CHAPTER 118

HYPERADRENOCORTICISM

Edward C. Feldman

CANINE CUSHING'S SYNDROME

In 1932, Dr. Harvey Cushing described 12 humans with a disorder that he suggested was "the result of pituitary-basophilism." Careful study of these and other individuals diagnosed years ago suggests multiple causes of this syndrome, with chronic excesses in serum cortisol concentration representing the final common denominator for their illnesses. The eponym Cushing's *syndrome* is an umbrella term referring to the constellation of clinical and chemical abnormalities that result from chronic exposure to excessive concentrations of glucocorticoids. The eponym Cushing's *disease* is applied to those cases of Cushing's syndrome in which hypercortisolism is specifically the result of inappropriate secretion of adrenocorticotropic hormone (ACTH) by the pituitary (i.e., pituitary-dependent hyperadrenocorticism [PDH]). Canine hyperadrenocorticism (canine Cushing's syndrome [CCS]) also has various pathophysiologic origins, but all have that one common denominator: chronic excesses of system cortisol.

A pathophysiologic classification of the causes of CCS include a pituitary tumor synthesizing and secreting excess ACTH with secondary adrenocortical hyperplasia; pituitary hyperplasia and, secondarily, adrenocortical hyperplasia resulting from excesses in corticotropin releasing hormone (CRH) secretion caused by a hypothalamic disorder; primary excesses in adrenal cortisol, autonomously secreted by an adrenocortical carcinoma or adenoma; and iatrogenic causes resulting from excessive ACTH administration (rare) or excessive glucocorticoid medication (common). A tumor outside the hypothalamus or pituitary that produces excessive quantities of ACTH has been described in humans but not in dogs or cats.

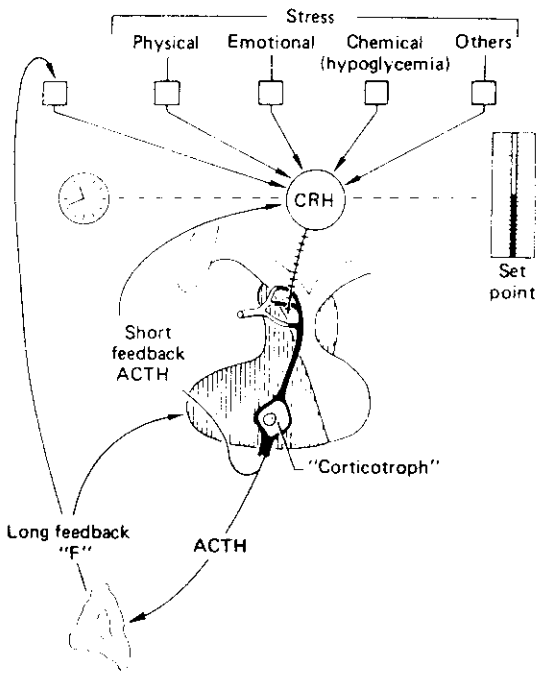

Figure 118–1. Hypothalamic-pituitary-adrenal axis, showing the various stimuli that enhance CRH secretion as well as negative feedback by cortisol (F) at the hypothalamic and pituitary levels. A short negative feedback loop of ACTH on the secretion of CRH is also shown.

REGULATION OF GLUCOCORTICOID SECRETION

Corticotropin Releasing Hormone

Since the early descriptions of portal circulation connecting the hypothalamus and the pituitary, it has been recognized that the hypothalamus exerts control over secretion of ACTH by the anterior pituitary. ACTH, in turn, exerts control over adrenocortical secretion of cortisol. Cortisol, in part, then completes the circle by effecting the control exerted by hypothalamic and pituitary hormones (Fig. 118–1). The factor released by the hypothalamus is CRH, a polypeptide containing 41 amino acid residues. The CRH-secreting neurons are located in the anterior portion of the paraventricular nuclei within the hypothalamus.

Adrenocorticotropic Hormone

Adrenocorticotropic hormone is a 39–amino acid peptide hormone (mol wt 4500) processed from a large precursor molecule, pro-opiomelanocortin (mol wt 28,500). Within the pituitary cells responsible for the synthesis of ACTH (corticotrophs), messenger RNA (mRNA) directs the synthesis of the precursor molecule. That prohormone is then ultimately processed into additional biologically active fragments (Fig. 118–2). The function and importance of these peptide fragments (beta-lipotropin [LPH], alpha-melanocyte–stimulating hormone [MSH], beta-MSH, beta-endorphin, N-terminal fragment) represent an evolving area of endocrinology. The basophilic staining characteristics of corticotrophs can be explained by the carbohydrate nature of these moieties.

Two of the fragments depicted in Figure 118–2 are contained within the structure of ACTH: alpha-MSH is identical to $ACTH_{1-13}$ and corticotropin-like intermediate-lobe peptide represents $ACTH_{18-39}$. Neither of these peptides is secreted as a separate hormone in humans. Beta-endorphin may act as an endogenous opiate, suggesting a role in pain sensation. Beta-endorphin may also affect the endocrine regulation of other pituitary hormones and have a role in the neural control of breathing.[1] Plasma concentrations of the N-terminal fragment have been demonstated to increase in response to hypoglycemic stress. It also may be an adrenal growth factor and/or potentiate ACTH action on steroidogenesis. The physiologic function of beta-LPH is not well understood. It is known, however, that both beta-LPH and beta-endorphin have the same secretory dynamics as ACTH: they increase

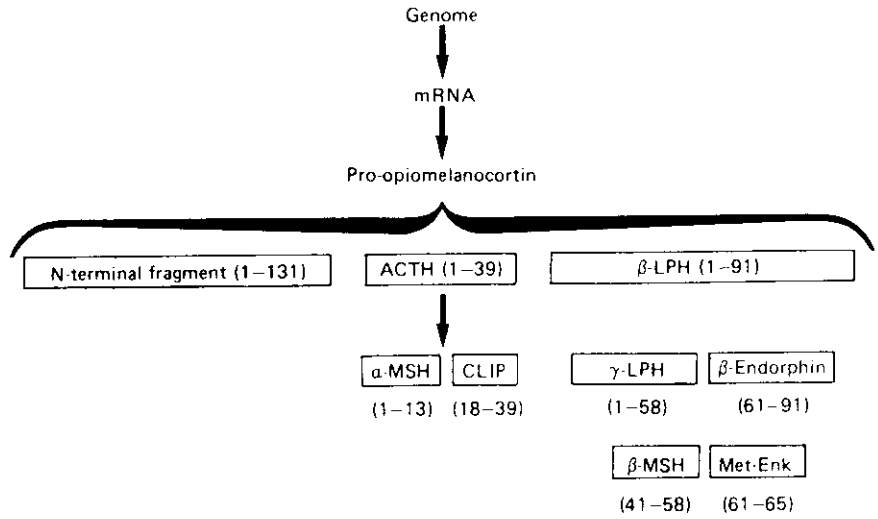

Figure 118–2. Processing of pro-opiomelanocortin into its biologically active peptide hormones. ACTH, adrenocorticotropic hormone; β-LPH, beta-lipotropin; α-MSH, alpha-melanocyte-stimulating hormone; CLIP, corticotropin-like intermediate-lobe peptide; γ-LPH, gamma-lipotropin; β-MSH, beta-melanocyte-stimulating hormone; met-enk, methionine-enkephalin.

in response to stress and hypoglycemia and are suppressible with glucocorticoids. These hormones also parallel ACTH in disease states. For example, they are elevated in Addison's disease, Cushing's disease, and Nelson's syndrome (growing pituitary tumor after removal of the adrenals).[2] They decrease in dogs with autonomously secreting adrenocortical tumors.

