CHAPTER 118

HYPERADRENOCORTICISM

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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.

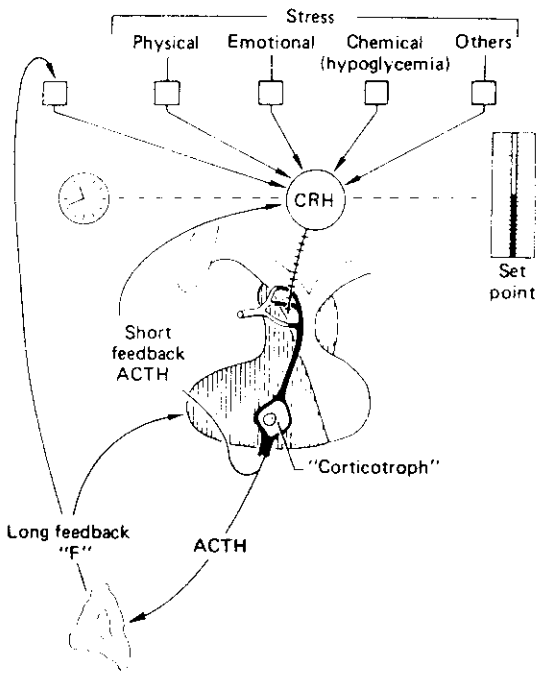

Figure 118–1. Hypothalamic-pituitary-adrenal axis, showing the various stimuli that enhance CRH secretion as well as negative feedback by cortisol (F) at the hypothalamic and pituitary levels. A short negative feedback loop of ACTH on the secretion of CRH is also shown.

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

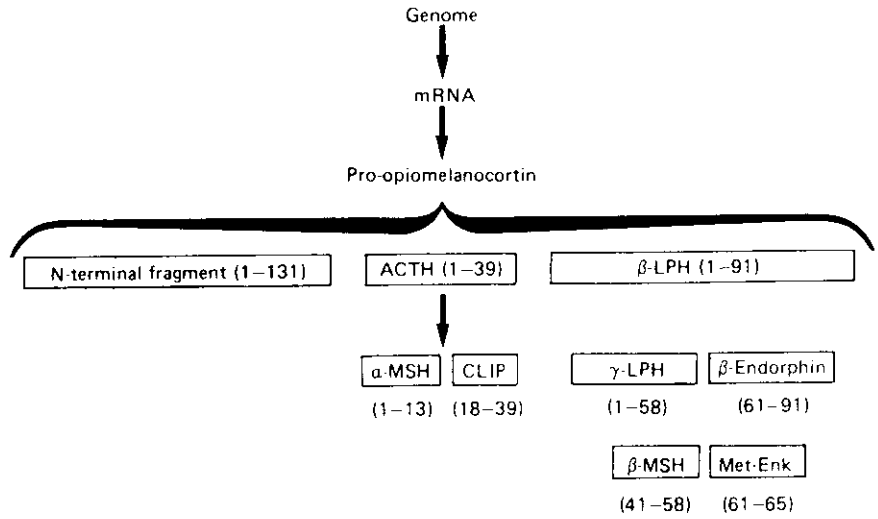

Figure 118–2. Processing of pro-opiomelanocortin into its biologically active peptide hormones. ACTH, adrenocorticotropic hormone; β-LPH, beta-lipotropin; α-MSH, alpha-melanocyte-stimulating hormone; CLIP, corticotropin-like intermediate-lobe peptide; γ-LPH, gamma-lipotropin; β-MSH, beta-melanocyte-stimulating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

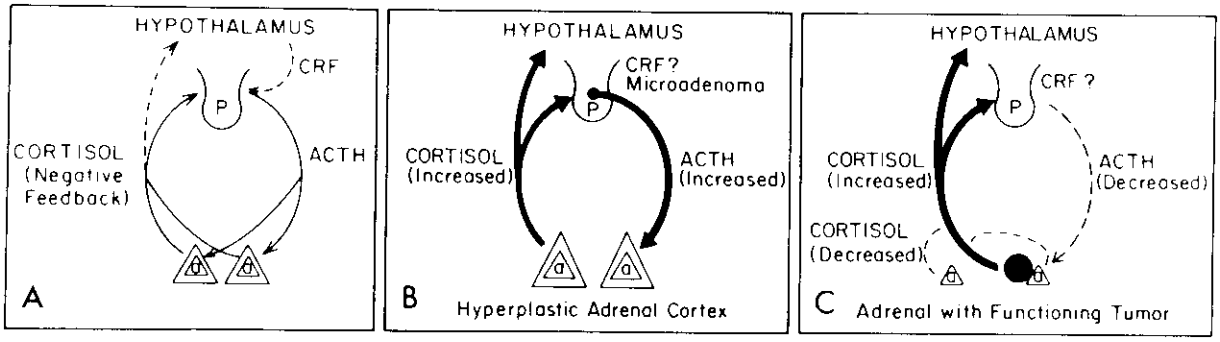

Figure 118–3. Pituitary-adrenal axis in normal dogs *(A)*, dogs with PDH *(B)*, and dogs with a functioning adrenocortical tumor *(C)*. a, adrenal; P, pituitary; CRF, corticotropin releasing factor.

"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.

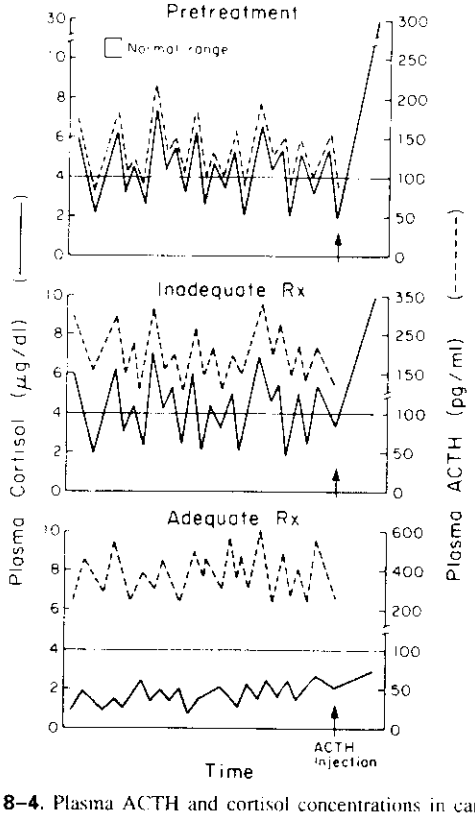

Figure 118–4. Plasma ACTH and cortisol concentrations in canine PDH before and after treatment with *o,p'*-DDD. Before treatment *(top panel)*, both ACTH and cortisol are secreted in a pattern of peaks and troughs, with frequent fluctuations above normal range throughout the day. During *o,p'*-DDD therapy, 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

