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Mechanisms that Lead to Disease of the Endocrine System in Animals*[1]

CHARLES C. CAPEN AND SHARRON L. MARTIN

The Ohio State University,
Departments of Veterinary Pathobiology and Veterinary Clinical Sciences,
Columbus, Ohio 43210-1093

ABSTRACT

Endocrine glands are collections of specialized cells that synthesize, store, and release their secretions directly into the blood stream. They are sensing and signalling devices located in the extracellular fluid compartment and are capable of responding to changes in the internal and external environments to coordinate a multiplicity of activities that maintain homeostasis. Diseases of the endocrine system are encountered in many animal species and present challenging diagnostic problems. The major pathogenic mechanisms responsible for disturbances in endocrine function include: 1) primary hyperfunction of an endocrine gland; 2) secondary hyperfunction; 3) primary hypofunction of an endocrine gland; 4) secondary hypofunction; 5) endocrine hyperactivity secondary to diseases of other organs; 6) hypersecretion by nonendocrine tumors of hormone-like substances; 7) failure of fetal endocrine function; 8) endocrine dysfunction due to failure of target cell response; 9) endocrine dysfunction resulting from abnormal degradation of hormone; and 10) iatrogenic syndromes of hormone-excess. For each major category, several specific disease problems have been selected to illustrate the morphologic and functional changes that characterize the response of a particular endocrine gland to disruption of function.

Keywords. Endocrine disease; hyperthyroidism; hyperparathyroidism; hyperadrenocorticism; pituitary dwarfism; congenital goiter; hypercalcemia of malignancy; fetal endocrine function

INTRODUCTION

The objective of this review will be to summarize our ideas on the major pathogenic mechanisms responsible for perturbations of endocrine function that result in important diseases in animals. For each major category, we have selected several specific disease problems to illustrate the morphologic and functional lesions that characterize the response of a particular endocrine gland to the disruption of function. Disorders of the endocrine system are encountered in a wide variety of animal species and often present challenging diagnostic problems.

Endocrine glands are collections of specialized cells that synthesize, store, and release their secretions directly into the bloodstream. They are interposed in the extracellular fluid compartment as sensing and signalling devices, capable of responding to changes both in the internal and external environment, in order to coordinate a multiplicity of activities concerned with the maintenance of homeostasis (Fig. 1).

The secretory products of endocrine glands are hormones that are released into the blood stream. These chemical substances either peptides, steroids, or iodothyronines are transported by the blood to influence the functional activity of target cells elsewhere in the body. Other populations of cells are concerned with degradation of hormone, after it has exerted its physiologic function. This is accomplished either by peptidases on the cell surface, the uptake and degradation by lysosomal enzymes, or conjugation with glucuronide or sulfate and excretion in the bile or urine (Fig. 1).

Endocrine glands are small compared with other body organs, widely distributed in the body, and connected with one another by the bloodstream. They are richly supplied with blood and there is a close anatomic relationship between endocrine cells

*Address correspondence to: Charles C. Capen, D.V.M., Ph.D., Department of Veterinary Pathobiology, The Ohio State University, Columbus, Ohio 43210-1093.

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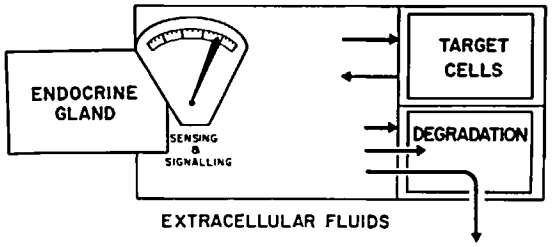

FIG. 1.—Schematic representation of the endocrine system. Endocrine glands are sensing and signalling devices that detect changes in concentrations of constituents of the extracellular fluid compartment. Hormones interact with specific target cells in the body to elicit a biologic response. They are degraded by cell surface enzymes, lysosomal enzymes within cells, or they are conjugated with glucuronic acid and sulfate for excretion in the urine or bile. Reprint with permission from Roth J: In: *Membrane Receptors for Viruses, Antigens and Antibodies, Polypeptide Hormones, and Small Molecules,* 1976.

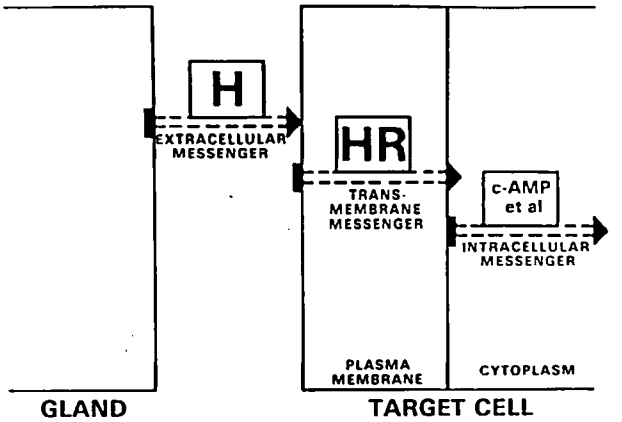

FIG. 2.—Mechanism of action of polypeptide hormones. A series of messengers are required for the initiation of hormone's action. The first message is a classical chemical messenger or hormone (H). The complex of hormone with receptor (HR) forms the transmembrane messenger that carries the signal from the outer surface to the inner surface of the plasma membrane. At the inner surface, cAMP and other intercellular messengers initiate the series of chemical reactions that result in the physiologic response to a particular hormone. Reprint with permission from Roth J: In: *Membrane Receptors for Viruses, Antigens and Antibodies, Polypeptide Hormones, and Small Molecules,* 1976.

and the capillary network. To facilitate rapid transport of raw materials and secretory products between the bloodstream and endocrine cells, the peripheral cytoplasmic extensions of capillary endothelial cells have fenestrae covered by a single membrane.

Polypeptide Hormones

The primary site of action for polypeptide hormones is the plasma membrane of target cells. Receptor proteins for the hormone are present on the outer surface of the plasma membrane. These hormones are water soluble, have a short half-life in blood (usually measured in minutes), and lack specific plasma-binding proteins.

The receptors for polypeptide hormones in the plasma membrane of target cells perform 2 key functions. First, they recognize the active hormone from among other proteins to which the cell is exposed. The concentration of hormone in extracellular fluids often is much lower (10^{-10} molar) than that of other proteins (10^{-3} to 10^{-4} molar). The hormone binds to the receptor site and forms a reversible hormone-receptor complex (Fig. 2). Second, the receptor conveys the message of the hormone bound to the plasma membrane from the outside to the inside of the target cell. The magnitude of this transmembrane signal depends on the concentration of hormone to which the target cell is exposed, the affinity of the receptor for the hormone, and the concentration of receptors on the target cell (Fig. 2).

There appears to be a single common intracellular pathway for many different polypeptide hormones. It begins with the activation of adenylate cyclase in the plasma membrane of target cells with cyclic adenosine monophosphate (cAMP) being formed intracellularly from adenosine triphosphate (ATP) that activates cAMP-dependent protein kinases (Fig. 2). These protein kinases activate or inactivate a variety of enzymes by phosphorylating them using ATP as a source of phosphate. The intracellular pathway for each polypeptide hormone subsequently branches into a multiplicity of different pathways leading to a variety of effects on any given target cell.

Cells that produce polypeptide hormones have a well-developed endoplasmic reticulum, many attached ribosomes where the hormone is assembled, and a prominent Golgi apparatus for packaging hormone into granules for intracellular storage and transport. Secretory granules are unique to polypeptide hormones- and catecholamine-secreting endocrine cells and provide a mechanism for intracellular storage of substantial amounts of preformed active hormone. These membrane-limited granules are macromolecular aggregations of active hormone, often associated with a specific binding protein. When the endocrine cell receives a signal for hormone secretion, secretory granules are directed to the periphery of the endocrine cell, probably by the contraction of microfilaments. The limiting membrane of the granule fuses with the plasma membrane of the cell and the hormone-containing core is extruded into the extracellular perivascular space by emiocytosis. Subsequently, the granule

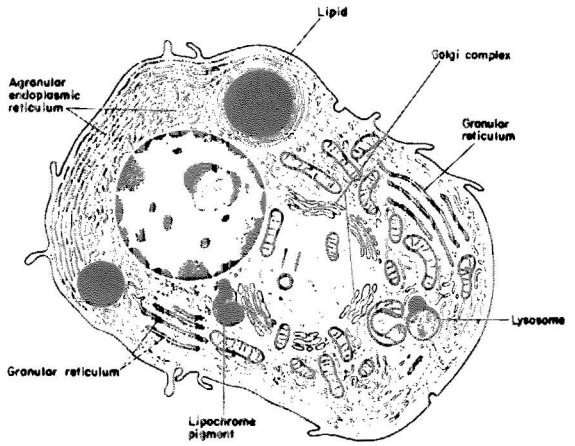

FIG. 3.—The structure of an endocrine cell that secretes steroid hormone is characterized by the presence of a prominent agranular endoplasmic reticulum, numerous mitochondria, large aggregations of lipid, and a prominent Golgi apparatus.