CRH stimulates ACTH in a pulsatile manner, with diurnal rhythm in humans causing a peak before awakening followed by a progressive decline in concentrations throughout the day. Diurnal rhythms have not been established in dogs.[3–5] ACTH secretion also increases in response to feeding in both humans and animals.[1] The primary function of ACTH is to stimulate the secretion of glucocorticoids from the adrenal cortex. The stimulatory properties ACTH has on adrenocortical secretion of mineralocorticoids and androgenic steroids are less important.

Many types of stress stimulate ACTH, often superceding normal daily fluctuations. Physical, emotional, and chemical stresses, such as pain, trauma, hypoxia, acute hypoglycemia, cold exposure, surgery, and pyrogens, have been demonstrated to stimulate ACTH and cortisol secretion. The increase in ACTH concentrations during stress is mediated by vasopressin as well as CRH. Although physiologic cortisol levels do not blunt the ACTH response to stress, high doses of exogenous corticosteroids do suppress ACTH.

Negative feedback of cortisol and synthetic glucocorticoids on ACTH secretion occurs at both the hypothalamic and the pituitary level and appears to act by two mechanisms: fast feedback is sensitive to the rate of change in cortisol concentration, whereas slow feedback is sensitive to the absolute cortisol concentration. The latter form of negative feedback is the type probed by the clinical dexamethasone suppression test. In addition to the negative feedback of corticoids, ACTH exerts a negative feedback effect on (i.e., inhibits) its own secretion (short-loop feedback), as shown in Figure 118–1.[1]

Steroids

The major hormones secreted by the adrenal cortex are cortisol, the androgens, and aldosterone. The synthesis of all steroid hormones begins with cholesterol. Plasma lipoproteins are the major source of adrenal cholesterol. Histologically, the adrenal cortex is composed of three zones. The outer *zona glomerulosa* produces aldosterone and is deficient in 17α-hydroxylase activity, rendering this zone incapable of synthesizing cortisol or androgens. Only these cells contain the enzymatic system necessary to dehydrogenate 18-hydroxycorticosterone, allowing the synthesis of aldosterone. Aldosterone synthesis is primarily regulated by the renin-angiotensin system and serum potassium concentrations.

The middle *zona fasciculata* is the thickest of the three adrenocortical layers. This is the zone from which cortisol and androgens are produced. It functions as a unit with the narrow, inner *zona reticularis*, which produces the same two hormones. Only cells within these two layers of the adrenal cortex have 17α-hydroxylase activity and can synthesize 17α-hydroxypregnenolone and 17α-hydroxyprogesterone, precursors of cortisol and adrenal androgens. These zones are primarily regulated by ACTH.[6]

The delivery of ACTH to the adrenal cortex leads to the rapid synthesis and secretion of glucocorticoids. Chronic stimulation leads to adrenocortical hyperplasia and hypertrophy; conversely, ACTH deficiency results in decreased steroidogenesis and is accompanied by adrenocortical atrophy, decreased weight of the gland, and decreased protein and nucleic acid content.[6]

PATHOPHYSIOLOGY

Pituitary-Dependent Hyperadrenocorticism

Pituitary Control and Feedback. In normal individuals (humans and animals), ACTH secretion appears random and episodic. This appearance is misleading because ACTH functions exquisitely in maintaining plasma cortisol concentrations at levels required for homeostasis. The most common abnormality in PDH is that the frequency and amplitude of ACTH secretory bursts are chronically excessive. Chronic excesses in ACTH secretion result in excess cortisol secretion and, eventually, adrenocortical hyperplasia. Feedback inhibition of this ACTH secreted from pituitary hyperplastic cells, an adenoma, or a carcinoma, by physiologic or excess levels of glucocorticoids, is relatively ineffective (Fig. 118–3). If glucocorticoids were effective in negative feedback and inhibition of ACTH secretion, PDH would not evolve. The episodic secretory pattern of ACTH secretion and, in turn, cortisol results in fluctuating plasma concentrations of each hormone that often are within the normal or reference ranges for most laboratories (Fig. 118–4).

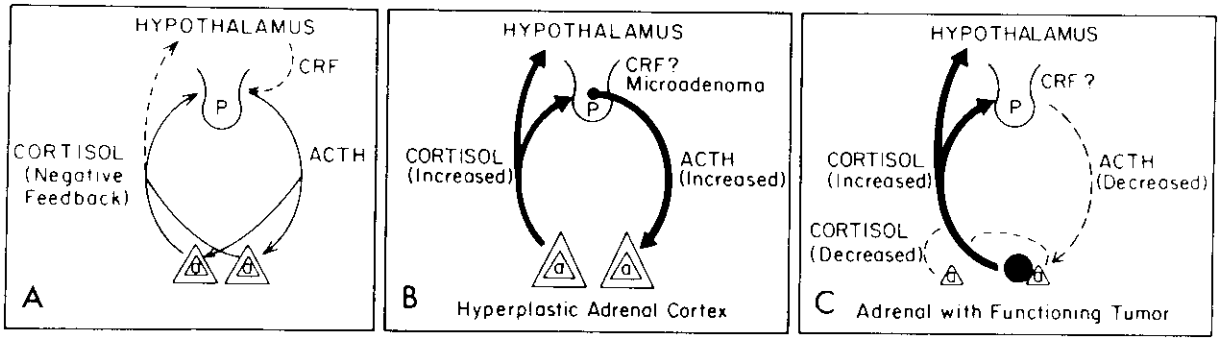

Figure 118–3. Pituitary-adrenal axis in normal dogs *(A)*, dogs with PDH *(B)*, and dogs with a functioning adrenocortical tumor *(C)*. a, adrenal; P, pituitary; CRF, corticotropin releasing factor.

"Normal" Cortisol Concentrations in Hyperadrenocorticism? Studies of cortisol production, such as urine cortisol excretion over 24 hours, can easily demonstrate the existence of excessive cortisol secretion. This excessive secretion and the absence of diurnal variation (if it exists) in glucocorticoid secretion cause the clinical manifestations of Cushing's syndrome. The excessive secretion of cortisol cannot be appreciated by assaying one basal cortisol concentration. As shown in Figure 118–5, most dogs with Cushing's have plasma cortisol concentrations within a normal range at any given moment. The dog or cat with hyperadrenocorticism, however, is exposed to more cortisol on a total daily basis than the normal animal. This chronic abnormality, after a period of months, results in the clinical syndrome associated with cortisol excess. An increased plasma cortisol concentration may be the result of momentary stress and is not diagnostic of hyperadrenocorticism.