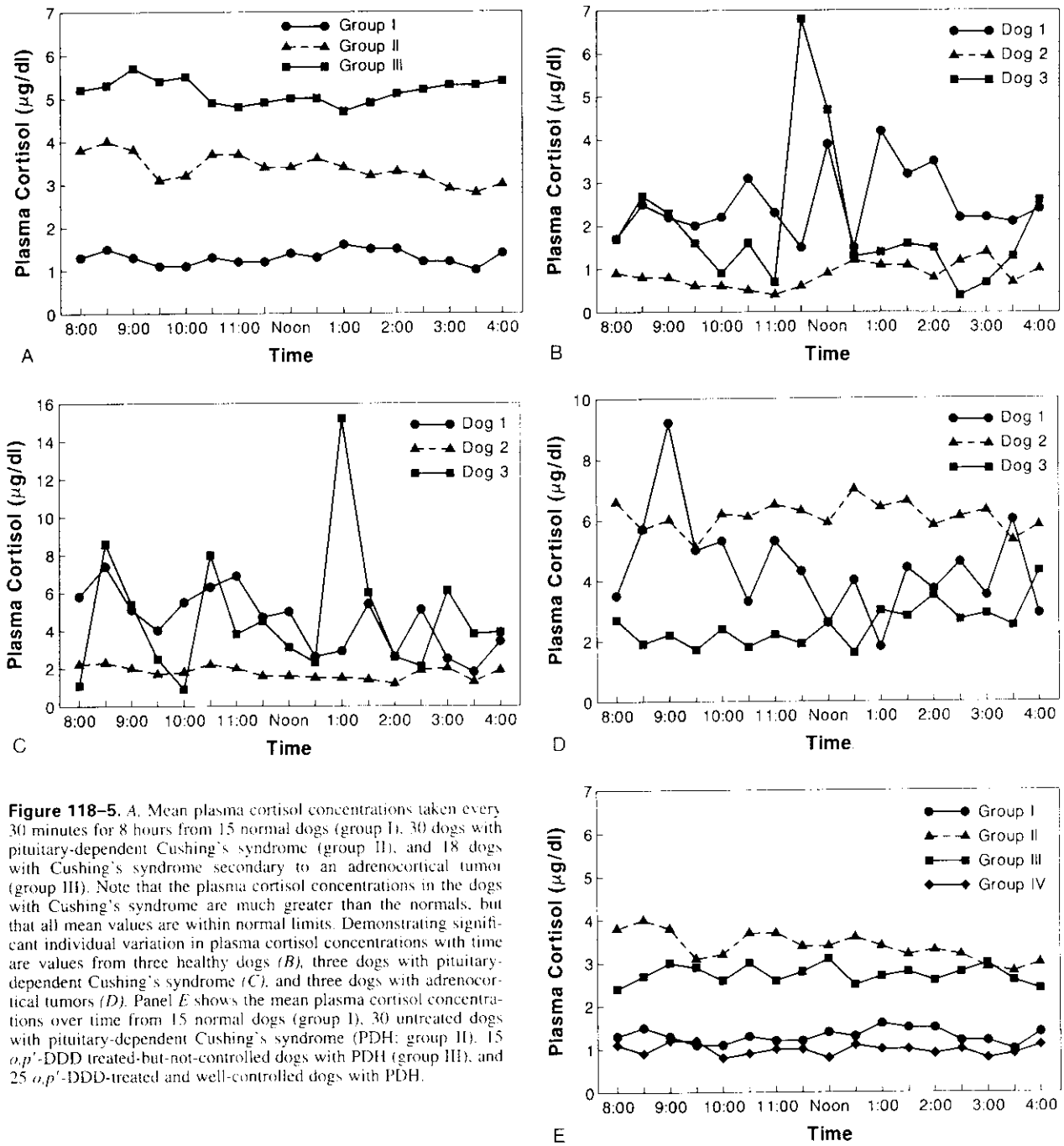

Figure 118–5. *A*, Mean plasma cortisol concentrations taken every 30 minutes for 8 hours from 15 normal dogs (group I), 30 dogs with pituitary-dependent Cushing's syndrome (group II), and 18 dogs with Cushing's syndrome secondary to an adrenocortical tumor (group III). Note that the plasma cortisol 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-

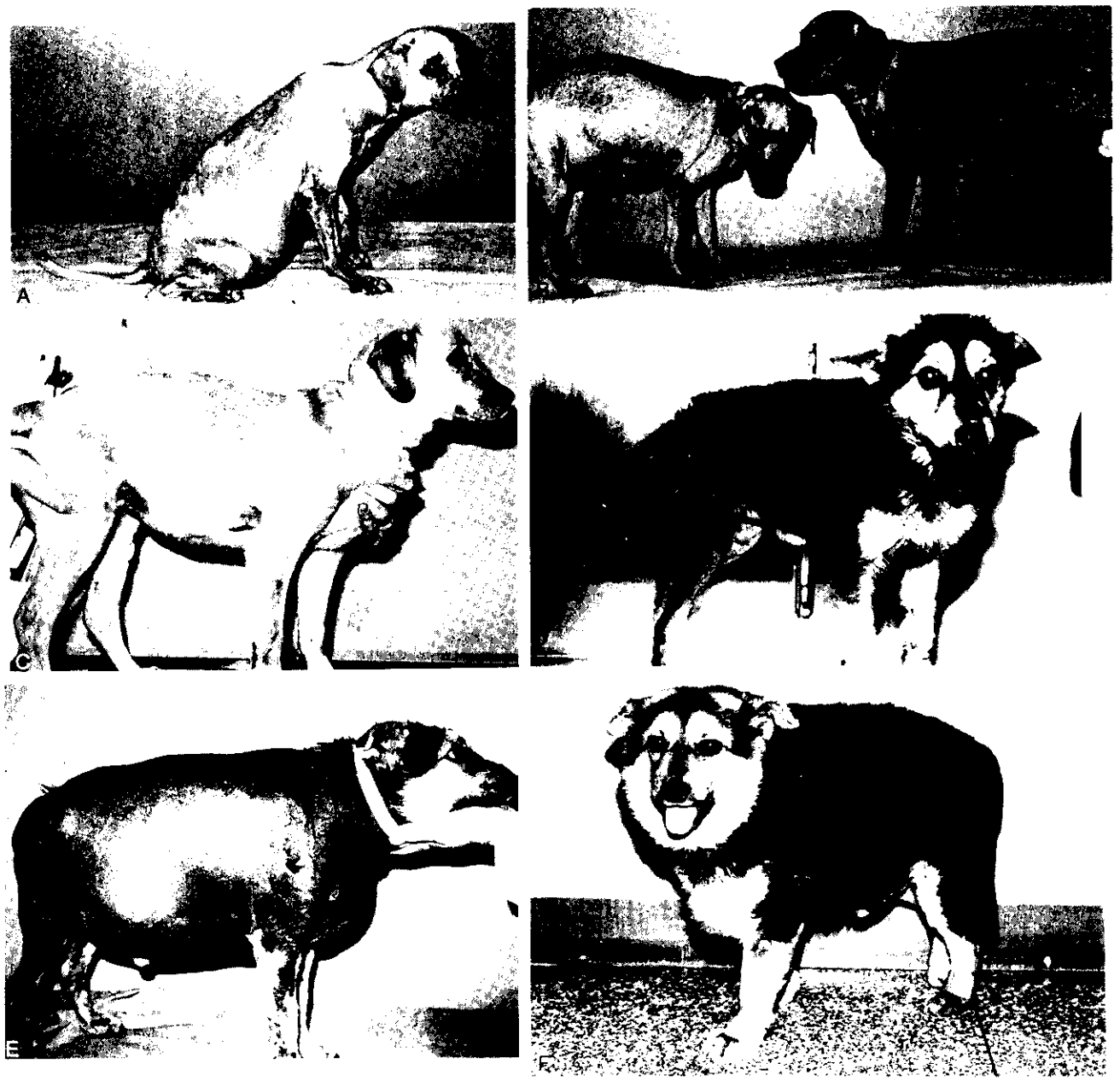

Figure 118–6. *A*, Mixed-breed 18 month old dog with hyperadrenocorticism. *B*, Same dog *(left)* and a normal littermate. *C*, Five months after initiation of *o,p'*-DDD therapy. *D*, A 6-month-old German shepherd with hyperadrenocorticism. *E*, Same dog as in *D* after 4 years without therapy. *F*, 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

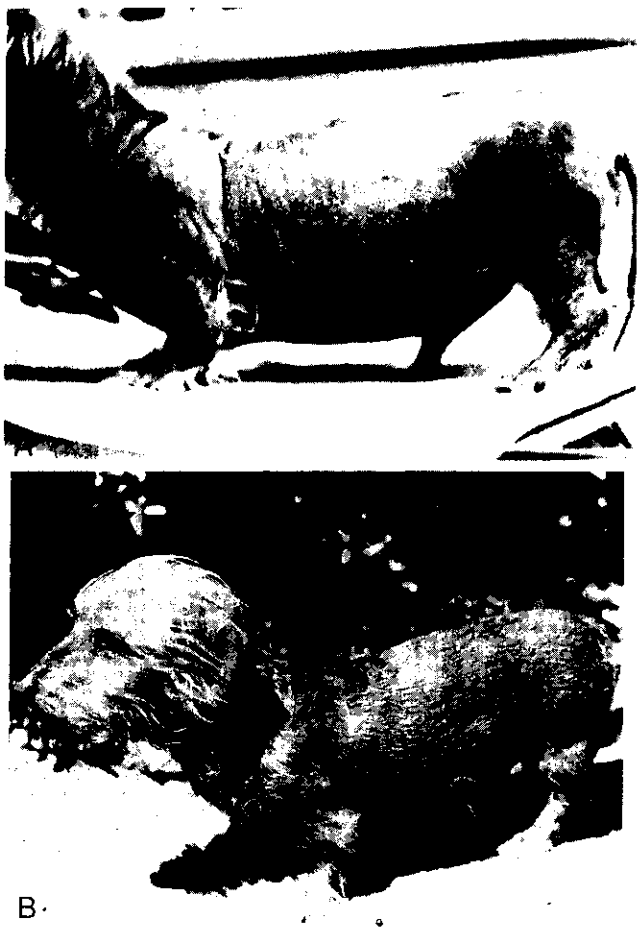

Figure 118–8. *A*, Dachshund with PDH, showing severe bilaterally symmetric alopecia. *B*, Same dog as in *A* 2 months after therapy with *o,p'*-DDD.

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.

that underwent ovariohysterectomy years before developing Cushing's syndrome, the metal sutures have caused bruising years later. These abnormalities are due to decreased subcutaneous tissue secondary to the hypercortisolism. Wounds that do heal do so tenuously, with fragile, thin scar tissue equivalent to the striae seen in humans (see Fig. 118–9). Healing skin lesions often undergo dehiscence because of the limited amount of fibrous tissue present.

