsequent removal of all mammary tissue in the progestin-treated dogs resulted in a rapid decline of plasma GH concentrations to values in the reference range (Figure 47). Measurement of GH immunoreactivity in tissue homogenates from progestin-administered dogs revealed that the highest GH content was present in normal and neoplastic mammary tissue (Figure 48). Immunohistochemical evaluation further confirmed the mammary gland as the source of the excessive GH production. In the dogs treated with progestins, GH immunoreactivity was present in the cytoplasm of both normal active ductal epithelial cells and benign neoplasms derived from mammary ductal epithelium (Figure 49). There was no GH immunoreactivity in the stroma or in mammary tissue from control dogs (103). Interestingly, progestins therapy has been used successfully to treat dogs with juvenile-onset panhypopituitarism and dwarfism due to a failure of development of the adenohypophysis and severe GH deficiency (54).

References


18. Capen CC (1997). Mechanistic data and risk assessment of several species (eg, cats) that have limited capacity to conjugate T4 with glucuronic acid and enhance bile excretion.

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