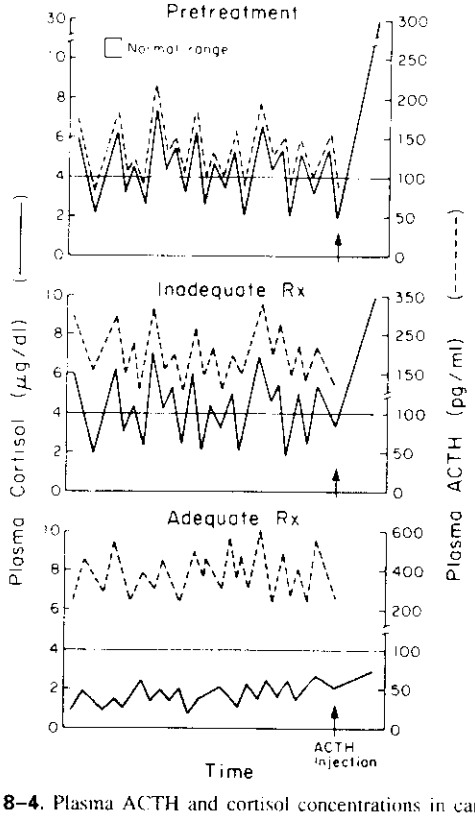

Figure 118–4. Plasma ACTH and cortisol concentrations in canine PDH before and after treatment with *o,p'*-DDD. Before treatment *(top panel)*, both ACTH and cortisol are secreted in a pattern of peaks and troughs, with frequent fluctuations above normal range throughout the day. During *o,p'*-DDD therapy, decreased cortisol secretion results in loss of negative feedback inhibition of pituitary ACTH secretion; therefore, ACTH concentrations rise to extremely high levels. Unless adrenocortical reserve is decreased below normal (adequate treatment, *bottom panel*) with both basal and postendogenous ACTH administration (↑) cortisol concentrations within normal resting range, such elevated endogenous ACTH concentrations still cause cortisol to rise above normal range at frequent intervals (inadequate treatment, *middle panel*). (From Peterson ME: Vet Clin North Am Small Anim Pract 14:731, 1984. Used with permission.)

Loss of Hypothalamic Control. One reflection of excessive ACTH secretion is the absence of stress responsiveness. Stimuli such as hypoglycemia and surgery fail to further elevate ACTH and cortisol secretion. Chronic hyperadrenocorticism suppresses hypothalamic function and CRH secretion. Hypothalamic control of ACTH secretion is thereby lost, probably because of suppression of hypothalamic function and CRH secretion as a result of the chronic hypercortisolism.[1,6,7]

Incidence of Pituitary Tumors. The vast majority (80 to 85 per cent) of dogs with naturally occurring Cushing's syndrome have PDH (i.e., excessive secretion of ACTH by the pituitary causing bilateral adrenal hyperplasia and excessive secretion of glucocorticoids). The reported incidence of recognized pituitary tumors in dogs with PDH varies tremendously but is probably dependent on the competence and persistence of the pathologist plus the microdissection capabilities and staining capacities of the laboratory performing the histology. More than 90 per cent of dogs with PDH have a pituitary tumor.[8,9]

Pars Distalis Versus Pars Intermedia. The pathogenesis of PDH in dogs is more complicated than that in humans. The pars distalis is common to all mammals. Unlike the human pituitary, which lacks a discrete intermediate lobe, the dog pituitary also has a defined pars intermedia. Further, this pars intermedia has been demonstrated to have two distinct cell types.[3,10] The predominant cells (A cells) immunostain intensely for alpha-MSH but only weakly for ACTH. The second population of pars intermedia cells (B cells) stain strongly for ACTH and only weakly for alpha-MSH. The intense ACTH staining of pars intermedia B cells is similar to the staining characteristics of pars distalis cells. Pars distalis pro-opiomelanocortin and, therefore, ACTH secretion are primarily regulated by the interaction of the stimulatory hypothalamic peptides (CRH) and the inhibitory adrenocortical glucocorticoids. The pars intermedia, however, is under negative regulation by dopamine, secreted from the arcuate nucleus, as well as by serotonin and the traditional CRH. Thus, the pars distalis is devoid of a nerve supply and controlled by hypothalamic CRH that reaches it through the hypophyseal portal vessels, whereas the relatively avascular pars intermedia is innervated and controlled by dopaminergic and serotoninergic fibers from the brain.