Calcinosis Cutis. Calcium deposition in the dermis and subcutis is an uncommon but well-described sign associated with Cushing's syndrome. On examination, these areas feel like firm plaques in or under the skin, almost as if a collar stay were inserted into these areas. Common locations for this calcium deposition, called calcinosis cutis, include the temporal area of the head and the dorsal midline, neck, ventral abdominal, and inguinal areas (Fig. 118–12). The exact pathogenesis is not known.

Obesity

Owners of hyperadrenal dogs usually comment on their pets' apparent weight gain. In fact, dogs with hyperadrenocorticism do not usually gain a large amount of weight. Rather, these dogs have fat redistribution, as mentioned previously, and a potbellied appearance, which mimics weight gain. Truncal obesity is a classic symptom of Cushing's syndrome. In dogs and humans, it appears to occur at the expense of muscle and fat wasting from the extremities and subcutaneous stores; true obesity is present in less than one-half the dogs.

Respiratory Signs

Panting. Dogs with hyperadrenocorticism often are noted to be short of breath or to have a rapid respiratory rate while at rest. These animals have increased fat deposition over the thorax plus the wasting and weakness of the muscles involved in respiration. The increased pressure placed on the diaphragm due to fat accumulation in the abdomen and liver enlargement further accentuates disturbances in ventilatory mechanics. Coughing is not a common owner complaint.

Signs of mild respiratory distress are believed to be exaggerated by a marked reduction in expiratory reserve volume and decreased chest wall compliance, which increase the work of breathing. If such a dog also has a collapsing trachea (a common problem in smaller breeds), the combination of expiratory distress associated with the tracheal problem and the changes seen with obesity can cause marked respiratory signs. Similar problems can easily be appreciated if the obese dog also has chronic mitral and/or tricuspid valvular fibrosis. Signs become further exaggerated with the stress of excitement or exercise.

Thromboembolism. Thromboembolism is a recognized problem in humans and dogs with Cushing's syndrome. Dogs with pulmonary thromboembolism can have chronic signs or develop acute severe respiratory distress (described elsewhere in this chapter).

Testicular Atrophy or Failure to Cycle

A male dog with Cushing's syndrome usually has bilaterally small, soft, spongy testicles. A female dog with Cushing's commonly ceases estrus cycle activity. The duration of anestrus often reflects the duration of subclinical or clinical hypercortisolism. These would be unusual owner concerns because so many pets are old, neutered, or both. If the pet is intact, the owner either is unaware of the problem or associates the change with age (see Physical Examination).

Myotonia (Pseudomyotonia)

Rarely, dogs with hyperadrenocorticism develop a distinct myopathy characterized by persistent active muscle contraction after cessation of voluntary effort (this has been noted in only 5 of more than 800 dogs with Cushing's syndrome). Historically, these dogs have had a stiff gait (especially in the pelvic limbs) that was present from the time the other signs of hyperadrenocorticism developed. One of our dogs could not ambulate with its rear legs. Pelvic limb muscle stiffness is obvious on physical examination. Myotonic, bizarre high-frequency discharges are noted on electromyography. Histologic, electron microscopic, and histochemical findings in the musculature of several dogs with Cushing's myotonia are characteristic of noninflammatory degenerative myopathy. Clinical signs may improve after successful therapy for hyperadrenocorticism. The cause for this unusual phenomenon in hyperadrenocorticism is not known.

Figure 118–12. *A* and *B*, Areas of skin altered dramatically by calcinosis cutis.

Neurologic Problems

See section, Central Nervous System Signs.

Physical Examination

General Review

The physical examination on a typical dog with Cushing's reveals an individual that is stable and hydrated, has good mucous membrane color, and is not in distress. Veterinarians typically observe many of the signs seen by owners on physical examination of hyperadrenocorticism dogs. Among these abnormalities are abdominal enlargement, increased panting, truncal obesity, bilaterally symmetric alopecia, skin infections, and comedones (hair follicles filled with keratin and debris that usually are black and easily expressed). Hyperpigmentation, ectopic calcification, testicular atrophy, clitoral hypertrophy, hepatomegaly, and easy bruisability are common (Table 118–4). There is a remarkable variation in the number and severity of these signs. These dogs may have a single dominant sign, or 10 signs.

Hyperpigmentation

Hyperpigmentation may be diffuse or focal (see Fig. 118-8*A*). Histologically, there are increased numbers of melanocytes in the stratum corneum, basal epidermis, and dermal tissues. Because hyperpigmentation has been observed in dogs with either pituitary or adrenal causes for Cushing's syndrome, the likelihood of excess secretion of alpha-MSH, as a by-product of ACTH production (see Fig. 118–2), being the sole cause of hyperpigmentation is not strongly supported.[1]

Hepatomegaly

An enlarged liver is typical of hyperadrenocorticism, contributing to the abdominal enlargement previously discussed. The liver typically is swollen, large, and pale. Hepatomegaly is easily palpated because of the weak abdominal muscles. The liver may be so large in some dogs that the veterinarian may become suspicious of a large abdominal tumor or tense ascites.

Liver biopsy samples from animals with hypercortisolism usually reveal steroid hepatopathy: centrilobular hepatocytic vacuolation with few, often single, large vacuoles displacing the nucleus to the periphery of the cell. Hepatocellular glycogen accumulation is concentrated in periportal hepatocytes. Lipid deposits are not demonstrable with Sudan III stains, and hepatocellular necrosis, although present, is not a significant feature. Vacuolization alone can be caused by various problems. Steroid hepatopathy does imply chronic elevation in circulating glucocorticoids.

TABLE 118–4. PHYSICAL EXAMINATION FINDINGS IN DOGS WITH HYPERADRENOCORTICISM

Thin skin	Hepatomegaly
Bilaterally symmetric alopecia	Panting
Acne (skin infection, comedones)	Bruising
Cutaneous hyperpigmentation	Exophthalmos
Calcinosis cutis	Testicular atrophy
Abdominal enlargement	Clitoral hypertrophy
Muscle wasting of extremities	

Testicular Atrophy, Anestrus, and Clitoral Hypertrophy

The negative feedback effects of hypercortisolism result in decreased pituitary gonadotropin secretion. This explains the testicular atrophy, decreased libido, and depressed plasma testosterone concentrations typically seen in male dogs. Testicular androgen secretion is reduced, whereas adrenal androgen secretion is increased. The physiologic effect of adrenal androgens, however, is negligible in males, and the reduction in testicular androgren is significant. The final result is that these males are feminized. Plasma testosterone concentrations averaged 4.7 ng/ml in normal males versus the significantly lower 1.2 ng/ml in male dogs with Cushing's.[19]

In female dogs, negative feedback effects of hypercortisolism depress pituitary secretion of gonadotropins, as in males. This results in prolonged anestrus. Abnormal adrenal function in Cushing's results in excessive secretion of adrenal androgens, and their peripheral conversion results in clinical androgen excess (virilization). A small number of these dogs have clitoral hypertrophy. The average plasma testosterone concentration in normal female dogs was 20 pg/ml, whereas in females with Cushing's, it was 30 pg/ml.[19]

Ectopic Calcification

In addition to hyperadrenocorticism's causing the previously described calcinosis cutis, ectopic calcification has been seen involving the tracheal rings and bronchial walls, kidneys, and, rarely, major arteries and veins. This calcification may be noted only histologically in some dogs but occasionally will be visible radiographically. Calcific band keratopathy, a syndrome characterized by a gray-white superficial corneal opacity horizontally oriented in the interpalpebral opening, was reported in two dogs with hyperadrenocorticism.[34]

Bruisability

Easy bruisability is common after venipuncture in dogs and cats with Cushing's (see Fig. 118–11). This reflects the poor wound healing associated with suppressed tissue granulation secondary to glucocorticoid excess (see p. 1546.)

Sudden Acquired Retinal Degeneration Syndrome

A retinal disorder of unknown etiology, sudden acquired retinal degeneration syndrome, causes sudden and permanent blindness in adult dogs. The syndrome is characterized by noninflammatory degeneration and loss of retinal photoreceptors. An association with hyperadrenocorticism has been suggested.[35] Strong evidence has yet to be presented that confirms the presence of hyperadrenocorticism in a significant number of these dogs.

In-Hospital Evaluation

General Approach

A dog or cat suspected of having hyperadrenocorticism should be thoroughly evaluated before specific endocrine procedures are undertaken. Initial tests should include clinicopathologic studies (complete blood count [CBC]; urinalysis with culture; and a chemistry profile, including liver en-

zymes, renal function tests, calcium, phosphorus, sodium, potassium, cholesterol, blood glucose, total plasma protein, plasma albumin, and total bilirubin). In addition to blood and urine testing, abdominal ultrasonography (less ideally radiography) should be completed in these dogs and cats. Finding a large percentage of abnormalities on initial screening tests that are consistent with hyperadrenocorticism allows the veterinarian to establish a presumptive diagnosis (Table 118–5). The more expensive and sophisticated studies needed to confirm a diagnosis and localize the cause of the syndrome can then be presented to the client.