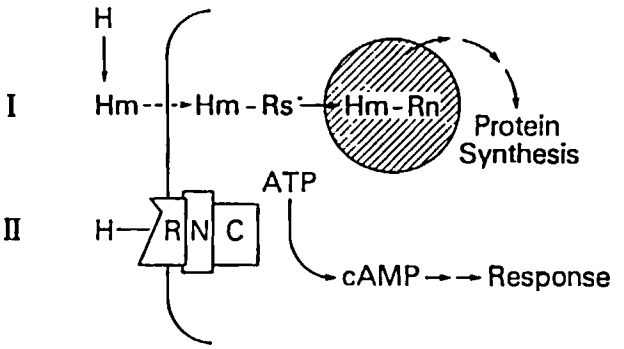

FIG. 4.—General mechanisms of hormone action. Type I mechanism: The hormone or its metabolite enters the cell, to interact with a cytoplasmic receptor for the hormone. The hormone–cytoplasmic-receptor complex (H_m-R_c) is then transported to the nucleus where the complex activates protein synthesis. Hormones that act through type II mechanism interact with a receptor that is an integral component of the cell membrane facing the exterior. Interaction of the hormone with receptor (R) is coupled to C (catalytic unit of adenylate cyclase) through a coupling factor known as N or G protein. The overall effect of hormone-receptor interaction is activation of adenylate cyclase (C) with consequent generation of cyclic AMP from the enzyme substrate ATP. Reprint with permission from Aurbach GD: In: *Animal Models of Inherited Metabolic Diseases,* 1982.

core is fragmented and hormone is rapidly transported through capillary fenestrae into the circulation. Hormone synthesized in excess of the body's requirement is degraded by fusion of the hormone-containing granules with lysosomes, a process termed crinophagy.

Steroid Hormones

Steroid hormone-secreting cells are characterized by large lipid bodies in the cytoplasm that contain cholesterol and other precursor molecules (Fig. 3). The lipid bodies are in close proximity to an extensive tubular network of smooth endoplasmic reticulum and large mitochondria which contain the hydroxylase and dehydrogenase enzyme systems. These enzyme systems function to attach various side chains to the basic steroid nucleus. Steroid-producing cells lack secretory granules and do not store significant amounts of preformed hormone. They are dependent on continued biosynthesis to maintain the normal secretory rate for a particular hormone.

Steroid hormones having a basic nucleus of 3 cyclohexane rings and 1 pentane ring account for approximately 15% of mammalian hormones. The primary site of their action is the nucleus of target cells (Fig. 4). The steroid hormones are lipid-soluble, which facilitates their transport through the cell membrane. They have a long half-life in blood (typically measured in hours) and reversibly bind to high-affinity, specific binding proteins in plasma. After steroids are within target cells and bound to receptors, the hormone-receptor complex is translocated to the nucleus where it binds to receptors in the nuclear chromatin (Fig. 4). The interaction of steroid hormones with the genetic information results in increased transcription of mRNA, which directs new protein synthesis by specific target cells (18).

Catecholamine and Iodothyronine Hormones

This chemical group of hormones are tyrosine derivatives. They account for approximately 5% of mammalian hormones and include the catecholamines (epinephrine, norepinephrine) secreted by

TABLE I.—Examples of primary hyperfunction of endocrine glands in animals.

Example	Hormone secreted in excess	Principal lesion or functional disturbance
Chief cell adenoma or carcinoma	Parathyroid hormone	Generalized osteitis fibrosa
Thyroid C-cell adenoma or carcinoma	Calcitonin	Osteosclerosis
Beta cell adenoma or carcinoma	Insulin	Hypoglycemia
Sertoli cell tumor	Estrogens	Feminization of male
Pheochromocytoma	Norepinephrine, epinephrine	Hypertension, hyperglycemia
Thyroid follicular cell adenoma or carcinoma	Thyroxine, triiodothyronine	Increased metabolic rate, weight loss
Pituitary acidophil adenoma	Somatotropin	Acromegaly

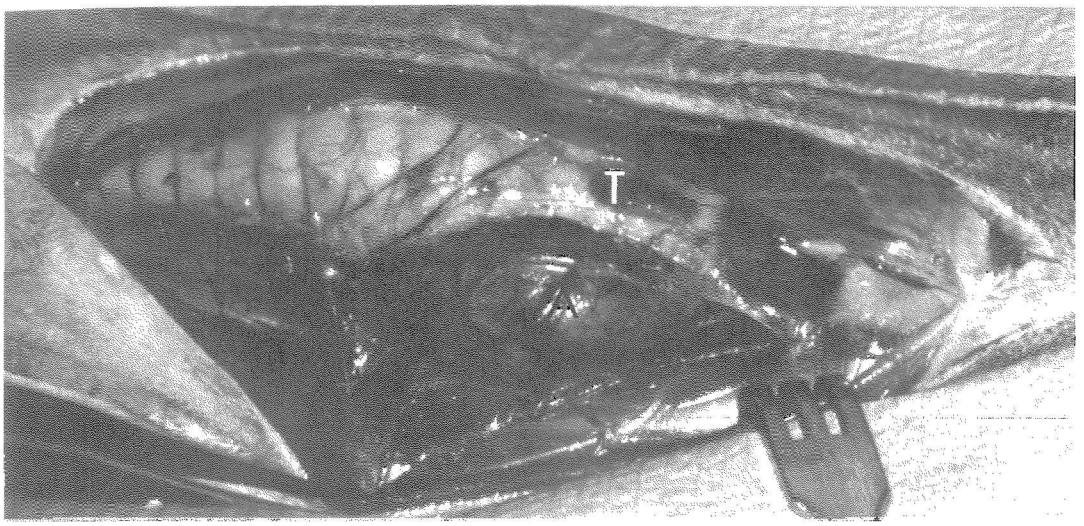

FIG. 5.—Primary hyperfunction of an endocrine gland. Functional adenoma derived from thyroid follicular cells in a cat. Dissection of the ventral cervical region reveals a large unilateral thyroid adenoma (A) and a small opposite thyroid (T).

the adrenal medulla and iodothyronines (thyroxine, triiodothyronine) produced by follicular cells of the thyroid gland. Catecholamines share similar mechanisms of action with polypeptide hormones, whereas iodothyronines more closely resemble the characteristics of steroid hormones.

MECHANISMS OF ENDOCRINE DISEASE

Primary Hyperfunction

One of the most important mechanisms of endocrine disease is primary hyperfunction of an endocrine gland. A lesion (most often a neoplasm derived from endocrine cells) synthesizes and secretes 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 examples occur in different animal species (Table I). These include hyperfunction of parathyroid chief cells (12), thyroid C-cells (9), beta cells of the pancreatic islets (11), secretory cells of the adrenal medulla (70), and follicular cells of the thyroid (38, 55) amongst others.

FIG. 6.—Primary hyperfunction of an endocrine gland. Hyperthyroidism in a cat with a functional adenoma derived from follicular cells. The cat lost considerable body weight in spite of a ravenous appetite due to the gluconeogenic effects of the elevated blood thyroid hormone levels.

The autonomous secretion of parathyroid hormone results in progressive and generalized demineralization of the skeleton, leading to hypercalcemia that predisposes to soft tissue mineralization and the development of renal calculi. The accelerated osteoclastic resorption of bone results in marked thinning and osteoclastic tunneling of cortical bone. Numerous large multinucleated osteoclasts are present intimately associated with bone surfaces.

Another important example is the autonomous hypersecretion of thyroxine and triiodothyronine that is being recognized with increasing frequency in cats associated with a spectrum of proliferative lesions of thyroid follicular cells. Many of the functional thyroid lesions are adenomas derived from follicular cells (Fig. 5) that develop in a thyroid gland with a background of multifocal nodular hyperplasia. Functional thyroid lesions in cats should be considered potentially malignant since a low percentage are adenocarcinomas that metastasize to regional lymph nodes. The functional disturbances of hyperactivity, weight loss despite increased appetite (Fig. 6), hyperthermia, and tachycardia reflect a long-term stimulation of multiple populations of target cells by the autonomous secretion of thyroid hor-

TABLE II.—cAMP (pmole/well) in FRTL-5 cells after incubation with serum IgG from hyperthyroid and normal cats (mean ± SD).

Assay	Normal cats	Hyperthyroid cats	Normal cats and forskolin (2 μM)	Hyperthyroid cats and forskolin (2 μM)
A	1.92 ± 0.1 (9)	1.88 ± 0.1 (8)	2.25 ± 0.2 (9)	2.50 ± 0.2 (8)
B	2.85 ± 0.5 (4)	2.88 ± 0.4 (5)	18.23 ± 3.9 (3)	20.56 ± 6.7 (3)
C	1.05 ± 0.3 (6)	1.41 ± 0.3 (9)	14.00 ± 7.2 (6)	12.53 ± 5.9 (9)

( ) = No. of cats, from: Peterson et al (52).