Dogs with hyperadrenocorticism have been diagnosed

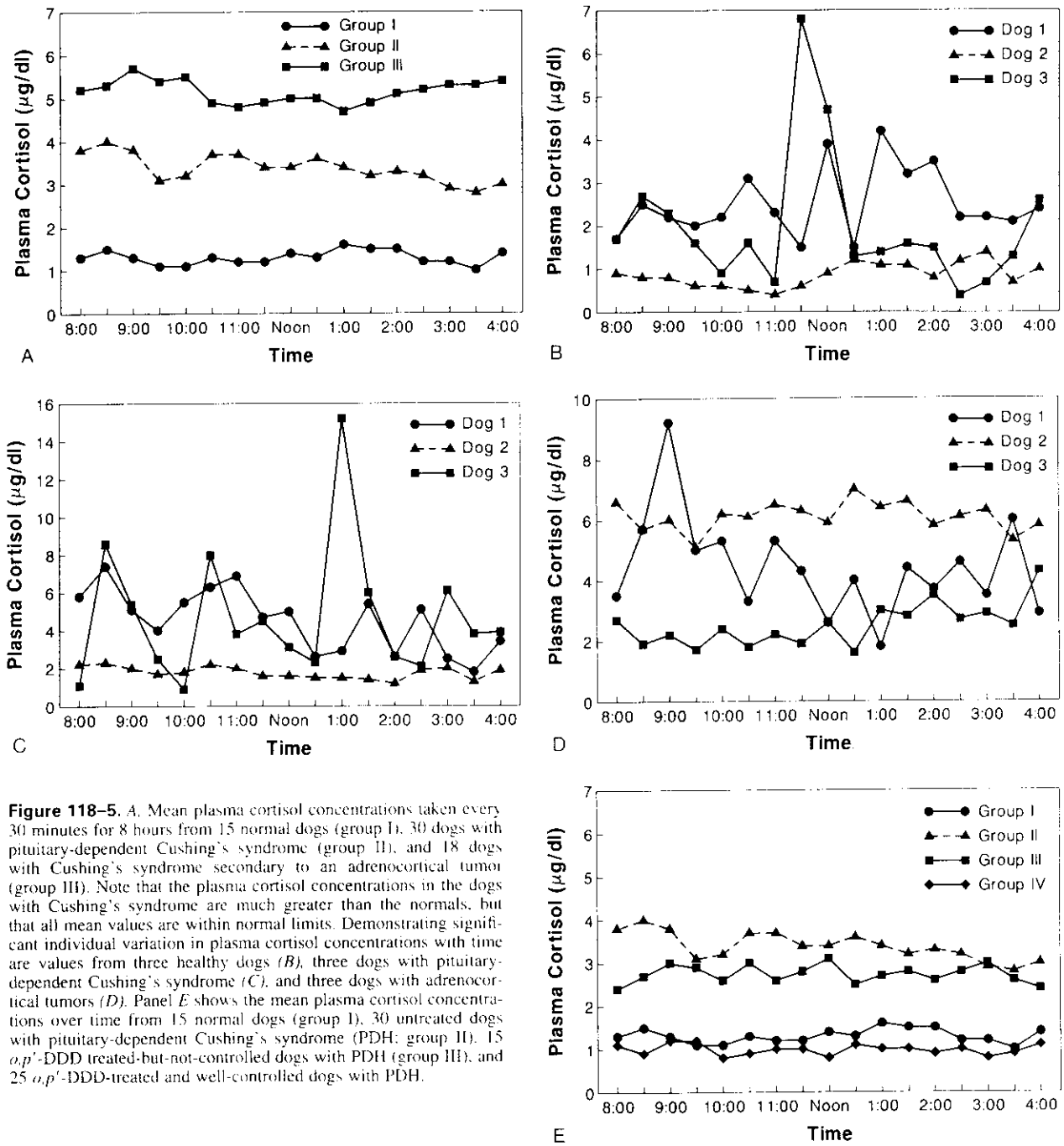

Figure 118–5. *A*, Mean plasma cortisol concentrations taken every 30 minutes for 8 hours from 15 normal dogs (group I), 30 dogs with pituitary-dependent Cushing's syndrome (group II), and 18 dogs with Cushing's syndrome secondary to an adrenocortical tumor (group III). Note that the plasma cortisol concentrations in the dogs with Cushing's syndrome are much greater than the normals, but that all mean values are within normal limits. Demonstrating significant individual variation in plasma cortisol concentrations with time are values from three healthy dogs *(B)*, three dogs with pituitary-dependent Cushing's syndrome *(C)*, and three dogs with adrenocortical tumors *(D)*. Panel *E* shows the mean plasma cortisol concentrations over time from 15 normal dogs (group I), 30 untreated dogs with pituitary-dependent Cushing's syndrome (PDH; group II), 15 *o,p'*-DDD treated-but-not-controlled dogs with PDH (group III), and 25 *o,p'*-DDD-treated and well-controlled dogs with PDH.

with A-cell pars intermedia adenomas, others with B-cell pars intermedia adenomas, and still others with adenomas of the pars distalis. A small percentage of dogs with PDH have been diagnosed with pituitary hyperplasia, and there also are individuals with functional pituitary carcinomas. Even more confusing are individual dogs with two pituitary adenomas, each tumor apparently arising from a different pituitary lobe, and those with both a tumor and hyperplasia of the pituitary. As is quickly appreciated, pituitary hyperadrenocorticism is a syndrome with potential for multiple causes. The final common pathway for these disorders remains similar, however. There is chronic systemic cortisol excess caused by adrenocortical hyperplasia resulting from chronic and excessive secretion of pituitary ACTH. We have not found it possible to easily distinguish etiology based on ante-mortem testing.[11] Further, such ante-mortem testing would probably be affected by numerous other factors (e.g., age, breed, duration of illness, tumor size, benign versus malignant nature of the tumor). These discussions are of academic interest but have not yet been demonstrated to have clinical significance.

Etiology of PDH. It has been suggested that chronic stimulation of pituitary corticotrophs by hypothalamic CRH could lead to excess secretion of ACTH, pituitary hyperplasia, and, eventually, neoplastic transformation of some corticotrophs, resulting in a polyclonal tumor. However, CRH concentrations in the cerebrospinal fluid of dogs with PDH were demonstrated to be decreased, whereas the ACTH concentrations were normal, despite the syndrome of excess cortisol secretion.[7] Adenomas of the pars distalis are the most common histologic finding in canine PDH and represent the

best evidence for pituitary tumors being a primary and autonomous cause for the disorder. In humans, microsurgical removal of pituitary tumors corrects ACTH hypersecretion and hypercortisolism.[1] Postoperatively, such patients experience transient ACTH deficiency with secondary hypocortisolism. This data weighs heavily against a hypothalamic cause for PDH.

Glucocorticoid Excess Versus Non-ACTH Pituitary Function. In addition to the systemic effects of glucocorticoids, excess cortisol concentrations inhibit normal pituitary and hypothalamic function, affecting thyrotropin (TSH), growth hormone (GH), and gonadotropin (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]) release. Inhibiting secretion of these trophic hormones results in reversible hypothyroidism (TSH), failure to cycle in female dogs or testicular atrophy in male dogs (FSH and LH), and short stature in growing puppies (GH).

Adrenal Tumors

Primary adrenocortical tumors, both adenomas and carcinomas, apparently develop autonomously. Functioning adrenocortical tumors secrete excessive quantities of cortisol independent of pituitary control. Thus, the steroid products of these tumors suppress hypothalamic CRH, circulating plasma ACTH, and pro-opiomelanocortin peptide (except alpha-MSH) concentrations.[2] The result of this chronic negative feedback is cortical atrophy of the uninvolved adrenal and atrophy of all normal cells in the involved adrenal (see Fig. 118–3).

Cortisol secretion is autonomous, random, and episodic (see Fig. 118–5). However, most, if not all, of these tumors retain ACTH receptors because they respond to administration of ACTH. These adrenocortical tumors typically are unresponsive to manipulation of the hypothalamic-pituitary axis with pharmacologic agents such as dexamethasone. There has been no consistent clinical or biochemical feature that aids in distinguishing dogs or cats with functioning adrenal adenomas from those with adrenal carcinomas. The only characteristic considered somewhat consistent is that adrenocortical carcinomas tend to be larger than adenomas.[12]

Ectopic ACTH Syndrome

Ectopic ACTH syndrome has not yet been diagnosed in the dog. In humans, it comprises a varying group of tumors that are capable of synthesizing and secreting ACTH. That ACTH, in turn, ultimately causes adrenocortical hyperplasia and hypercortisolism. Tumors with the potential for causing ectopic ACTH syndrome in humans include oat cell (small-cell) carcinomas of the lung, thymoma, pancreatic islet cell tumors, carcinoid tumors (lungs, gut, pancreas, ovaries), medullary carcinoma of the thyroid, and pheochromocytoma.[6]

Adrenocortical Nodular Hyperplasia

Macronodular hyperplasia occurs in about 20 per cent of people with adrenocortical hyperplasia. Dogs and cats with bilateral adrenal nodular hyperplasia are well recognized, accounting for 5 to 10 per cent of hyperadrenocorticism cases. The exact pathogenesis of this syndrome is unclear, although most cases in humans, dogs, and cats are presumed to represent an anatomic variant of PDH. A minority of cases seem to have autonomous adrenocortical function and/or unilateral disease. The adrenals usually are grossly enlarged with multiple nodules of varying size within the cortex.