The initial results not only ensure that the veterinarian is pursuing the correct diagnosis but also alert the clinician to concomitant medical problems. These problems may be common (urinary tract infection) or unexpected (congestive heart failure), but in either case, they should not be ignored.

Complete Blood Count

Excessive production of cortisol results in neutrophilia and monocytosis caused by steroid-produced capillary demargination of these cells and by the subsequent prevention of normal egress of cells from the vascular system. Lymphopenia is probably the result of steroid lympholysis, and eosinopenia results from bone marrow sequestration of eosinophils. These changes are seen as a stress response in the white blood cell differential. About 80 per cent of hyperadrenal dogs have reduced lymphocyte and eosinophil counts, and 20 to 25 per cent have increased total white blood cell numbers. The red blood cell count usually is normal, although mild polycythemia occasionally may be noted because of the previously described ventilatory problems or, in females, because of androgen stimulation of the bone marrow.

TABLE 118–5. HEMATOLOGIC, SERUM BIOCHEMICAL, URINE, AND RADIOGRAPHIC ABNORMALITIES TYPICAL OF HYPERADRENOCORTICISM*

TEST	ABNORMALITY
Complete blood count	Mature leukocytosis
	Neutrophilia
	Lymphopenia
	Eosinopenia
	Erythrocytosis (females)
Serum chemistries	Increased alkaline phosphatase (sometimes extremely elevated)
	Increased ALT
	Increased cholesterol
	Increased fasting blood glucose
	Increased or normal insulin
	Abnormal bile acids
	Decreased BUN
	Lipemia
Urinalysis	Urine specific gravity <1.015, often <1.008
	Urinary tract infection
	Glycosuria (<10% of cases)
Radiograph/Ultrasound	Hepatomegaly
	Excellent abdominal contrast
	Pot belly
	Distended bladder
	Osteoporosis
	Calcinosis cutis/dystrophic calcification
	Adrenal calcification (usually adrenal tumor)
	Congestive heart failure (rare)
	Pulmonary thromboembolism (rare)
	Calcified trachea and mainstem bronchi
	Pulmonary metastasis of adrenal carcinoma
Miscellaneous	Low T_4/T_3 concentrations
	Response to TSH that parallels normal but both pre and post values are low
	Hypertension

*It would be unusual for an individual animal to have all these abnormalities.

Blood Glucose and Plasma Insulin

Dogs and cats with hyperadrenocorticism occasionally have mild increases in fasting plasma glucose concentrations and, less commonly, overt diabetes mellitus. Glucocorticoids increase gluconeogenesis and decrease peripheral utilization of glucose by antagonizing the effects of insulin. Glycosuria may be manifested if the renal threshold for plasma glucose (180 to 220 mg/dl) is exceeded. In comparing fasted normal dogs with fasted non-diabetic dogs with Cushing's (those without glucose in their urine), the average morning plasma insulin concentration was 12 μU/ml in the controls and 38 μU/ml in the dogs with naturally occurring hyperadrenocorticism. Plasma glucose concentrations averaged 85 mg/dl in the control dogs and 111 mg/dl in the hyperadrenal dogs.[19] In most dogs with Cushing's, the increased secretion of insulin partially controls carbohydrate intolerance but may not be adequate to normalize glucose parameters. These abnormalities usually dissipate with successful therapy for Cushing's syndrome.

Blood Urea Nitrogen

The diuresis stimulated by glucocorticoids causes a continual urinary loss of blood urea nitrogen (BUN). Because a differential diagnosis for polydipsia and polyuria in an older dog would be renal disease, the normal-to-decreased BUN values (similar results are seen in the creatinine concentration) quickly dismiss that concern.

Quite uncommonly, a dog is diagnosed with renal failure and concurrent hyperadrenocorticism. If the Cushing's diagnosis is certain, major concerns remain regarding treatment. Such a dog may be helped by the Cushing's (i.e., the appetite) and well-being may be enhanced by the cortisone excess. Further, renal perfusion may be enhanced by or hindered by the Cushing's condition.

Alanine Aminotransferase

The alanine aminotransferase (ALT) concentration commonly is elevated in dogs with Cushing's. This usually is a mild elevation believed to occur secondary to liver damage caused by swollen hepatocytes, glycogen accumulation, or interferences with hepatic blood flow. Hepatocellular necrosis, a minor but significant feature of steroid hepatopathy, is seen with enough frequency to account for mild increases in serum ALT.[19]

Alkaline Phosphatase

Sources. An increase in serum alkaline phosphatase (ALP) activity is the most common routine laboratory abnormality in canine hyperadrenocorticism.[26] ALP is increased in 95 per cent of dogs with hyperadrenocorticism. The serum ALPs are a group of enzymes that catalyze the hydrolysis of phosphate esters. The main source of ALP is the liver, with bone ALP contributing smaller amounts to the circulation. Both have serum half-lives of about 3 days. Intestinal, placental, and renal ALPs are not detectable in serum because their half-lives are only 3 to 6 minutes.[27]

Corticosteroid-Induced ALP. The major contributor to

the increased ALP in canine hyperadrenocorticism is induction of a specific and unique (to this species) isoenzyme of ALP by either endogenous or exogenous glucocorticoids.[28] In dogs with hyperadrenocorticism, 70 to 100 per cent of their ALP is specifically the steroid-induced fraction (SIALP). The subcellular source of this isoenzyme was found to be on the bile canalicular membrane of hepatocytes. ALP is one of the most common biochemical measurements used to screen for the presence of liver disease, and the ability to discriminate between steroid-induced and liver isoenyzmes of ALP is important. Heat inactivation is a reliable method for distinguishing between these two isoenzymes of ALP.[26] If a steroid-induced increase in ALP is established, further laboratory investigation to characterize a liver problem could be omitted. Alternatively, can identification of the steroid-induced isoenzyme be used to diagnose hyperadrenocorticism?

Several groups have evaluated the clinical application of assaying for SIALP. These studies have demonstrated rather uniform agreement. The greater the increase in ALP, the more reliable the results of SIALP measurement. SIALP is present in increased concentrations in most dogs with Cushing's. As such, the test is considered quite sensitive. The finding of increases in SIALP, however, is nonspecific. SIALP may be abnormal in dogs with primary hepatopathies as well as in those being treated with anticonvulsants, such as phenobarbital, diphenylhydantoin, and primidone. A major concern with an abnormal SIALP is the inability to distinguish three disorders commonly confused with naturally occurring hyperadrenocorticism: iatrogenic Cushing's, diabetes mellitus, and hepatopathies (Fig. 118–13). The conclusion reached by most groups has been that finding no SIALP in the serum may have diagnostic value in ruling out the diagnosis of hyperadrenocorticism but that an increase in SIALP can be caused by a variety of disorders and must be considered nonspecific.[28–32]

Cholesterol and Lipemia

Glucocorticoid stimulation of lipolysis causes an increase in blood lipid and cholesterol concentrations. Ninety per cent of dogs with Cushing's have increased plasma cholesterol concentrations. Lipemia is at least as frequent, and it may interfere with the accurate assessment of several clinicopathologic test results.

Serum Phosphate

Hypophosphatemia has been reported to occur in about one-third of dogs with hyperadrenocorticism.[23] This has been explained as resulting from a glucocorticoid-induced increase in the urinary excretion of phosphate.

BSP and Bile Acids

Bile acid measurements are more sensitive than the sulfobromophthalein (Bromsulphalein [BSP]) excretion and equivalent to ammonia tolerance tests in many conditions. These test results frequently are abnormal in dogs with Cushing's and do not aid in separating dogs with primary liver disorders from those with Cushing's.