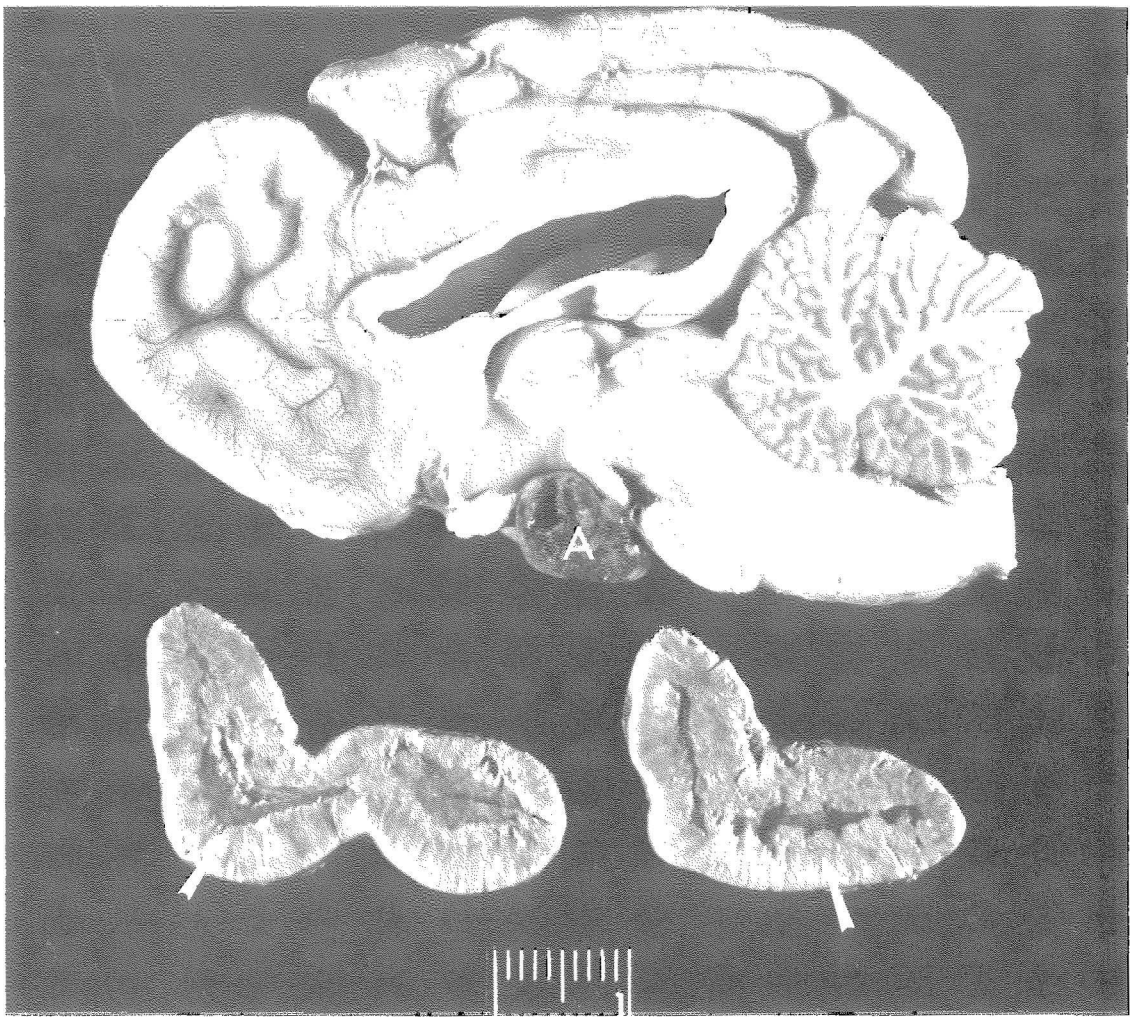

FIG. 7.—Secondary hyperfunction of an endocrine gland. Corticotrophic (ACTH-secreting) adenoma (A) in the pituitary gland resulting in bilateral hyperplasia of the adrenal cortices (arrows). This is the most common pathogenic mechanism for the syndrome of cortisol-excess in dogs. The scale represents 1 cm.

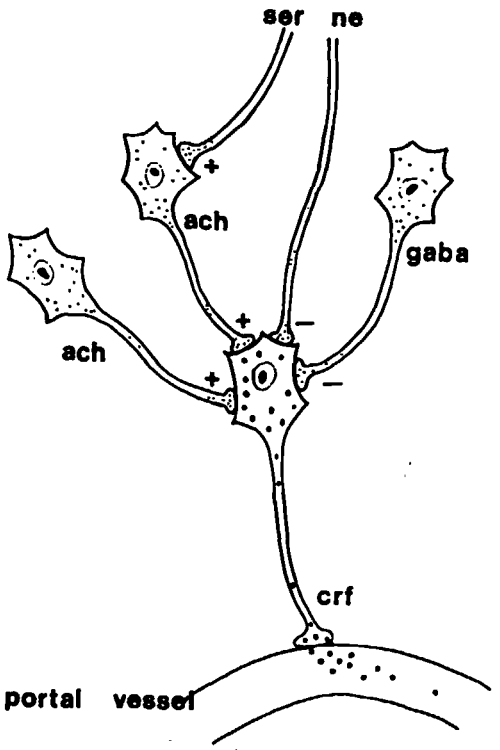

FIG. 8.—Secondary hyperfunction of an endocrine gland. The abnormal accumulation of neurotransmitter substance (e.g., serotonin) near hypothalamic neurons that synthesize and secrete corticotrophic hormone-releasing factor (CRF) may be responsible for the abnormal secretion of ACTH. The increased secretion of ACTH leads to a syndrome of cortisol-excess in certain breeds of dogs (e.g., poodles) that do not have a neoplastic proliferation of corticotrophs in the adenohypophysis. From Meijer (Thesis) (43).

mones. Circulating thyroid stimulating immunoglobulin levels are similar in hyperthyroid and normal cats (Table II), and follicles in the thyroid surrounding the adenoma undergo colloid involution with little evidence of endocytotic activity. The adenomatous tissue is transplantable into nude mice where it continues to secrete thyroid hormone at an uncontrolled rate (51, 52).

Secondary Hyperfunction

In secondary hyperfunction of an endocrine gland, a lesion in one organ secretes an excess of a trophic hormone that leads to long-term stimulation and hypersecretion of a target organ (e.g., adrenal cortex). The classic example of this pathogenic mechanism in animals is the ACTH-secreting tumor derived from pituitary corticotrophs in dogs (Fig. 7) (8, 10, 17). The functional disturbances and lesions primarily are the result of the elevated blood cortisol levels resulting from the ACTH-stimulated hypertrophy and hyperplasia of the zonae fasciculata and reticularis of the adrenal cortex. In some dogs (particularly poodles) with a similar marked adrenal cortical enlargement and functional disturbances of cortisol-excess, there is no gross or histopathologic evidence of a neoplasm in the pituitary gland. These animals appear to have a change in the "set point" to the negative feedback signal, possibly due to an abnormal accumulation of certain neurotransmitter substances, such as serotonin, near neurones in the hypothalamus that secrete corticotrophin-releasing hormone (Fig. 8) (44). The end result is severe corticotroph hyperplasia, elevated ACTH levels in the blood, and long-term stimulation of the adrenal cortex (Fig. 9) resulting in a syndrome of cortisol-excess.

Primary Hypofunction

The third pathogenic mechanism is primary hypofunction of an endocrine gland. Hormone secretion is subnormal either due to extensive destruction of secretory cells by a disease process, the failure of an endocrine gland to develop properly, or the result of a specific biochemical defect in the synthetic pathway of a hormone. Immune-mediated injury appears to be an important mechanism resulting in hypofunction of endocrine glands in animals, including the parathyroid, adrenal cortex, and thyroid gland (28, 29, 41).

Thyroiditis caused by this mechanism is characterized by marked lympho-plasmacytic infiltration between follicular cells and within follicles as well as deposition of electron-dense immune complexes along basement membranes (Fig. 10) (30). The resulting progressive destruction of secretory parenchyma leads to subnormal secretion of thyroxine and triiodothyronine with the resulting functional disturbances of hypothyroidism.

A failure of development also results in primary hypofunction of an endocrine gland. The classic example of this mechanism in animals is the inability of oro-pharyngeal ectoderm to differentiate completely into trophic hormone-secreting cells of the adenohypophysis in dogs, resulting in pituitary dwarfism and a failure to attain somatic maturation (Fig. 11) (3, 14). The pituitary dwarf illustrated weighed between 8 and 9 pounds at 6 months of age while the normal littermate German shepherd weighed approximately 60 pounds. A large, multicompartmented cyst was present on the ventral aspect of the brain in the pituitary region that compressed and interfered with function of the normally developed neurohypophysis.