One subset of this syndrome includes people with clinical features of hyperadrenocorticism, nodular adrenocortical hyperplasia, and subnormal morning and suppressed ACTH responsive plasma cortisol concentrations.[13-15] Food intake had stimulated cortisol secretion in these people. Each had inappropriate adrenal sensitivity to normal postprandial increases in the secretion of gastric inhibitory polypeptide (GIP). In view of the poor homology between GIP and ACTH, it was unlikely that the adrenocortical ACTH receptors were modified to bind GIP.

Unilateral Versus Bilateral Adrenal Tumors

Bilateral Adrenocortical Tumors. Hyperadrenocorticism caused by bilateral functioning adrenocortical neoplasia is rare in dogs. In four such dogs, three had bilateral adrenocortical adenomas and one had bilateral adrenocortical carcinomas.[16]

Adrenocortical Tumor and Pheochromocytoma. We have diagnosed several dogs with a pheochromocytoma in one adrenal and an adrenocortical tumor in the contralateral gland. This can be confusing because ultrasound may reveal bilateral adrenomegaly, and endocrine testing will suggest adrenocortical tumor.

Simultaneous Pituitary Tumor and Adrenal Cushing's Syndrome

Several dogs have had a functioning adrenocortical tumor and a pituitary microadenoma. These dogs have both adrenal tumor and bilateral adrenocortical hyperplasia. The endocrine evaluation would be diagnostic for hyperadrenocorticism. However, tests to distinguish between PDH and adrenocortical tumor may be confusing.

PATHOLOGY

The Pituitary

Microadenomas. Most (80 to 85 per cent) of the dogs with naturally occurring hyperadrenocorticism have pituitary-dependent disease. It is fair to say that recognition of some pituitary tumors requires careful microdissection, experience, special stains, and a great deal of patience. Because these criteria are not always met, the reported incidence of recognized pituitary tumors in dogs with PDH is underrepresented. About 50 per cent of dogs with PDH have pituitary tumors less than 3 mm in diameter. The remainder of evaluated dogs with PDH, specifically those without central nervous system signs, had tumors 3 to 12 mm in diameter.[17] Tumors larger than 3 mm in diameter should be grossly visible and are more likely to be recognized than smaller masses.

Most ACTH-secreting pituitary tumors are defined as microadenomas because they are less than 1 cm in diameter.[1] They usually are not encapsulated but may be surrounded by a rim of compressed normal pituitary cells. With routine histologic stains, such tumors typically are composed of compact sheets of well-granulated basophilic cells in a sinusoidal arrangement. ACTH-secreting adenomas typically show Crooke's changes (a zone of perinuclear hyalinization that results from chronic exposure of corticotroph cells to hypercortisolism). Electron microscopy demonstrates secretory granules that vary in size from 200 to 700 mm.

Macroadenomas. A significant percentage of dogs with PDH (perhaps as many as 10 to 15 per cent) have large

pituitary tumors.[18] Macroadenomas are visible on gross examination of the pituitary or greater than 1 cm in diameter. They have the potential of compressing or invading adjacent structures. The masses usually extend dorsally into the hypothalamus, often causing signs (see discussion in this chapter). Because the canine sella turcica is shaped like a saucer rather than like a cup (as in humans), destruction of bone making up the walls of the sella is not observed. Large, expanding masses need not contact bone to expand into the overlying structures of the brain. Such tumors may appear chromophobic on routine histologic study, but they typically contain ACTH and its related peptides. Malignant pituitary tumors occur uncommonly.

Pituitary Hyperplasia. Diffuse hyperplasia of corticotroph cells has been reported in a small number of dogs with PDH (see Pathophysiology). These cases may but are not likely to be the consequence of excessive stimulation of the anterior pituitary by CRH. Most dogs with pituitary hyperplasia also have pituitary tumors. The experience in humans is no different. With surgical removal of the tumor in afflicted people, signs of hyperadrenocorticism typically resolve, negating the significance of histologically observed hyperplasia.[1]

Adrenocortical Hyperplasia

Typical Bilateral Hyperplasia. The histologic observation of bilateral hyperplasia usually occurs secondary to PDH. Combined adrenal weight commonly is modestly or greatly increased. Histologically, there is equal hyperplasia of the compact cells of the zona reticularis and the clear cells of the zona fasciculata; consequently, the width of the cortex is increased.

Nodular Hyperplasia of the Adrenal. As discussed in the section on pathophysiology, nodular hyperplasia of the adrenal is a poorly understood and uncommon feature in dogs or cats afflicted with Cushing's syndrome. Grossly, there are multiple nodules within the adrenal cortices, with widening of the intervening cortex. The nodules typically are yellow and, on histologic examination, resemble the clear cells of the normal zona fasciculata. The remainder of the adrenal cortices show the histologic features of simple adrenocortical hyperplasia.

Adrenal Tumors

Problems in Classification. Pathologists may have difficulty distinguishing between normal and hyperplastic endocrine tissue. It may also be difficult to distinguish diffuse hyperplasia from adenomatous hyperplasia or to identify an adenoma from either of these other possibilities. Not only can it be difficult to distinguish between an adenoma and a carcinoma, but it can also be challenging to identify an adrenocortical tumor from an adrenal medullary tumor (pheochromocytoma).

Adenomas. Adrenal adenomas usually are encapsulated and grossly visible, ranging in size from 1 to 6 cm. They typically are three-fourths the size of a normal kidney or smaller. Microscopically, clear cells of the zona fasciculata predominate, although cells typical of the zona reticularis may also be seen. About 50 per cent of adrenocortical adenomas are partially calcified.

Carcinomas. Adrenal carcinomas can become quite large. They tend to be much larger than one-half the size of a normal kidney. Grossly, they may not be encapsulated. They are highly vascular; necrosis, hemorrhage, and cystic degeneration are common. Partial calcification is identified in about 50 per cent of these masses. The histologic appearance of adrenocortical carcinomas varies considerably; they may appear to be benign, or may exhibit considerable pleomorphism. Vascular or capsular invasion is predictive of malignant behavior, as is local extension. Carcinomas invade local structures (kidneys, liver, vena cava, aorta, and retroperitoneum) and metastasize hematogenously to the liver and lungs.

Uninvolved Adrenocortical Tissue. The cortical tissue contiguous to a functioning adrenocortical adenoma or carcinoma and that of the contralateral gland are atrophic. The cortex is markedly thinned, whereas the capsule is thickened. Histologically, the zona reticularis is virtually absent; the remaining cortex is composed of clear zona fasciculata cells. The architecture of the zona glomerulosa usually is normal.

SIGNALMENT

Age

Hyperadrenocorticism is a disease of middle-aged and older dogs. It is generally agreed that dogs with pituitary-dependent Cushing's syndrome usually are older than 6 years of age. More than 75 per cent of these dogs are older than 9 years of age, and their median age is 10 years.[12, 17] We have seen only four dogs with Cushing's syndrome less than 2 years of age at the time of diagnosis (Fig. 118–6).