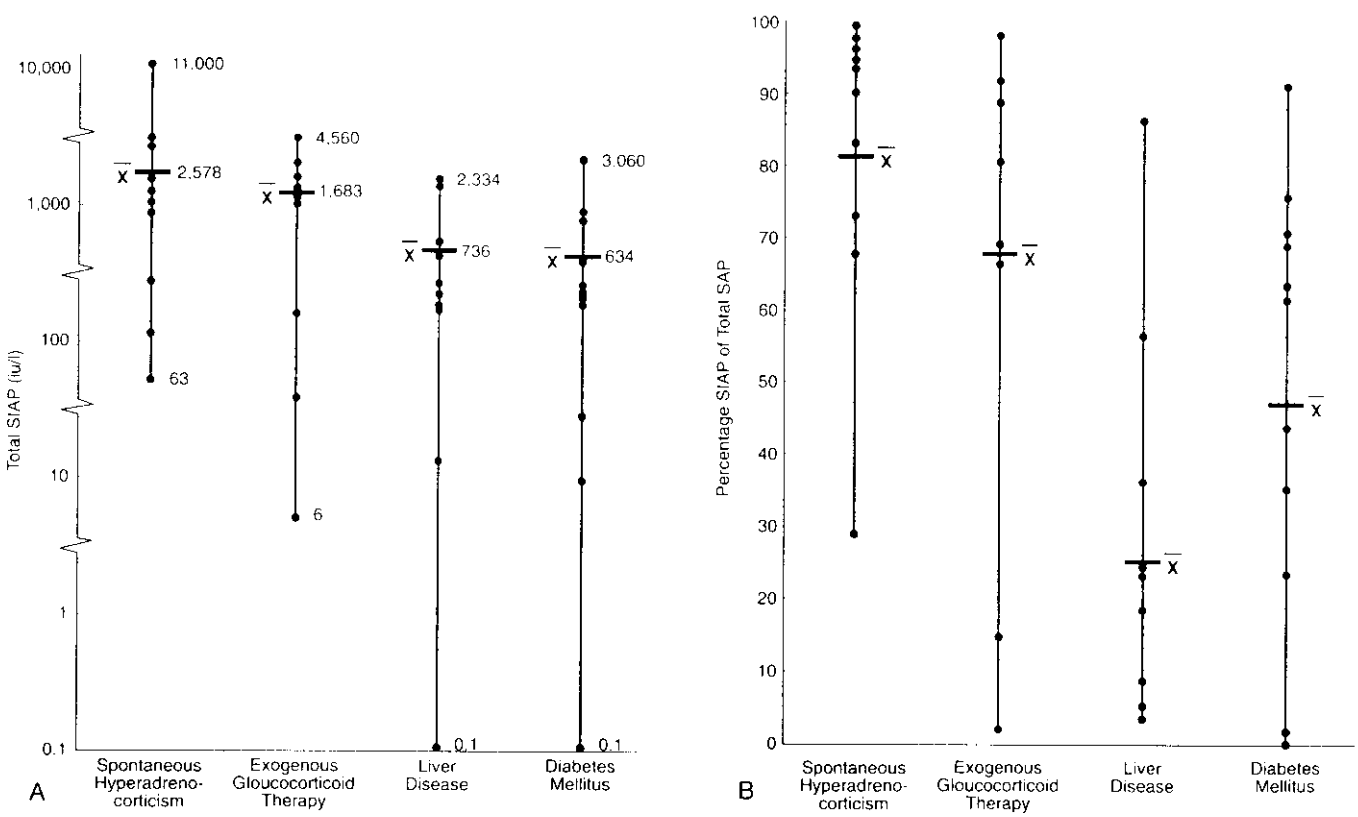

Figure 118–13. *A*, Group means and ranges of total serum steroid-induced alkaline phosphatase (SIAP) isoenzyme concentrations showing that this parameter lacks the specificity necessary to be a reliable screening test for canine hyperadrenocorticism. *B*, Percentage of total serum alkaline phosphatase (SAP), which is the steroid-induced isoenzyme of alkaline phosphatase (SIAP), by group.

Serum Electrolytes

Although of little diagnostic or clinical significance, mild abnormalities in the serum sodium (elevation) and potassium (depression) concentrations are seen in about one-half the dogs with Cushing's. Assessment of serum electrolyte concentrations becomes extremely important if a dog with hyperadrenocorticism develops anorexia, vomiting, or diarrhea because exaggerations of these abnormalities may become life-threatening.

Amylase and Lipase

If pancreatitis occurs, it is likely to be secondary to the lipemia or to the fact that such polyphagic dogs may eat garbage or large quantities of fat. In these instances, the lipase levels are elevated and may be an important diagnostic aid.

Urinalysis

Concentration. The urinalysis is perhaps one of the most important initial studies in the evaluation of a dog for hyperadrenocorticism. It is strongly recommended that owners obtain a urine sample by clean-catch before bringing the pet to the hospital or that a urine sample be collected at the time of initial examination. The most frequent abnormality is the finding of dilute urine (specific gravity less than 1.013), which occurs in 85 per cent of our cases. Other investigators have found dilute urine less frequently, perhaps because samples were obtained after the dogs had been hospitalized for hours or even days. It is less reliable to measure water intake in the hospital. Most water-deprived or frightened dogs with Cushing's can concentrate their urine to an osmolality well above plasma osmolality, although their concentrating ability usually remains less than normal.

Glucose. In addition to determining specific gravity, the veterinarian can assess the urine sample for the presence of glycosuria. Such a finding has been noted in 5 to 10 per cent of cases and would indicate that overt diabetes mellitus is present.

Infection. Because urinary tract infection is a common sequela to Cushing's, cystocentesis urine for culture should be obtained. About 50 per cent of dogs with Cushing's have a urinary tract infection at the time of initial examination. There are several potential explanations for this worrisome incidence of infection. First, glucocorticoid excess does increase the risk for infection. Second, the polyuria combined with muscle weakness in housebroken dogs creates a potential for bladder retention of urine, despite urination. Finally, dilute urine increases susceptibility to lower urinary tract infection.[33] Thus, the bladder constantly has dilute urine, which acts as a ready site for infection in an immunosuppressed dog. Control of these infections is important, although in some dogs, the infection is difficult to resolve because of pyelonephritis.

Thyroid Function Tests

Some of the clinical signs of hypothyroidism overlap with those of Cushing's (i.e., listlessness, bilateral symmetric nonpruritic alopecia, apparent weight gain, hypercholesterolemia). Chronic hypercortisolism (iatrogenic or naturally occurring) suppresses pituitary secretion of TSH, leading to secondary hypothyroidism.[34] Hypercortisolism may also change thyroid hormone binding to plasma proteins, enhance the metabolism of thyroid hormone, and decrease peripheral deiodination of thyroxine (T_4) to triiodothyronine (T_3). About 70 per cent of dogs with naturally occurring Cushing's have decreases in basal serum T_4, free T_4, and/or T_3 concentrations. Administration of TSH increased serum T_4 concentrations in a manner parallel to normal but usually not to normal concentrations (Fig. 118–14).[23, 35, 36]

Radiographs

General Approach. Radiographs of the chest and ultrasonography of the abdomen (the preferred tool for evaluating the abdomen) should be used in looking for changes consistent with the diagnosis of Cushing's. Veterinarians should also remember that most of these dogs are older and may have serious concurrent (perhaps subclinical) diseases that may be revealed radiographically.

Abdominal Detail and Hepatomegaly. Good contrast usually is observed in dogs and cats with Cushing's because of abdominal fat deposition. The potbellied appearance (60 per cent of dogs with Cushing's) and hepatomegaly may be obvious. About 80 to 90 per cent of these dogs have hepatomegaly. There is no obvious association between the duration of illness and the degree of hepatomegaly.[37]

Urinary Bladder. Distention of the urinary bladder may be seen radiographically. Some of these dogs have atonic bladders and may not be capable of voiding completely, maintaining large, partially filled bladders (Fig. 118–15).

Visualizing the Adrenals. Perhaps the most important but least common finding on abdominal radiographs is an adrenal mass. Positive identification of such a mass occurs infrequently because only 10 to 20 per cent of dogs with

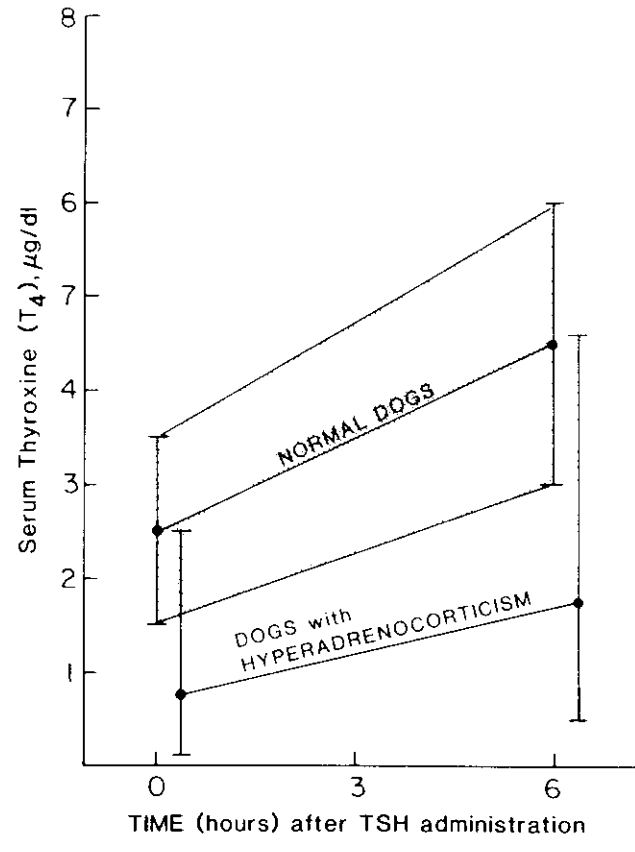

Figure 118–14. T_4 concentrations before and after TSH administration in normal dogs and those with hyperadrenocorticism. The Cushing's syndrome dogs may have normal or below normal values which parallel normal increases in serum T_4 concentrations.