Another form of primary hypofunction that has been recognized recently is a failure of hormone synthesis due to a genetically determined defect in a biosynthetic pathway or to the lack of a specific

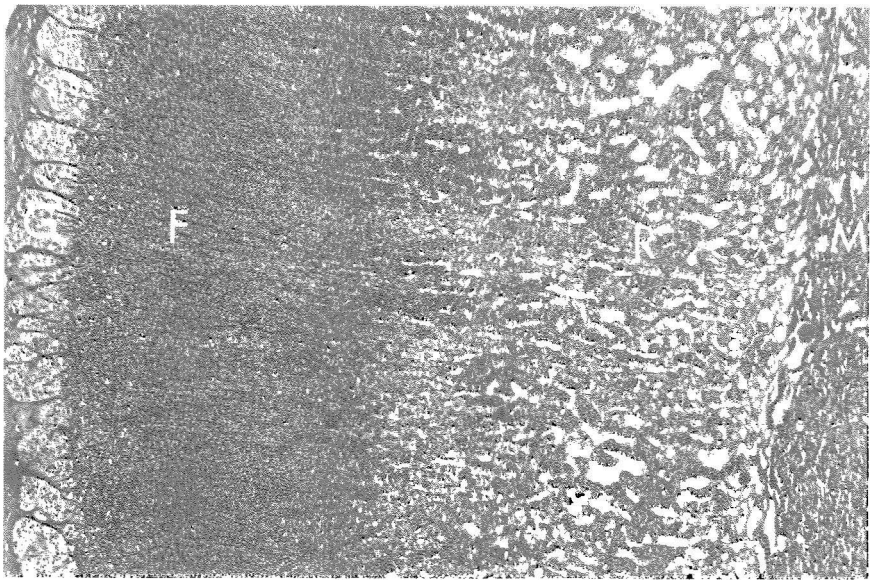

FIG. 9.—Secondary hyperfunction of an endocrine gland. Adrenocorticotropin-stimulated hyperplasia of the zonae fasciculata (F) and reticularis (R) in a dog with the syndrome of cortisol-excess. The outer zona glomerulosa (G) immediately beneath the adrenal capsule is compressed. M = cortico-medullary junction. ×50.

enzyme. The best documented examples in animals include congenital goiter and vitamin D-dependent rickets. In pigs and children with vitamin D-dependent rickets due to a lack of 1-alpha-hydroxylase in the proximal convoluted tubules of the kidney, there is an interference in the synthesis of the hormonal form of vitamin D (32, 68). The low ion product of calcium and phosphorus results in a failure of mineralization of osteoid and overgrowth of cartilage in the physis, leading to severe deformities in the axial and abaxial skeleton (69).

Congenital dyshormonogenetic goiter in sheep,

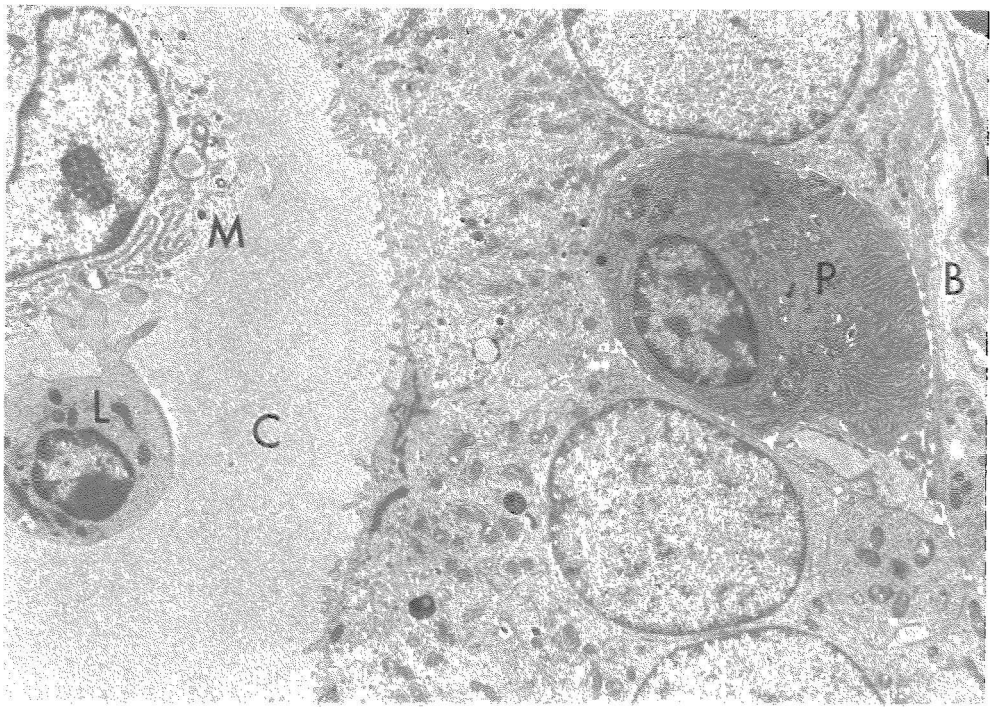

FIG. 10.—Primary hypofunction of an endocrine gland. Lymphocytic thyroiditis in a dog with clinical hypothyroidism with a lymphocyte (L) and macrophage (M) in the colloid (C)-filled lumen of a thyroid follicle. A plasma cell (P) has migrated through the follicular basement membrane (B) and between adjacent thyroid follicular cells (×5,600). Reprint with permission from Gosselin SJ et al: *Vet. Pathol.* 18: 299–309, 1981.

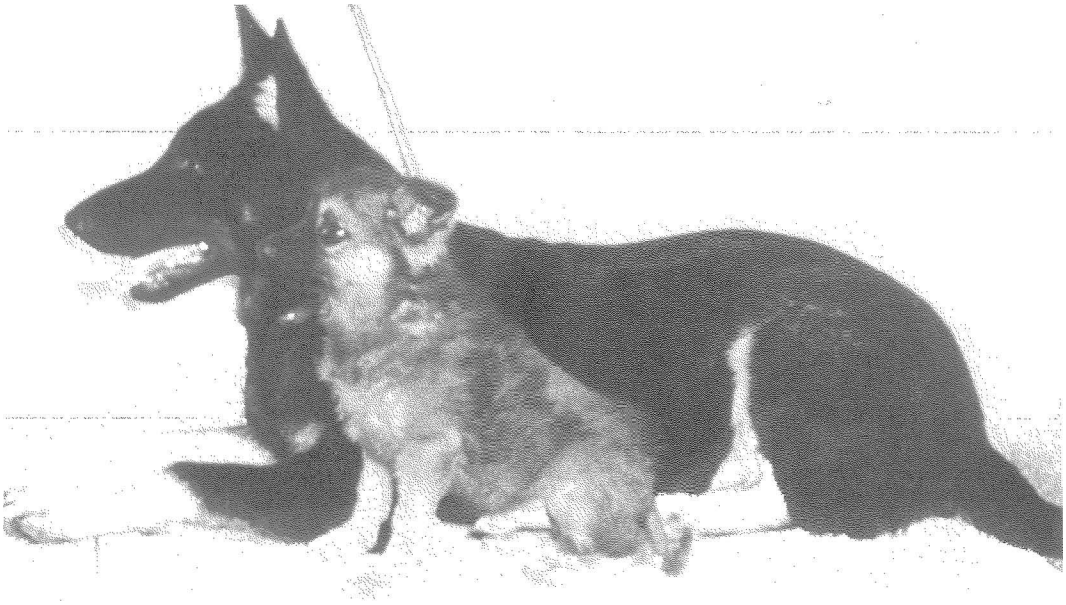

FIG. 11.—Primary hypofunction of an endocrine gland resulting from failure of development of the adenohypophysis. Panhypopituitarism ("pituitary dwarfism") in a 5-month-old German shepherd. The unaffected littermate weighs 27.3 kg and the dwarf puppy weighs only 4 kg. The pituitary dwarf has retained the puppy hair-coat. Reprint with permission from Alexander JE: *Can. Vet. J.* 3: 83, 1962.

goats, and cattle is another example of primary hypofunction due to a failure of hormone synthesis. The low blood thyroxine and triiodothyronine levels with clinical evidence of severe hypothyroidism in these animals, are due to an inability of follicular cells to synthesize thyroglobulin (21, 26, 49, 54, 56, 66). The molecular defect has been shown to be a defective processing of primary transcripts for thyroglobulin mRNA and aberrant transport from the nucleus to ribosomes. This results in subnormal amounts (i.e., 1–2%) of thyroglobulin mRNA in follicular cells, particularly mRNA attached to membranes of the endoplasmic reticulum in the cytoplasm (65, 67). Follicular cells in animals with congenital goiter often have numerous distended profiles of rough endoplasmic reticulum. However, the lack of specific mRNA associated with ribosomes necessary for the synthesis of thyroglobulin results in few apical granules near the Golgi apparatus and in the luminal aspect of the follicular cells.

Thyroglobulin is one of the major components of colloid in the lumen of thyroid follicles (66). It is a high molecular weight glycoprotein that is synthesized on ribosomes of the rough endoplasmic reticulum in follicular cells. Thyroglobulin is packaged into apical granules that are secreted into the follicular lumen to serve as an extracellular matrix for the stepwise iodination of the tyrosyl residue incorporated into its structure, resulting in the formation of thyroxine and triiodothyronine (24, 25, 50). There is no defect in the ability of the thyroid glands of animals with congenital goiter to concentrate ^{131}iodine; however, there is a greatly reduced ability to iodinate tyrosyl residues and form thyroid hormones thereby resulting in low radio-labeled hormonal iodine levels (56). The subnormal blood levels of thyroxine and triiodothyronine are detected by the hypothalamus and adenohypophysis. This results in an increased secretion of pituitary thyrotropin (TSH) and intense hyperplasia of follicular cells, resulting in bilateral enlargement of the thyroid lobes.