Dogs with hyperadrenocorticism caused by functioning adrenocortical tumors tend to be older than those with pituitary-dependent disease. Most of these dogs are 6 to 16 years of age at the time of diagnosis.[12] The median age in dogs with adrenocortical tumors is 11.3 years, and more than 90 per cent of dogs with this disease are older than 9 years of age.

Sex

Dogs with hyperadrenocorticism do not have a significant difference in sex distribution. Fifty-five to 60 per cent of dogs with PDH and 60 to 65 per cent of dogs with functioning adrenocortical tumors were female.[12, 17]

Breed and Body Weight

Pituitary-Dependent Hyperadrenocorticism. Various poodle breeds, dachshunds, various terrier breeds, beagles, and German shepherd dogs are most commonly represented among the breeds of dogs afflicted with PDH. Boston terriers and boxers have been mentioned to be at increased risk. PDH has been diagnosed in numerous breeds (Table 118–1). About 75 per cent of dogs with PDH weigh less than 20 kg, emphasizing the concept that PDH occurs more frequently in smaller dogs.[12, 17]

Adrenocortical Tumor. Dogs with naturally occurring Cushing's due to a functioning adrenocortical tumor include toy poodles (and other poodle breeds), German shepherd dogs, dachshunds, Labrador retrievers, and various terrier breeds (Table 118–2). About 45 to 50 per cent of dogs with adrenocortical tumors (adenomas or carcinomas) weigh more than 20 kg.[12]

HISTORY

Items of Importance NOT in the History

Most dogs with Cushing's syndrome are not critically ill. Vomiting, diarrhea, pain, seizures, and bleeding, for exam-

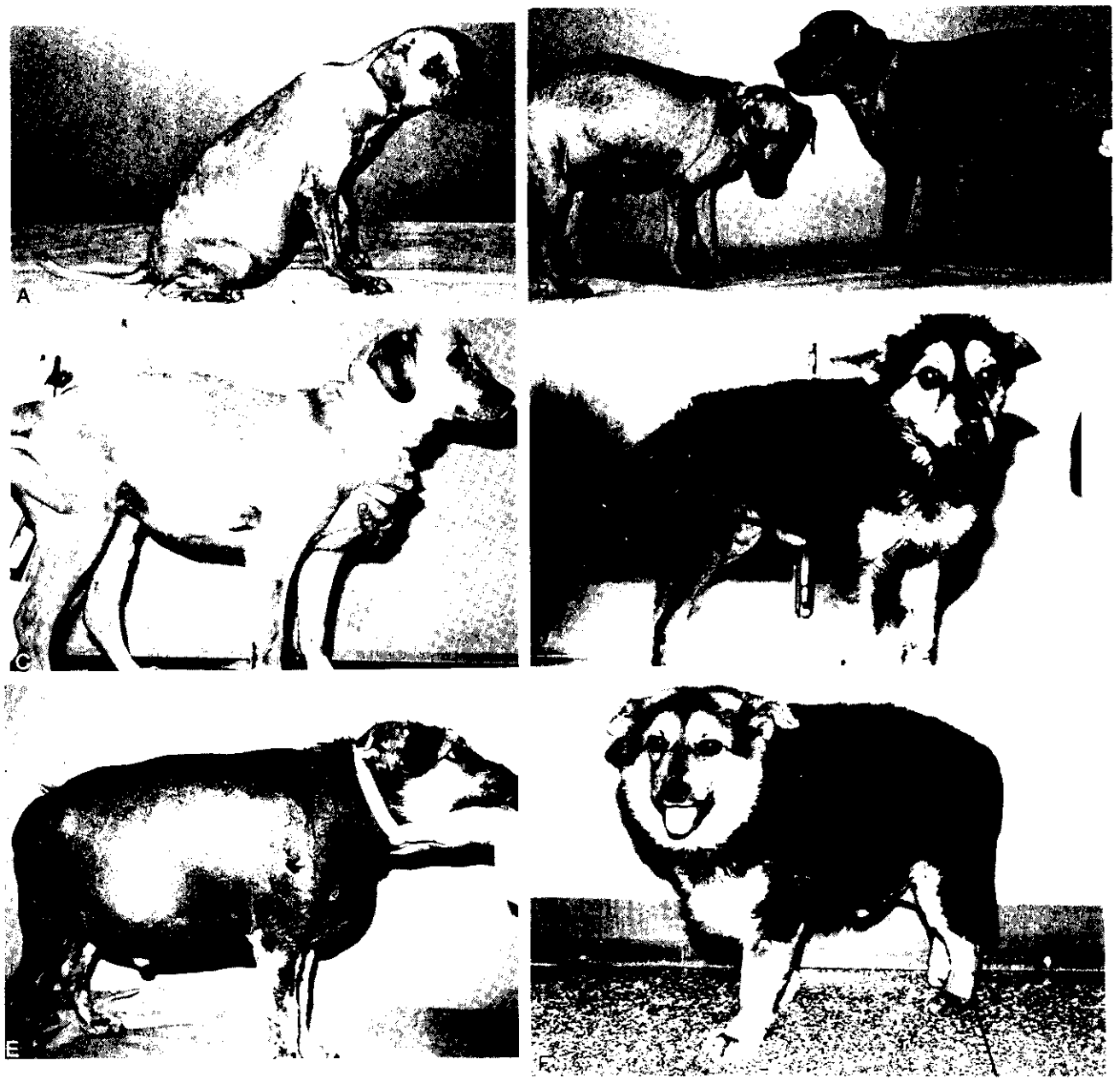

Figure 118–6. *A*, Mixed-breed 18 month old dog with hyperadrenocorticism. *B*, Same dog *(left)* and a normal littermate. *C*, Five months after initiation of *o,p'*-DDD therapy. *D*, A 6-month-old German shepherd with hyperadrenocorticism. *E*, Same dog as in *D* after 4 years without therapy. *F*, Same dog as in *D* and *E* 4 months after initiating therapy with *o,p'* DDD. (From Feldman EC and Nelson RW: Canine and Feline Endocrinology and Reproduction. Philadelphia, WB Saunders, 1987, p 143; the author thanks Dr. Candice Souza for photograph *D*.)

ple, are not typical concerns. Most dogs with Cushing's have signs that slowly progress; they are not problems of an acute nature. Nor do they often frighten the owner into action.

General Review

Chronic exposure to excess cortisol often results in development of a classic combination of dramatic clinical signs and lesions.[18] These include polydipsia, polyuria, polyphagia, abdominal enlargement, alopecia, pyoderma, panting, muscle weakness, and lethargy. Not all dogs with hyperadrenocorticism develop the same signs. From this long list of potential signs (plus others), most dogs exhibit several problems. Hyperadrenocorticism is a clinical disorder, and animals with this disease have some associated clinical signs. The signs are the sequelae of the combined gluconeogenic, lipolytic, protein catabolic, anti-inflammatory, and immunosuppressive effects of glucocorticoid hormones on various organ systems.