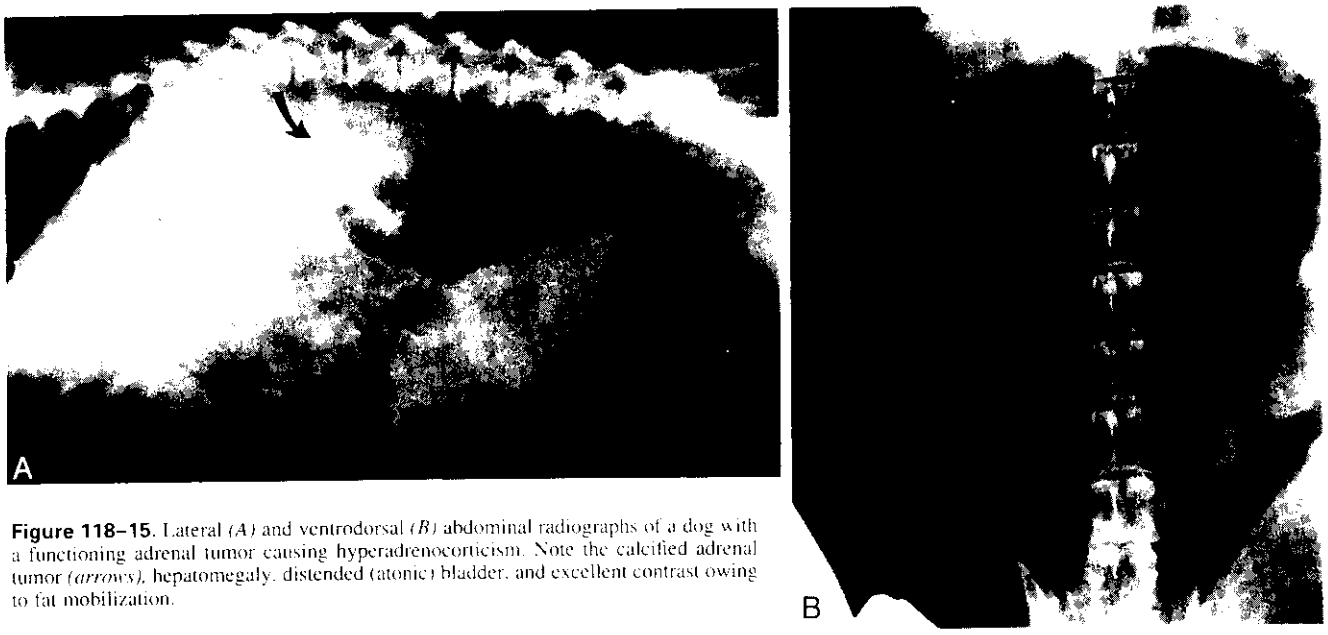

Figure 118–15. Lateral *(A)* and ventrodorsal *(B)* abdominal radiographs of a dog with a functioning adrenal tumor causing hyperadrenocorticism. Note the calcified adrenal tumor *(arrows)*, hepatomegaly, distended (atonic) bladder, and excellent contrast owing to fat mobilization.

naturally occurring hyperadrenocorticism have an adrenocortical tumor, and only about 50 per cent of these can be visualized radiographically because of calcification. Adenomas and carcinomas are calcified in relatively equal numbers (see Fig. 118–15).[12, 37, 38]

Osteoporosis. A distinct reduction in the radiographic density of the lumbar vertebral bodies relative to vertebral end plates may be detected in about 15 per cent of dogs with Cushing's syndrome. Glucocorticoids have a catabolic effect on bone matrix, increase urinary calcium excretion, and inhibit gastrointestinal absorption of calcium by interfering with the action of vitamin D. Thus, depletion of matrix accompanied by loss of mineral may be the cause of osteoporosis.

Dystrophic (Ectopic) Calcification. Radiographic signs of calcinosis cutis are seen in 10 to 20 per cent of dogs with Cushing's syndrome; a smaller number have dystrophic calcification that involves the renal pelvis, liver, gastric mucosa, or branches of the abdominal aorta. Ectopic calcification frequently is seen involving the tracheal rings and mainstem bronchi. Calcification of these structures, however, can be seen in normally aging dogs.

Thoracic Radiographs. The most common finding is calcification of tracheal rings. Osteoporosis may be suspected from the appearance of the thoracic vertebrae. Most important, radiographs must be evaluated for evidence of adrenocortical carcinoma lung metastasis, which occurs in a small percentage of these dogs. Another major concern is pulmonary thromboembolism.

Skull. Radiographs of the skull are not recommended. The studies usually are normal and require anesthesia. The bone destruction seen in the area of the sella turcica of some people with expanding pituitary tumors is not seen in the dog.

Ultrasonography

Background. Perhaps more than with any other tool, the value of ultrasonography directly correlates with the skill of the operator. Transverse, longitudinal, and oblique scanning from the ventral abdomen must be performed to thoroughly evaluate the adrenals.[39] Most (75 to 85 per cent) normal dog adrenals and 50 to 60 per cent of normal cat adrenals can be visualized.[40-42] In our recent experience, these estimates are quite conservative.[40] In both species, the left adrenal is easier to visualize than the right because of overlying bowel and several other factors.

Dogs or Cats with Cushing's. In hyperadrenocorticism, abdominal ultrasonography serves three major functions. First, it is part of the routine data base used to evaluate the abdomen for unexpected abnormalities (e.g., urinary calculi, masses, cysts). Second, if an adrenal tumor is identified, ultrasound is an excellent screening test for hepatic or other organ metastasis, tumor invasion of the vena cava or other structures, and compression of adjacent tissues by a tumor. Third, the study is used to evaluate the size and shape of the adrenals. If bilaterally normal-sized or large adrenals are visualized in a dog or cat otherwise diagnosed as having Cushing's, this is considered strong evidence in favor of adrenal hyperplasia caused by pituitary-dependent disease. Visualization of a normal or slightly enlarged left adrenal is nonspecific evidence that weakly points toward pituitary dependence. Visualization of only the right adrenal is considered suspicious because this adrenal usually is more difficult to see. If either adrenal is remarkably enlarged, irregular, or invading or compressing adjacent structures and the opposite adrenal cannot be visualized, suspicion of an adrenal tumor is heightened (Fig. 118–16).

Incidentally Discovered Adrenal Mass. With the increased use of sophisticated aids for evaluating the abdomen, unsuspected abnormalities are being identified with increased frequency. As many as 2 per cent of humans evaluated with ultrasonography and imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) have an adrenal mass.[43, 44] Dogs with clinical evidence of hyperadrenocorticism that have an adrenal mass should be evaluated for an adrenocortical tumor. If the dog or cat with an adrenal mass has no historical or physical examination findings suggestive of Cushing's, endocrine evaluation is not recommended. Some adrenal masses are normal. Other differential diagnoses include adrenal cysts, myelolipomas, hemorrhage, non-functioning (non–hormone-producing) tumor, pheochromocytoma, metastatic tumor, and granuloma.