Secondary Hypofunction

In secondary hypofunction of an endocrine gland, a destructive lesion in 1 organ (i.e., pituitary) interferes with the secretion of trophic hormones and results in subnormal function of the target endocrine glands (8). Large, endocrinologically inactive, pituitary neoplasms may interfere with the secretion of multiple pituitary trophic hormones and result in clinically detectable hypofunction of the adrenal cortex, follicular cells of the thyroid, and gonads. The adrenal cortex of an animal with a large pituitary neoplasm of this type often has marked atrophy and degeneration of the ACTH-dependent inner 2 zones but the aldosterone-secreting outer zona multiformis remains intact since it is not under direct ACTH control (Fig. 12). Thyroid function may be subnormal due to a lack of thyrotropin (TSH) resulting in trophic atrophy of follicular cells but the calcitonin-secreting C-cells remain intact and con-

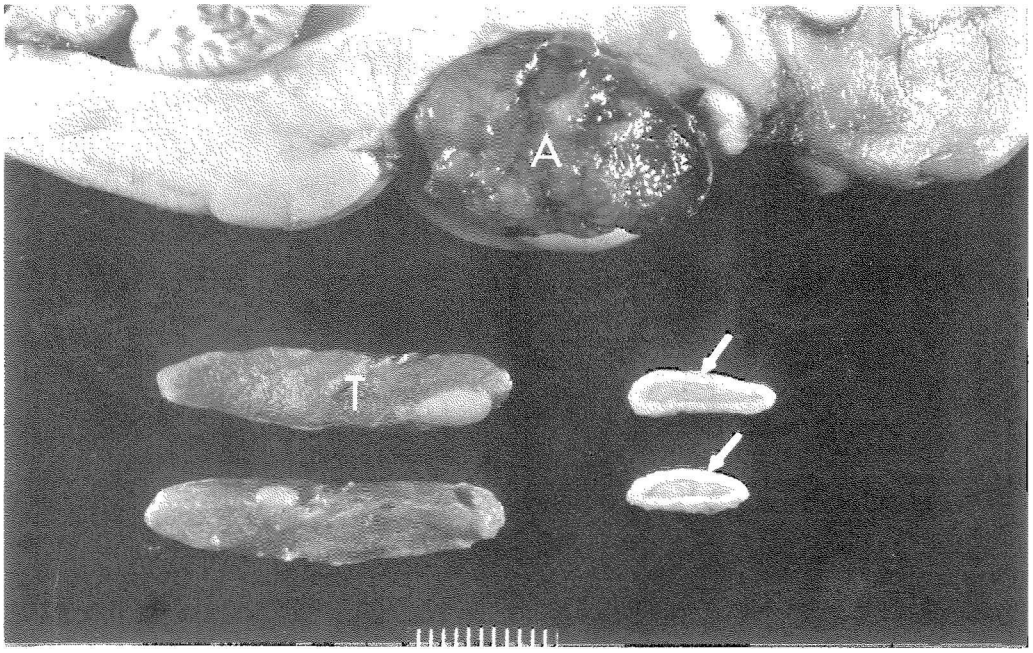

FIG. 12.—Secondary hypofunction of endocrine gland. A large nonfunctional chromophobe adenoma (A) has completely incorporated and destroyed the adenohypophysis and hypothalamus, thereby interrupting the secretion of TSH, ACTH, and other trophic hormones. There is severe trophic atrophy of the adrenal cortex (white arrows), especially the ACTH-dependent zonae fasciculata and reticularis. Although follicular cells were atrophic, thyroid follicles had increased amounts of colloid resulting in an overall near normal gland size. The scale represents 1 cm.

tinue to function normally since they are not under the control of the pituitary. The disruption in growth hormone secretion has little effect on body stature because lesions of this type usually develop in adult to aged animals (13).

Endocrine Hyperactivity Secondary to Diseases of Other Organs

The best known example of endocrine hyperactivity secondary to diseases of other organs in animals is the hyperparathyroidism that develops secondary to either chronic renal failure or nutritional imbalances (12). 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 1-alpha-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 factors, including the serum phosphorus and other hormones (13). The impaired intestinal absorption of calcium results in the development of progressive hypocalcemia that lead to long-term parathyroid stimulation and development of generalized demineralization of the skeleton. Many bones but particularly the cancellous bone of the skull are weakened and more susceptible to fractures.

Nutritional hyperparathyroidism develops in animals fed abnormal diets that are low in calcium (2, 16, 64), high in phosphorus (35, 37), or deficient in cholecalciferol (for certain nonhuman primates) (34). Unsupplemented all-meat diets fed to carnivores fail to supply the daily requirements for calcium. This leads to progressive hypocalcemia that stimulates the parathyroid gland to increased activity (17). The normal kidneys in these animals respond to the increased parathyroid hormone secretion by increasing phosphorus excretion and lowering blood phosphorus levels. After carnivores are fed an imbalanced diet for several months, the skeleton becomes severely demineralized and predisposed to the development of fractures. The cortices of long bones are thin and the medullary cavity is widened due to intense osteoclastic resorption of bone stimulated by the increased secretion of parathyroid hormone (64).

Hypersecretion of Humoral ("Hormone-like") Factors by Non-Endocrine Tumors

It has been appreciated in recent years that certain neoplasms of non-endocrine tissues in both animals and man secrete "humoral substances" that are similar chemically and/or biologically to the "native" hormone secreted by an endocrine gland. Most of the humoral substances secreted by non-endocrine tumors are peptides, rather than steroids or iodothyronines, which require more complex biosyn-

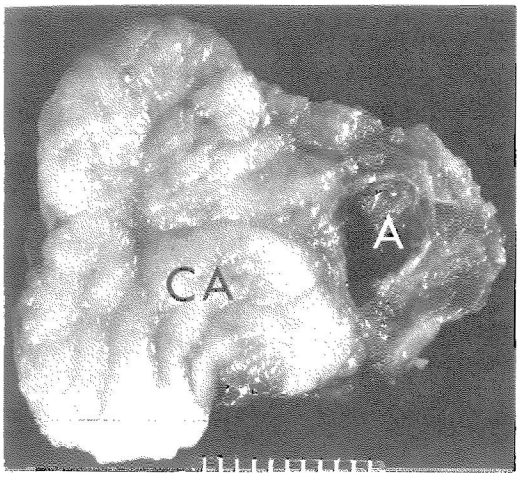

FIG. 13.—Adenocarcinoma (CA) arising from apocrine glands in the wall of the anal sac (A) from a dog with persistent hypercalcemia. Neoplastic cells invade locally and often metastasize to regional lymph nodes. The scale represents 1 cm.

thetic pathways. Hypercalcemia of malignancy ("pseudohyperthyroidism") is the autonomous hypersecretion of parathyroid hormone-related protein and other humoral factors by cancer cells that interact with the parathyroid hormone receptor in target cells (e.g., bone, kidney, and intestine) and result in persistent hypercalcemia.

One of the best characterized examples of this disease mechanism in animals is the adenocarcinoma derived from apocrine glands of the anal sac that occurs predominately in elderly female dogs (45, 57). The primary tumor often is small, arises in the wall of the anal sac, and either projects into its lumen or extends into adjacent tissues (Fig. 13). Histopathologically, the carcinoma is bimorphic with solid areas interspersed with distinct glandular acini lined by pseudostratified epithelial cells that have distinctive apical cytoplasmic projections extending into the lumen (45). Small electron-dense, membrane-bound secretory granules are present occasionally in the cytoplasm of tumor cells; however, it is uncertain whether they contain the hypercalcemia producing factor (46). These tumor cells produce a parathyroid hormone-related protein that results in an accelerated mobilization of calcium from bone by osteoclasts and leads to the development of persistent hypercalcemia. Both the total resorptive surface and numbers of osteoclasts per mm bone surface are increased in dogs with this tumor when compared to normocalcemic controls (47). The parathyroid glands are all smaller than normal and the chief cells become atrophic in response to the long-term hypercalcemia (45). Serum immunoreactive parathyroid hormone (iPTH) levels are lower in dogs with apocrine carcinomas than control dogs either with and without other tumors, and iPTH levels are undetectable in tumor tissue (47).

Recent evidence suggests that solid tumors, such as the canine apocrine adenocarcinoma, that do not metastasize to bone secrete a 16-kd parathyroid hormone-related protein. This peptide is able to use the PTH receptor in bone to increase resorption and in kidney to increase tubular reabsorption of calcium, decrease phosphorus reabsorption and stimulate the 1-alpha hydroxylase to synthesize the active form vitamin D (1,25-dihydroxycholecalciferol). The activation of renal 1-alpha-hydroxylase results in the maintenance of an inappropriately high serum 1,25-dihydroxy vitamin D level for the degree of hypercalcemia (44, 59–61).

Endocrine Dysfunction Due to a Failure of Target Cell Response

This mechanism of endocrine disease has been appreciated coincident with a more complete understanding of how hormones interact with target cells to convey their biologic message. The hydrophobic steroid and iodothyronine hormones penetrate the cell membrane, bind to cytosolic receptors, and are transported to the nucleus where they interact with the genetic information in the target cell to increase new protein synthesis (Fig. 4). Polypeptide and catecholamine hormones bind to receptors on the surface of target cells and activate a membrane-bound enzyme that generates an intracellular messenger, cyclic AMP, that elicits the physiologic response of the target cells (Figs. 2, 4) (4).