The course of the disease usually is insidious and slowly progressive. Owners often retrospectively report the presence of some alterations typical of hyperadrenocorticism in their pets for 1 to 6 years before the diagnosis is made (Table 118-3). A similar time period elapses before the owners seek veterinary attention for their animals because these changes are gradual in onset and often believed by the clients to be a result of simple aging. It is only when the signs become intolerable to the clients or after alterations are specifically pointed out by people who see the pets infrequently (therefore noting obvious changes that have developed so slowly the owners themselves do not observe them) that professional

TABLE 118–1. BREEDS MOST COMMONLY AFFLICTED WITH PDH (TOTAL: 750 DOGS)

PERCENTAGE	ABSOLUTE NO.	BREED
16	119	Poodle (various breeds)
11	84	Dachshund
10	76	Terrier (various breeds)
7	54	Beagle
6	48	German shepherd
5	38	Labrador retriever
5	36	Australian shepherd
4	30	Maltese
4	28	Spaniel (various breeds)
3	22	Schnauzer
3	22	Lhasa apso
2	19	Chihuahua
2	18	Boston terrier
2	15	Golden retriever
2	14	Shih Tzu
2	12	Boxer
16	115	Other breeds (38)

opinions are sought. The most common reasons owners give for finally seeking veterinary help for their dogs are polydipsia and polyuria, polyphagia, lethargy, panting, and/or hair coat changes.[19]

Dogs with rapidly growing adrenocortical tumors and some with PDH may be reported by their owners to have a rapid onset and progression of illness. This is more likely the result of an owner's not noticing changes rather than the signs truly being acute in onset. The duration of clinical signs and the type of signs noticed have not been reliable aids in distinguishing PDH from adrenal-dependent hyperadrenocorticism.

Polydipsia and Polyuria

Polydipsia and polyuria are common signs associated with hyperadrenocorticism and represent the most frequently cited reason for owners to bring their pets to veterinarians. Previously housebroken animals are no longer able to endure the night without urinating. The pet pesters the owner to be let outside or urinates indoors, and the situation eventually becomes intolerable for the client. Polydipsia and polyuria have been documented in about 80 to 85 per cent of these dogs. Although there are many striking similarities between human and canine Cushing's syndrome, these signs are not typical of the disease in people.

TABLE 118–2. BREEDS MOST COMMONLY AFFLICTED WITH FUNCTIONING ADRENOCORTICAL ADENOMA OR CARCINOMA CAUSING HYPERADRENOCORTICISM (TOTAL: 102 DOGS)

PERCENTAGE	BREED
15	Poodle (various breeds)
12	German shepherd
11	Dachshund
10	Labrador retriever
8	Terrier (various breeds)
5	Cocker spaniel
4	Alaskan malamute
4	Boston terrier
4	Shih Tzu
3	Boxer
3	Shetland sheepdog
3	English springer spaniel
3	Australian shepherd
15	Other breeds (12)

TABLE 118–3. INITIAL HISTORY FOR DOGS WITH HYPERADRENOCORTICISM

Polydipsia and polyuria
Polyphagia
Abdominal enlargement
Decreased exercise tolerance (muscle weakness)
Increased panting
Lethargy
Obesity
Alopecia (sparing head and distal extremities)
Calcinosis cutis
Anestrus
Testicular atrophy
Heat intolerance
Acne (skin infection, comedones)
Cutaneous hyperpigmentation
Exophthalmos

Normal water intake for the average dog is about 20 to 30 ml/lb/day. Owners usually report water intake in polydipsic hyperadrenal dogs that is 2 to 10 times normal. Some investigators believe that the polyuria is the result of interference by cortisol with the action of antidiuretic hormone (ADH) at the level of the renal collecting tubules (a form of nephrogenic diabetes insipidus). It has also been proposed that cortisol may increase the glomerular filtration rate, thus initiating diuresis.

Experience suggests that most dogs with hyperadrenocorticism have a form of central diabetes insipidus (deficiency in ADH). Most hyperadrenal dogs respond to administration of natural or synthetic ADH by dramatically reducing their urine output and water intake. Therefore, cortisol interference with release of ADH is the most plausible explanation for this clinical sign.[20, 21] It is unlikely that direct compression of the posterior pituitary gland or the hypothalamus by an enlarging pituitary tumor would cause the diabetes insipidus, even in those dogs with large pituitary tumors.

Polyphagia

Increased appetite may be troublesome to some owners because the dog with Cushing's may resort to stealing food, eating garbage, begging continuously, and, occasionally, aggressively attacking or protecting food. In most instances, however, it is a dog's continued excellent appetite, despite other abnormalities, that convinces an owner that his pet is healthy and does not require veterinary attention. Increased appetite is assumed to be a direct effect of glucocorticoids, a unique effect in the dog. Polyphagia, or an "excellent appetite," is present in 80 to 90 per cent of dogs with Cushing's syndrome.[19]

It is possible but not common for the glucocorticoid-induced anti-insulin effect to produce a subclinical (sometimes overtly clinical) case of diabetes mellitus. This could result in an increased appetite as the patient attempts to compensate for starvation. Only about 5 per cent of dogs with Cushing's syndrome have overt diabetes mellitus.

Abdominal Enlargement

The potbellied or pendulous abdominal profile in hyperadrenocorticism is a classic symptom in humans and is present in 90 to 95 per cent of affected dogs. This sign is believed to be the cumulative result of several factors: the increased weight of abdominal contents coupled with a decrease in

muscle strength. Part of the increased abdominal content weight is due to redistribution of fat from various storage areas to the abdomen. The mechanism responsible for this redistribution of fat is not understood, but the result is a significant amount of abdominal fat deposition.

When the weight of abdominal fat is added to the increased size and weight of the liver (secondary to cortisol's effect), the chronically full and large urinary bladder, and the muscle wasting that is a direct result of excess cortisol, a pendulous abdomen results. Urine accumulation is due to polyuria and, in part, a reduced ability to completely void the bladder during urination. Protein catabolism accounts for muscle wasting. The abdominal muscles, weakened by glucocorticoid effects, simply cannot prevent bulging of the belly (Figs. 118–6 and 118–7).

Muscle Weakness, Lethargy, Lameness

Common Signs. Muscle weakness, lethargy, and lameness are seldom major concerns of the owner. Most hyperadrenal dogs are capable of rising from a prone position and going for short walks. Muscle weakness in small dogs usually is reflected as an inability to climb stairs and jump onto furniture or into a car. Most of the dogs with these signs can come down stairs without hesitation or jump down from furniture or a car. Many owners fail to even notice this phenomenon, think that their pet is spoiled, or associate the problem with aging. Exercise tolerance often is reduced. Although dogs with hyperadrenocorticism can walk without problem, normal running may cause undue fatigue. As with abdominal distention, muscle weakness is at least partly the result of muscle wasting caused by protein catabolism. Weakness has been noted in 75 to 85 per cent of dogs with Cushing's.

Lethargy is probably an expression of muscle weakness and muscle wasting. Hyperadrenal dogs usually are alert, but they often are not active. As mentioned, this vague sign is certainly one most clients attribute to simple aging.