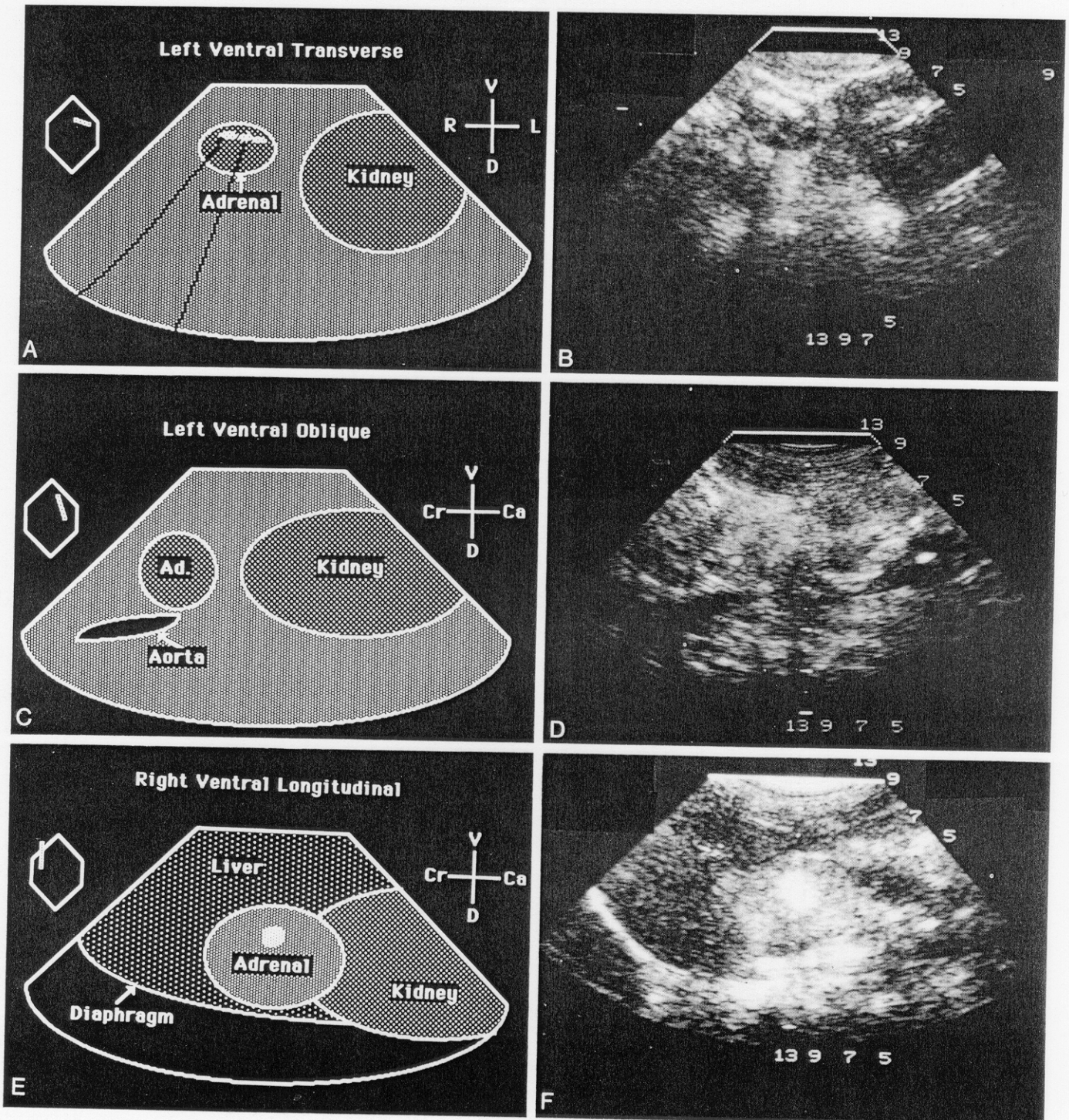

Figure 118–16. *A*, Diagrammatic illustration of the ultrasound image shown in *B*, showing the appearance of a calcified adrenal carcinoma in a dog with hyperadrenocorticism. *C*, Diagrammatic illustration of the ultrasound image shown in *D*, showing a hyperplastic adrenal gland in a dog with PDH. *E*, Diagrammatic illustration of the ultrasound image shown in *F*, showing the opposite hyperplastic adrenal in the same dog with bilateral adrenal hyperplasia. V, ventral; D, dorsal; Cr, cranial; Ca, caudal; the symbol in the upper left corner of *A*, *C*, and *E* is the location and orientation of the transducer in the ventral abdomen. (*A*, *C*, and *E* used courtesy of Dr. Brett Kantrowitz; *B*, *D*, and *F* from Kantrowitz BM et al.: Vet Radiol 27:15, 1986. Used with permission.)

Associated Medical Complications

Most dogs with hyperadrenocorticism are stable and not severely ill when initially examined. However, various problems may arise secondary to prolonged steroid excess. In a few circumstances, such problems can be catastrophic.

Hypertension

Hypertension has been documented in more than 90 per cent of humans with naturally occurring hyperadrenocorticism. Multiple factors have been implicated in this hypertension, including excessive production of renin substrate (the circulating protein that acts to release angiotensin I), activation of the renin-angiotensin system by means of alternative stimulators, enhanced vascular sensitivity to pressors (e.g., catecholamines, adrenergic agonists), reduction of vasodilator prostaglandins, and increased secretion of non–zona glomerulosa mineralocorticoids.[45,46]

Why be concerned about hypertension? Specific problems are related to this disorder. Hypertension-induced blindness may be due to intraocular hemorrhage and/or retinal detachments.[47] Hypertension may exacerbate left ventricular hypertrophy, heart failure, and glomerulopathies. The latter may predispose these dogs to thromboembolic disorders. More than 50 per cent of dogs with Cushing's syndrome are hypertensive on random testing.[48] Normal dogs have systolic, diastolic, and mean blood pressures of about 150, 90, and 110 mmHg, respectively. Dogs with Cushing's have systolic, diastolic, and mean blood pressures of 180, 120, and 145 mmHg, respectively. Hypertension may resolve after resolution of the Cushing's.

Pyelonephritis and Urinary Calculi

As previously reviewed, urinary tract infections are common in dogs with Cushing's, and such infections can ascend to the kidneys. Lowered resistance to infection may result from glucocorticoid inhibition of neutrophils and macrophages into infected areas, and dilute urine increases susceptibility to lower urinary tract infection but decreases susceptibility to pyelonephritis.[33] The anti-inflammatory effects of glucocorticoids not only predispose to these problems but often mask clinical signs. Suspicion of pyelonephritis should be raised if a urinary tract infection cannot be cleared, even after proper antibiotic therapy. Pyelonephritis is difficult to diagnose without contrast (dye) studies or biopsy.

About 5 to 10 per cent of dogs with Cushing's syndrome have urinary calculi. Glucocorticoids increase calcium excretion, which may result in calculi formation. Further, the increased incidence of infection contributes to calculi. Dysuria, a major sign caused by urolithiasis, may not be obvious (masked) because the glucocorticoid excess may interfere with inflammation.

Glomerulopathies

The incidence of glomerulopathies in dogs with Cushing's exceeds 50 per cent. This protein loss seldom causes significant hypoalbuminemia and has not been related to development of edema, ascites, or pleural effusion. Whether these losses relate to other documented problems in Cushing's (e.g., hypertension, pyelonephritis [sepsis], thromboembolism) remains to be seen.

Congestive Heart Failure

One sequelae of excess glucocorticoids is hypertension resulting from hypervolemia, which may increase the workload of the myocardium and cause myocardial hypertrophy. Congestive heart failure may occur as hypertension and fluid retention become severe.

Pancreatitis

Dogs with hyperadrenocorticism have been described as being predisposed to development of pancreatitis. Although various facets of Cushing's fit this impression (e.g., hyperlipidemia, hypercholesterolemia, infection), pancreatitis is not common.

Diabetes Mellitus

Diabetes mellitus is an extremely straightforward disease to diagnose in dogs and cats. Hyperadrenocorticism is not as easily diagnosed, but the clinical picture of Cushing's is striking, making the diagnosis in most dogs relatively uncomplicated. It is easy to realize when a dog with established Cushing's develops diabetes mellitus because of a sudden increase in thirst, urine output, and glucose in the urine. A major dilemma is encountered, however, when attempting to determine whether a dog or cat with established diabetes mellitus has Cushing's.

The major clue used by practitioners is the presence of insulin resistance. Resistance, however, is a subjective phenomenon that has myriad differential diagnoses. The clinician is best served by relying on the clinical presentation of the dog. Does it have an appearance consistent with the diagnosis of Cushing's? This question deserves careful consideration because the clinical signs (polydipsia, polyuria, polyphagia, hepatomegaly) and the CBC (increase in white blood cell count, and stress leukogram), serum chemistry profile (increases in cholesterol, ALP, and ALT), radiograph, and ultrasound results of the two diseases are similar. The urine of a dog with diabetes usually is more concentrated than that of a dog with Cushing's and diabetes, but with either condition dogs are prone to infection.