A failure of target cells to respond to hormone may be due either to a lack of adenylate cyclase in the cell membrane or to an alteration in hormone receptors on the cell surface. Hormone is secreted in normal or increased amounts by cells of the endocrine gland in this mechanism of endocrine disease. Certain forms of insulin-resistance associated with obesity in both animals and humans result from a decrease or "down regulation" of receptors on the surface of target cells (19). This develops in response to the chronic increased insulin secretion stimulated by the hyperglycemia resulting from the excessive food intake. Secretory cells in the corresponding endocrine gland (i.e., pancreatic islets) undergo compensatory hypertrophy and hyperplasia in an attempt to secrete additional hormone. The normal pancreatic islets contain predominately granulated beta cells, whereas the beta cells in the enlarged islets from an obese diabetic animal are markedly hyperplastic and depleted of insulin-containing secretory granules.

An interesting form of hypoparathyroidism has been reported in human patients in which the inability of target cells to respond is due to the lack

of a specific nucleotide regulatory protein in the cell membrane that is necessary for generation of the intracellular message for the hormone (Fig. 4) (27). Patients with "pseudohypoparathyroidism" develop hypocalcemia and hyperphosphatemia in spite of hyperplastic parathyroids and elevated blood levels of immunoreactive PTH (15, 53, 63).

Failure of Fetal Endocrine Function

Endocrine dysfunction due to a failure of fetal endocrine function is the next mechanism of endocrine disease to be discussed in this review. Subnormal activity of the fetal endocrine system, especially in ruminants, may disrupt normal fetal development and result in prolongation of the gestation period. In Guernsey and Jersey cattle, there is a genetically determined failure of development of the adenohypophysis (36). This results in a lack of fetal pituitary trophic hormone secretion during the last trimester and hypoplastic development of target endocrine organs. Fetal development is normal up to approximately 7 months gestation, but then fetal growth ceases irrespective of how long the viable fetus is retained *in utero.* The body size is small and there is subnormal development of hair in the retained fetus. The adenohypophysis fails to develop completely but the neurohypophysis is normally developed since it is derived from separate embryologic primordia.

Prolongation of the gestation period in sheep results following maternal ingestion of a plant early in gestation that results in extensive CNS-hypothalamic malformations in the lamb (48). Although the adenohypophysis is present, it lacks the necessary fine control from releasing hormones of the hypothalamus to result in normal secretion of trophic hormones (especially ACTH). Target endocrine organs in the fetus, particularly the adrenal cortex, are hypoplastic and fail to differentiate completely into the 3 distinctive steroid hormone-secreting zones. *Veratrum californicum* contains a potent steroidal alkaloid that inhibits neural tube development when ingested by the ewe between the 9th and 14th day of gestation. The lambs develop extensive CNS malformations including arrhinencephaly with lack of development of nasal bones and formation of a proboscis-like structure and cyclopia (5–7). Lambs retained *in utero* beyond the normal gestational interval continue to grow as evidenced by a larger body size and greater development of the wool and hooves compared to normal lambs at term.

The concepts that have emerged from the study of these 2 valuable experiments of nature are: first, fetal hormones are necessary for final growth and development *in utero* in certain animals; and second, normal parturition at term in these species

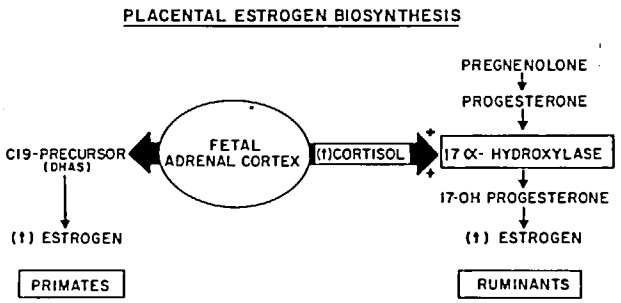

FIG. 14.—Failure of fetal endocrine function leads to prolongation of the gestation period in ruminants. Hypoplasia of the fetal adrenal cortex and subnormal secretion of cortisol result in a lack of induction of placental 17-α-hydroxylase. This enzyme is necessary for the conversion of precursors (i.e., progesterone) to estrogens near the normal termination of the gestation period. An increased maternal estrogen level normally results in the synthesis of prostaglandins in the uterus that leads to muscular contractions and the biochemical changes in collagen along the birth canal that permits delivery of the fetus.

requires an intact fetal hypothalamic-adenohypophyseal-adrenocortical axis working in concert with trophoblasts of the placenta (22, 39, 40). 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 2 examples. The subnormal development of the fetal adrenal cortex in the calves and lambs results in an inadequate secretion of cortisol and a failure of induction of the 17-alpha-hydroxylase in the placenta that converts precursor molecules, such as progesterone, to estrogens (Fig. 14). This results in maintenance of circulating progesterone near midgestational levels in the dam and a lack of the marked increase in estrogens that normally occurs at term and results in parturition. The estrogen surge stimulates the synthesis of prostaglandins in the uterus. The local accumulation of prostaglandins results in the smooth muscle contractions and biochemical changes in collagen along the birth canal that normally permits delivery of the fetus.

Endocrine Dysfunction Resulting from Abnormal Degradation of Hormone

Secretion of hormone by an endocrine gland is normal with this mechanism but blood levels are persistently elevated, thereby simulating a state of hypersecretion due to the decreased rate of degradation. A classic example of this pathogenic mechanism is the syndrome of feminization due to hyperestrogenism associated with cirrhosis and decreased hepatic degradation of estrogens in men. In laboratory rodents, the long-term administration

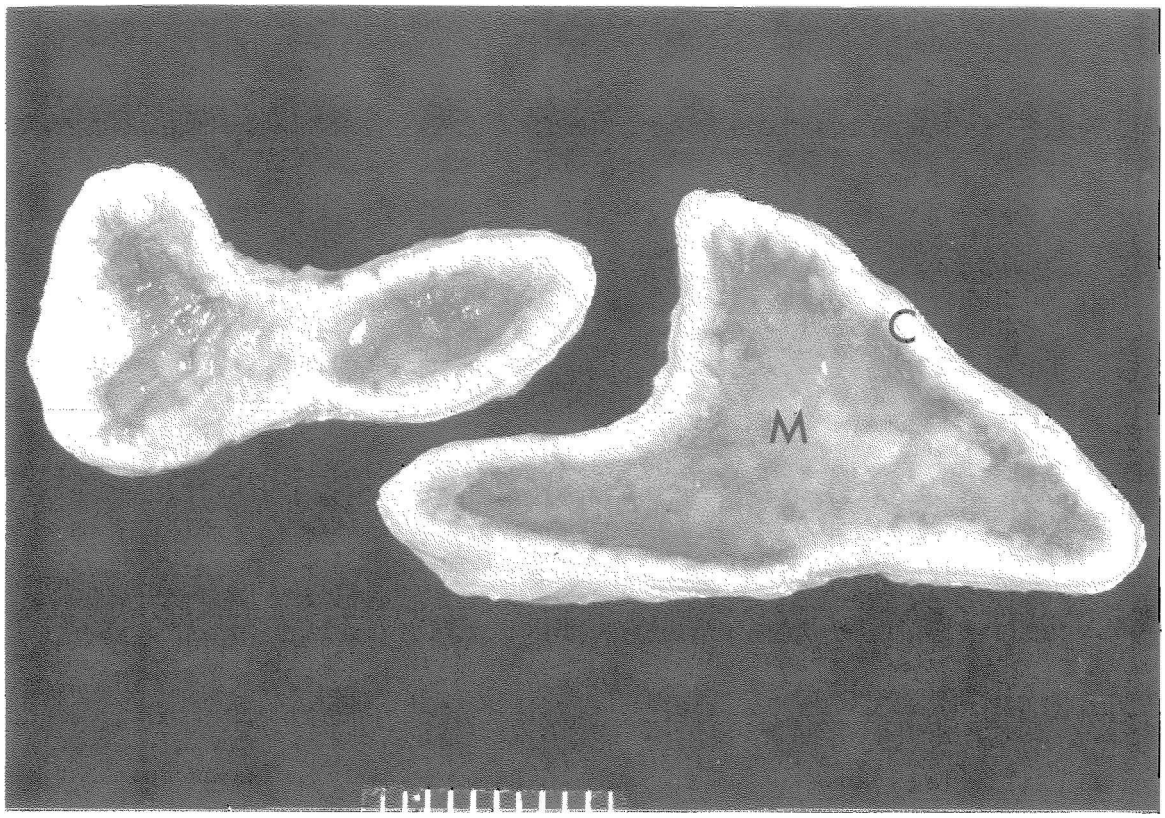

FIG. 15.—Iatrogenic syndrome of hormone excess. Hyperadrenocorticism resulting from long-term administration of exogenous corticosteroids in dogs results in marked trophic atrophy of the ACTH-dependent zonae fasciculata and reticularis of the adrenal cortex (C). The adrenal medulla (M) occupies a relatively greater percentage of the atrophic adrenal gland. The scale represents 1 cm.

FIG. 16.—Iatrogenic acromegaly in a beagle (center) compared with unaffected littermates (left and right). The coarseness of facial features with marked thickening and folding of the skin of the face are the result of the protein anabolic effects of somatotropin stimulated by the exogenous administration of medroxyprogesterone acetate. Courtesy of Dr. P. Concannon, Department of Physical Biology, New York State College of Veterinary Medicine, Cornell University.