More Profound Signs. Infrequently, muscle weakness is more profound, and dogs may not be capable of rising, may have difficulty standing for any length of time, and may develop pressure ulcers because they spend so much time down. Pressure ulcers are more common in large dogs with Cushing's syndrome because of their predisposition to remain recumbent plus the effect of their weight.

Uncommon signs of muscle weakness include unilateral or bilateral facial nerve paralysis. Chronic hypercortisolism can result in an exaggeration of common problems such as anterior cruciate ligament rupture and patellar luxation lameness.

Lameness Caused by Treatment. Many older dogs suffer from chronic degenerative joint disease and arthritis. Hyperadrenocorticism may mask the signs related to these problems by inhibiting this inflammation. Successful management of Cushing's has the potential for unmasking some of these occult, age-related joint diseases, and owners should be so warned before initiating treatment.

Figure 118–7. Poodle with PDH, showing the potbellied appearance frequently seen. (From Feldman EC and Nelson RW: Canine and Feline Endocrinology and Reproduction. Philadelphia, WB Saunders, 1987, p 145.)

Cutaneous Markers of Hyperadrenocorticism

Alopecia and Pruritus. The reported incidence of alopecia and other skin abnormalities in dogs with hyperadrenocorticism is affected by the interests of authors who publish this material. One group of dermatologists described dematologic signs in 100 per cent of 60 dogs with hyperadrenocorticism, with 80 per cent of the dogs having some form of alopecia.[22] Internists note that a percentage of hyperadrenal dogs have no apparent dermatologic signs.[17, 18, 23] In any case, cutaneous signs are common. Classically, these dermatologic problems are not associated with pruritus. However, 25 per cent of dogs with hyperadrenocorticism were described as pruritic because of seborrhea, calcinosis cutis, demodicosis, or pyoderma.[22]

The hair loss associated with Cushing's syndrome is one of the most common and major concerns for an owner. This slow, progressive problem may begin with hair loss at points of wear (such as bony prominences) and eventually involve the flanks, perineum, and abdomen. The end result (Figs. 118–7 and 118–8) is severe alopecia with only the head and distal extremities retaining a coat. Atrophy of hair follicles and the pilosebaceous apparatus with keratin accumulation within the hair follicle is common.

Endocrine alopecia commonly is associated with thyroid, ovarian, testicular, and GH disturbances as well as with hypercortisolism. Each of these disorders, especially hyperadrenocorticism, has potential for causing a bilaterally symmetric alopecia, which may be severe (see Figs. 118–6 to 118–8) or mild or involve a poor and abnormal hair coat (Fig. 118–9). Bilaterally symmetric alopecia has also been noted in cats with Cushing's, although this appearance is much less common than in dogs (Fig. 118–10). The alopecia is not always bilaterally symmetric and may not involve the trunk. Less than 10 per cent of dogs have alopecia that involves only the face.

Failure to Regrow Shaved Hair. Atrophy of the hair follicles disrupts the attachment of the hair shaft to the follicle, causing hair loss and lack of hair regrowth. If hair is shaved, regrowth is poor or nonexistent (Fig. 118–9), and any new hair is likely to be brittle, sparse, and fine.

Thin Skin, Pyoderma, Seborrhea. Thin skin, poor healing, and susceptibility to infection is typical of hypercortisolism in dogs and cats. The skin of these animals is thin and easily wrinkled. One often can view subcutaneous blood vessels with ease. In addition, keratin-plugged follicles (comedones) often are found around the nipples and groin and along the dorsal midline, although they may be present anywhere on the trunk. Pyoderma was observed in 55 per cent of hyperadrenal dogs. Skin infection is especially common along the dorsal midline and trunk. At times, it may be severe and may be worse in areas of hyperpigmentation. The suppressed immune system associated with hyperadrenocorticism exaggerates the problem. Among the less common infections is demodicosis.

In one study of 60 dogs, thin skin was observed in 13 per

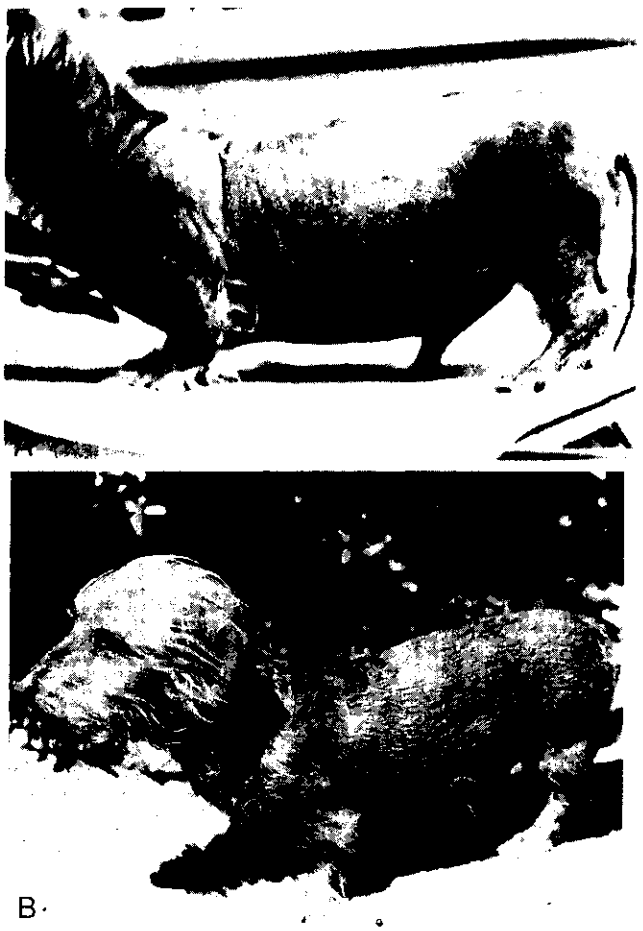

Figure 118–8. *A*, Dachshund with PDH, showing severe bilaterally symmetric alopecia. *B*, Same dog as in *A* 2 months after therapy with *o,p'*-DDD.

cent of hyperadrenal dogs. More than 33 per cent of dogs had a form of seborrhea, and comedones were observed in 5 per cent.[2] As previously described, many of the larger-breed dogs with muscle weakness spend much of their time lying down and tend to develop pressure ulcers, which may become in-

Figure 118–9. Several areas of this Cushing's syndrome dog's coat had been shaved 8 months earlier by a referring veterinarian before removing small skin tumors. Note the failure of the hair to grow back as well as the obvious scars from the surgeries. These scars are the result of poor wound healing with resultant striae formation.

Figure 118–10. This cat with PDH shows the resulting unkempt hair coat with patchy alopecia typical of the syndrome in this species.

fected and usually heal slowly, if at all. Management of these lesions requires treatment of the Cushing's, diligent cleaning, plus provision of soft bedding to minimize further trauma.

Bruising, Reduced Subcutaneous Fat, and Striae. The fragility observed with thin skin is also present in the blood vessels. Excessive bruising can follow venipuncture (Fig. 118–11) or other minor trauma. In a number of dogs

Figure 118–11. This dog with hyperadrenocorticism had two blood samples obtained from the jugular vein. The bruising was obvious within several hours.