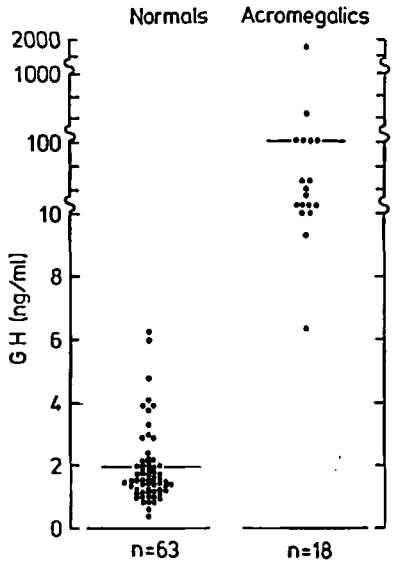

FIG. 17.—Iatrogenic syndrome of hormone excess. Immunoreactive growth hormone levels in normal and acromegalic dogs. Horizontal lines indicate the mean for each group. Reprint with permission from Eigenmann JE: *Vet. Clin. North Am.* 14: 827–836, 1984.

of various xenobiotics (i.e., phenobarbital and others) results in the induction of liver enzymes that increase the degradation of thyroxine (42). This 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 long-term studies with certain drugs and chemicals (71).

Chronic renal disease in dogs may be associated either with subnormal, normal, or elevated blood concentrations of calcium. The phosphorus retention and low blood levels of the hormonal form of vitamin D initially result in hypocalcemia leading to secondary hyperparathyroidism. The hypercalcemia associated with certain forms of renal disease appears to be related, in part, to diminished degradation of PTH along with decreased urinary excretion of calcium by the diseased kidney. Parathyroid hormone is degraded either by peptidase on the surface of tubular cells or by lysosomal enzymes following uptake from the glomerular filtrate (33).

Iatrogenic Syndromes of Hormone Excess

The administration of hormone either directly or indirectly influences the activity of target cells and results in functional disturbances. It is well recognized that the administration of potent preparations of adrenal corticosteroids 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. This includes the muscle weakness, marked hair loss, and mineral deposition in the skin associated with cortisol-excess. The elevated blood levels of exogenous cortisol result in marked trophic atrophy of the animal's adrenal cortex, particularly the ACTH-dependent zonae fasciculata and reticularis (Fig. 15).

In addition, the administration of certain progestagens to dogs will indirectly result in a syndrome of growth hormone-excess. The injection of medroxyprogesterone acetate for the prevention of estrus in dogs stimulates an increased secretion of growth hormone by pituitary somatotrophs resulting in many of the clinical manifestations of acromegaly (20, 31, 58). The excessive skin folds (Fig. 16), expansion of interdigital space, increased soft tissue in oro-pharyngeal area, and abdominal enlargement in dogs with iatrogenic acromegaly are related to the protein anabolic effects of the significantly elevated growth hormone levels on connective tissues (Fig. 17) (23).

REFERENCES

1. Alexander JE (1962). Anomaly of craniopharyngeal duct and hypophysis. *Can. Vet. J.* 3: 83.
2. Anderson MP, Hunt RD, Griffiths HJ, McIntyre KW, and Zimmerman RE (1977). Long-term effect of low dietary calcium: Phosphate ratio on the skeleton of *Cebus albifrons* monkeys. *J. Nutr.* 107: 834–839.
3. Andresen E and Willeberg P (1976). Pituitary dwarfism in Carelian bear-dogs: Evidence of simple, autosomal recessive inheritance. *Hereditas* 84: 232–242.
4. Aurbach GD (1982). Inherited disorders of hormone resistance. In: *Animal Models of Inherited Metabolic Diseases,* R Desnick, D Patterson, and D Scarpelli (eds). Alan R. Liss, Inc., New York, pp. 353–368.
5. Binns W, Anderson WA, and Sullivan DJ (1960). Further observations on a congenital cyclopian-type malformation in lambs. *J. Am. Vet. Med. Assoc.* 137: 515–521.
6. Binns W, James LF, Keeler RF, and Balls, LD (1968). Effects of teratogenic agents in range plants. *Cancer Res.* 28: 2323–2326.
7. Binns W, James LF, Shupe JL, and Everett G (1963). A congenital cyclopian-type malformation in lambs induced by maternal ingestion of a range plant, *Veratrum californicum. Am. J. Vet. Res.* 24: 1164–1175.
8. Capen CC (1978). Tumors of the endocrine glands. In: *Tumors in Domestic Animals,* 2nd ed., JE Moulton (ed). University of California Press, Berkeley, CA, pp. 372–429.
9. Capen CC and Black HE (1974). Calcitonin-secreting ultimobranchial neoplasms of the thyroid gland in bulls: Animal model for medullary thyroid carcinoma in man (Sipple's syndrome). *Am. J. Pathol.* 74: 377–380.
10. Capen CC and Koestner A (1967). Functional chromophobe adenomas of the canine adenohypophysis:

An ultrastructural evaluation of a neoplasm of pituitary corticotrophs. *Vet. Pathol.* 4: 326–347.
11. Capen CC and Martin SL (1969). Hyperinsulinism in dogs with neoplasia of the pancreatic islets. A clinical, pathologic and ultrastructural study. *Vet. Pathol.* 6: 309–341.
12. Capen CC and Martin SL (1977). Calcium metabolism and disorders of parathyroid glands. *Vet. Clin. North Am.* 7: 513–548.
13. Capen CC and Martin SL (1982). Calcium regulating hormones and diseases of the parathyroid glands. In: *Textbook of Veterinary Internal Medicine,* 2nd ed., SJ Ettinger (ed). W. B. Saunders Co., Philadelphia, pp. 1550–1592.
14. Capen CC and Martin SL (1982). Diseases of the pituitary gland. In: *Textbook of Veterinary Internal Medicine,* SJ Ettinger (ed). W. B. Saunders Co., Philadelphia, pp. 1523–1549.
15. Capen CC and Roth SI (1973). Ultrastructural and functional relationships of normal and pathologic parathyroid cells. In: *Pathobiology Annual,* HL Ioachim (ed). Appleton-Century-Crofts, New York, pp. 267–320.
16. Capen CC and Rowland GN (1968). Ultrastructural evaluation of the parathyroid glands of young cats with experimental hyperparathyroidism. *Z. Zellforsch.* 90: 495–506.
17. Capen CC, Martin SL, and Koestner A (1967). Neoplasms in the adenohypophysis of dogs. *Vet. Pathol.* 4: 301–325.
18. Chan L and O'Malley BW (1976). Mechanism of action of the sex steroid hormones. *N. Engl. J. Med.* 294: 1322–1328.
19. Coleman DL (1979). Diabetes mellitus in rodents. In: *Spontaneous Animal Models of Human Disease,* Vol. I, EJ Andrews, BC Ward, and NH Altman (eds). Academic Press, New York, pp. 126–131.
20. Concannon P, Altszuler N, Hampshire J, Butler WR, and Hansel W (1980). Growth hormone, prolactin, and cortisol in dogs developing mammary nodules and an acromegaly-like appearance during treatment with medroxyprogesterone acetate. *Endocrinology* 106: 1173–1177.
21. de Vijlder JJM, van Voorthuizen WF, van Dijk JE, Rijnberk A, and Tegelaers WHH (1978). Hereditary congenital goiter with thyroglobulin deficiency in a breed of goats. *Endocrinology* 102: 1214–1222.
22. Drost M and Holm LW (1968). Prolonged gestation in ewes after foetal adrenalectomy. *J. Endocrinology* 40: 293–296.
23. Eigenman JE (1984). Acromegaly in the dog. *Vet. Clin. North Am.* 14: 827–836.
24. Ekholm R and Wollman S (1975). Site of iodination in the rat thyroid gland deduced from electron microscopic autoradiographs. *Endocrinology* 97: 1433–1444.
25. Ekholm R, Engstrom G, Erichson LE, and Melander A (1975). Exocytosis of protein into the thyroid follicle lumen: An early effect of TSH. *Endocrinology* 97: 337–346.
26. Falconer IR (1966). Studies of the congenitally goitrous sheep: The iodinated compounds of serum, and circulating thyroid-stimulating hormone. *Biochem. J.* 100: 190–196.
27. Farfel Z, Brickman AS, Kaslow HR, Brother VM, and Bourne HR (1980). Defect of receptor-cyclase coupling protein in pseudohypoparathyroidism. *N. Engl. J. Med.* 303: 237–242.
28. Gosselin SJ, Capen CC, and Martin SL (1981). Histopathologic and ultrastructural evaluation of thyroid lesions associated with hypothyroidism in dogs. *Vet. Pathol.* 18: 299–309.
29. Gosselin SJ, Capen CC, Martin SL, and Krakowka S (1982). Autoimmune lymphocytic thyroiditis in dogs. *Vet. Immunol. Immunopathol.* 3: 185–201.
30. Gosselin SJ, Martin SL, Capen CC, and Targowski SP (1980). Biochemical and immunological investigations of hypothyroidism in dogs. *Can. J. Comp. Med.* 44: 158–168.
31. Hansel W, Concannon PW, and McEntee K (1977). Plasma hormone profiles and pathological observations in medroxyprogesterone acetate-treated beagle bitches. In: *Pharmacology of Steroid Contraceptive Drugs,* S Garattini and HW Berendes (eds). Raven Press, New York.
32. Haussler MR, Drezner MK, Pike JW, Chandler JS, and Hagan LA (1979). Assay of 1,25-dihydroxyvitamin D and other vitamin D metabolites in serum: Application to animals and humans. In: *Vitamin D Basic Research and Its Clinical Application,* AW Norman et al (eds). Walter de Gruyter, Berlin, pp. 189–196.
33. Hruska KA, Martin K, Mennes P, Greenwalt A, Anderson C, Klahr S, and Slatopolsky E (1977). Degradation of parathyroid hormone and fragment production by the isolated perfused dog kidney. The effect of glomerular filtration rate and perfusate Ca^{++} concentration. *J. Clin. Invest.* 60: 501–510.
34. Hunt RD, Garcia FG, and Hegsted DM (1967). A comparison of vitamin D_2 and D_3 in new world primates. I. Production and regression of osteodystrophia fibrosa. *Lab. Anim. Care* 17: 222–234.
35. Joyce JR, Pierce KR, Romane WM, and Baker JM (1971). Clinical study of nutritional secondary hyperparathyroidism in horses. *J. Am. Vet. Med. Assoc.* 158: 2033–2042.
36. Kennedy PC, Kendrick JW, and Stormont C (1957). Adenohypophyseal aplasia, an inherited defect associated with abnormal gestation in Guernsey cattle. *Cornell Vet.* 47: 160–178.
37. Krook L and Lowe JE (1964). Nutritional secondary hyperparathyroidism in the horse. *Vet. Pathol.* 1(Suppl. 1): 1–98.
38. Leav I, Schiller AL, Rijnberk A, Legg MA, and der Kinderen PJ (1976). Adenomas and carcinomas of the canine and feline thyroid. *Am. J. Pathol.* 83: 61–122.
39. Liggens GC and Kennedy PC (1968). Effects of electrocoagulation of the fetal lamb hypophysis on growth and development. *J. Endocrinol.* 40: 371–381.
40. Liggens GC, Kennedy PC, and Holm LW (1967). Failure of initiation of parturition after electroco-

agulation of the pituitary of the fetal lamb. *Am. J. Obstet. Gynecol.* 98: 1080.
41. Lupulescu A, Potorac E, Pop A, Heitmanek C, Merculiev E, Chisiu N, Oprisan R, and Neacsu C (1968). Experimental investigations on immunology of the parathyroid gland. *Immunology* 14: 475–482.
42. McClain RM, Posch RC, Bosakowski T, and Armstrong JM (1988). Studies on the mode of action for thyroid gland tumor promotion in rats by phenobarbital. *Toxicol. Appl. Pharmacol.* 94: 254–265.
43. Meijer JC (1980). An investigation of the pathogenesis of pituitary-dependent hyperadrenocorticism in the dog. University of Utrecht, The Netherlands, Thesis.
44. Merryman JI, Rosol TJ, Brooks CL, and Capen CC (1989). Separation of parathyroid hormone-like activity from transforming growth factor (TGF)-α and -β in the canine adenocarcinoma (CAC-8) model of humoral hypercalcemia of malignancy. *Endocrinology* 124 (in press [May]).
45. Meuten DJ, Cooper BJ, Capen CC, Chew DJ, and Kociba GJ (1981). Hypercalcemia associated with an adenocarcinoma derived from the apocrine glands of the anal sac. *Vet. Pathol.* 18: 454–471.
46. Meuten DJ, Capen CC, Kociba GJ, and Chew DJ (1982). Ultrastructural evaluation of an adenocarcinoma derived from apocrine glands of the anal sac associated with hypercalcemia in dogs. *Am. J. Pathol.* 107: 167–175.
47. Meuten DJ, Segre GV, Capen CC, Kociba GJ, Tashjian AH Jr, Voelkel EF, Levine L, Chew DJ, and Nagode LA (1983). Hypercalcemia in dogs with adenocarcinoma derived from apocrine glands of anal sac. Biochemical and histomorphometric investigations. *Lab. Invest.* 48: 428–435.
48. Mulvihill JJ (1972). Congenital and genetic disease in domestic animals. *Science* 176: 132–137.
49. Pammenter M, Albrecht C, Kiebenberg vdW, and van Jaarsveld P (1978). Afrikander cattle congenital goiter: Characteristics of its morphology and iodoprotein pattern. *Endocrinology* 102: 954–965.
50. Pelletier G, Puviana R, and Dussault JH (1976). Electron microscope immunohistochemical localization of thyroglobulin in the rat thyroid gland. *Endocrinology* 98: 1253–1259.
51. Peter HJ, Gerber H, Studer H, and Smeds S (1985). Pathogenesis of heterogeneity in human multinodular goiter. *J. Clin. Invest.* 76: 1992–2002.
52. Peterson ME, Livingston P, and Brown RS (1987). Lack of circulating thyroid stimulating immunoglobulins in cats with hyperthyroidism. *Vet. Immunol. Immunopathol.* 16: 277–282.
53. Potts JT Jr (1978). Pseudohypoparathyroidism. In: *The Metabolic Basis of Inherited Disease*, JB Stanbury et al (eds). McGraw-Hill, New York.
54. Rac R, Hill GN, Pain RW, and Mulhearn CJ (1968). Congenital goitre in Merino sheep due to an inherited defect in the biosynthesis of thyroid hormone. *Res. Vet. Sci.* 9: 209–223.
55. Rijnberk A and der Kinderen PJ (1969). Toxic thyroid carcinoma in the dog. *Acta Endocrinol.* 138(Suppl.): 177.
56. Rijnberk A, de Vijlder JJM, van Dijk JE, Jorna TJ, and Tegelaers WHH (1977). Congenital defect in iodothyronine synthesis: Clinical aspects of iodine metabolism in goats with congenital goitre and hypothyroidism. *Br. Vet. J.* 133: 495–503.
57. Rijnberk A, Elsinghorst AM, Koeman JP, Hackeng WHL, and Lequin RM (1978). Pseudohyperparathyroidism associated with perirectal adenocarcinomas in elderly female dogs. *Tijdschr. Diergeneeskd.* 103: 1069–1075.
58. Rijnberk A, Eigenmann JE, Belshaw BE, Hampshire J, and Altszuler N (1980). Acromegaly associated with transient overproduction of growth hormone in a dog. *J. Am. Vet. Med. Assoc.* 177: 534–557.
59. Rosol TJ, Capen CC, and Brooks CE (1987). Bone and kidney adenylate cyclase-stimulating activity produced by a hypercalcemic canine adenocarcinoma line (CAC-8) maintained in nude mice. *Cancer Res.* 47: 690–697.
60. Rosol TJ and Capen CC (1988a). Pathogenesis of humoral hypercalcemia of malignancy. *Domestic Animal Endocrinology* 5: 1–21.
61. Rosol TJ and Capen CC (1988b). Inhibition of *in vitro* bone resorption by a parathyroid hormone receptor antagonist in the canine adenocarcinoma model of humoral hypercalcemia of malignancy. *Endocrinology* 122: 2098–2102.
62. Roth J (1976). Polypeptide hormone receptors. In: *Membrane Receptors for Viruses, Antigens and Antibodies, Polypeptide Hormones, and Small Molecules.* Raven Press, New York.
63. Roth SI and Capen CC (1974). Ultrastructural functional correlations of the parathyroid glands. In: *Int. Rev. of Exp. Pathol.*, Vol. 13, GW Richter and MA Epstein (eds). Academic Press, New York, pp. 162–221.
64. Rowland GN, Capen CC, and Nagode LA (1968). Experimental hyperparathyroidism in young cats. *Vet. Pathol.* 5: 504–519.
65. van Herle AJ, Vassart G, and Dunmont JE (1979). Control of thyroglobulin synthesis and secretion. *N. Engl. J. Med.* 301: 239–249, 307–314.
66. van Jaarsveld PP, Albrecht CF, Theron CN, and van Zyl A (1976). The biosynthesis of thyroid hormone. *S. Afr. J. Med. Sci.* 41: 165–188.
67. van Voorthuizen WF, Dinsort C, Flavell RA, de Vijlder JJM, and Vassart G (1978). Abnormal cellular localization of thyroglobulin mRNA associated with hereditary congenital goiter and thyroglobulin deficiency. *Proc. Natl. Acad. Sci. USA* 75: 74–78.
68. Wilke R, Harmeyer J, von Grabe C, Hehrmann R, and Hesch RD (1979). Regulatory hyperparathyroidism in a pig breed with vitamin D-dependency rickets. *Acta Endocrinol.* 92: 295–308.
69. Winkler I, Grave C, and Harmeyer J (1982). Pseudovitamin D deficiency rickets in pigs: In vitro measurements of renal 25-hydroxycholecalciferol-1-hy-

droxylase activity. *Zentralbl. Veterinaermed.* 29: 81–88.

70. Yarrington JT and Capen CC (1981). Ultrastructural and biochemical evaluation of adrenal medullary hyperplasia and pheochromocytoma in aged bulls. *Vet. Pathol.* 18: 316–325.

71. Zbinden G (1987). Assessment of hyperplastic and neoplastic lesions of the thyroid gland. *Trends in Pharmacol. Sci.* 8: 511–514.