Pulmonary Thromboembolism

Pulmonary thromboembolism is a potential complication of hyperadrenocorticism as well as of several other disorders (e.g., amyloidosis, renal failure, pancreatitis, sepsis, diabetes mellitus). Thromboembolism is no doubt related to the hypercoagulable state typical of Cushing's. In Cushing's, this embolic tendency may be related to glomerular protein loss resulting in antithrombin III alterations and/or increased concentrations of coagulation factors V, VIII, IX, and X as well as fibrinogen and plasminogen. Increases in antithrombin III and fibrinogen are inconsistent with the development of a hypercoagulable state. Additional predisposing factors include obesity, hypertension, increased hematocrit (resulting in vascular stasis), sepsis, and prolonged periods of recumbency.[49]

Most of our dogs that have developed this serious complication had recently undergone medical treatment for Cushing's syndrome or had an adrenocortical tumor surgically removed when the embolic episode began. Most of these dogs have acute respiratory distress, orthopnea, and, less commonly, a jugular pulse. Panting may occur secondary to hypoxia and/or pleuritic pain. Radiographs of the thorax may reveal no abnormalities or pleural effusion. Alternatively,

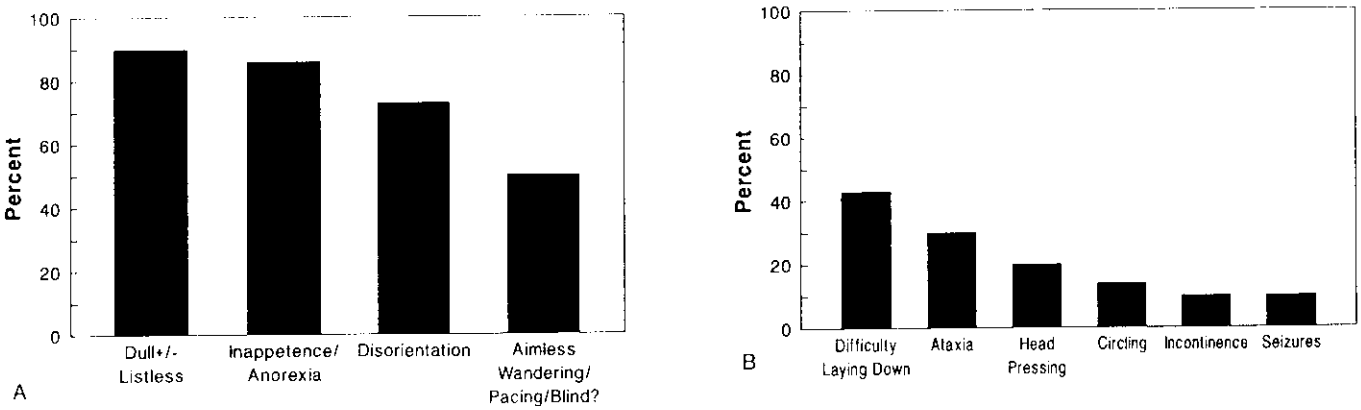

Figure 118–17. Common clinical signs observed by owners and veterinarians in dogs with large pituitary tumors that are causing CNS signs.

there may be an increased diameter and blunting of the pulmonary arteries, lack of perfusion of the obstructed pulmonary vasculature, and overperfusion of the unobstructed pulmonary vasculature. Arterial blood gas analysis demonstrates decreases in the P_{O_2} (mmHg) to the mid-50s to mid-60s (normal, 80 to 100 mmHg) and decreases in the P_{CO_2} (mmHg) to 17 to 30 (normal, 35 to 45 mmHg). Thrombosis may be confirmed with angiography of the lungs or with a radionuclear lung scan. Therapy consists of general support, oxygen, anticoagulants (heparin and/or a coumarin compound), and time. The prognosis for this condition is grave.

Central Nervous System Signs

Pathophysiology. PDH occasionally results from a functioning, large (greater than 1 cm in diameter) pituitary tumor. Such a mass with dorsal expansion may compress the optic chiasm and hypothalamus, invaginate the pituitary stalk that connects the hypothalamus with the pituitary, and dilate the infundibular recess and third ventricle. The clinical signs exhibited by dogs with macrotumors often reflect both the endocrine and the space-occupying effects of the tumor. The endocrine manifestations are those signs that are typical of Cushing's. Synthesis and/or secretion of all anterior pituitary hormones is suppressed by excesses in cortisone, making the diagnosis of hypopituitarism resulting from tumor destruction almost impossible to confirm.

Identification of a pituitary tumor that will cause clinical signs because of its mass is difficult. We evaluated 21 dogs with untreated and recently diagnosed PDH with no clinical signs suggestive of a large intracranial mass. Each dog underwent brain magnetic resonance imaging. Eleven of these dogs had easily visualized pituitary tumors (3 to 13 mm at greatest vertical height). No clinical or endocrine tests distinguished dogs with large tumors from those with tumors smaller than 3 mm.[17] In studies of dogs with PDH and clinical signs caused by enlarging pituitary tumors, no data base or endocrine test result consistently distinguished dogs with small tumors from those with large tumors or distinguished dogs that had clinical signs of an intracranial tumor from those that did not.[8, 50]

Clinical Signs. Most dogs with PDH with a pituitary mass greater than 1 cm in diameter do not have clinical signs because of the tumor size. When neurologic signs are recognized, they are almost always subtle but obvious to an owner. Such signs, however, may not be obvious to a veterinarian. Therefore, knowing the owner and his observation skills are important. Signs commonly reported include dullness, listlessness, and a poor appetite. The signs may progress to anorexia, restlessness, loss of interest in normal household activities, delayed response to stimuli, and brief episodes of disorientation. The differential diagnosis for these signs includes mitotane (*o,p'*-DDD; Lysodren) overdosage. More definitive signs exhibited by dogs with macrotumors include altered mentation (obtundation, stupor), ataxia, tetraparesis, and aimless pacing (Fig. 118–17). Less frequently observed problems include nystagmus, circling, head pressing, behavior changes, blindness, seizures, and coma. Anisocoria, strabismus, and facial paralysis may result from damage to cranial nerves. Blindness may be misdiagnosed because mental dullness results in inappropriate responses to visual stimuli (absent menace).

Diagnosis. Macrotumor syndrome has been diagnosed before Cushing's is diagnosed (less than 25 per cent of dogs), within 30 to 60 days (25 to 35 per cent) or greater than or equal to 6 months after (40 to 60 per cent of dogs) beginning treatment for Cushing's. The diagnosis of macrotumor is dependent on eliminating a concurrent illness or *o,p'*-DDD overdosage, which might explain clinical signs. No endocrine test results reliably correlate with the size of a pituitary tumor.[8, 17, 50] The diagnosis can be confirmed only with advanced imaging technology (CT or MRI).

Differential Diagnosis

The combination of clinical signs seen in most dogs with hyperadrenocorticism is strongly suggestive of the final diagnosis. With most dogs, the veterinarian gains a suspicion of Cushing's after completing the history and physical examination. As seen in Table 118–6, however, several diseases do have signs, with or without laboratory data, that may overlap with those of Cushing's. The obvious differential diagnoses include diabetes mellitus, acromegaly, diabetes insipidus, kidney disease, liver disease, pyelonephritis, hypothyroidism, hyperthyroidism, Sertoli cell tumors, and hypercalcemia. The endocrine alopecia and hyperpigmentation found in dogs with adult-onset GH deficiency may mimic the dermatologic signs of Cushing's.

Specific Evaluation of the Pituitary-Adrenocortical Axis

General Approach

Data Base. After establishing a presumptive diagnosis of canine or feline hyperadrenocorticism from review of the

TABLE 118–6. DIFFERENTIAL DIAGNOSES FOR CANINE CUSHING'S SYNDROME (CCS) AND MAJOR AREAS OF OVERLAP

DIFFERENTIAL DIAGNOSIS	OVERLAP WITH CCS
Diabetes mellitus	PD/PU/polyphagia ↑ ALP, ↑ ALT, ↑ FBG, ↑ Cholesterol Hepatomegaly Urinary tract infection
Kidney disease	PD/PU
Liver disease	Hepatomegaly ↑ ALP, ↑ ALT, ↑ liver function test results
Hypothyroidism	Bilaterally symmetric alopecia Apparent weight gain ↑ Cholesterol
Sertoli cell tumor	Bilaterally symmetric alopecia
Pyelonephritis	Chronic recurring urinary tract infection PD/PU
Hypercalcemia	PD/PU
Diabetes insipidus	
Nephrogenic	PD/PU
Central	PD/PU
Primary (psychogenic) polydipsia	PD/PU/polyphagia
Acromegaly	Poor hair coat PD/PU ↑ ALP Enlarged abdomen Muscle weakness Inspiratory stridor ↑ Blood glucose Hepatomegaly
Ascites	Enlarged abdomen (may be difficult to palpate)
Anticonvulsant therapy	PD/PU Lethargy Polyphagia ↑ ALP, ↑ ALT Abnormal plasma cortisol concentrations

ALP, alkaline phosphatase; ALT, alanine aminotransferase; FBG, fasting blood glucose; PD, polydipsia; PU, polyuria.

owner's impressions, physical examination, laboratory data base, radiographs, and/or ultrasonography, the clinician usually attempts to confirm the diagnosis. When necessary and if possible, an attempt can also be made to determine the source of the disorder.

Endocrine Assays. The mainstay of these diagnostic procedures is the measurement of plasma, serum, or urine cortisol concentrations, based on commercially available radioimmunoassays (RIAs). These tests are reliable, inexpensive, easily performed, and commonly used. Commercially available plasma ACTH assays are also being used more frequently, although the hormone is more fragile and the assays more expensive.

Cortisol Collection Method. Heparinized blood should be centrifuged soon after obtaining the sample, with the separated plasma placed in a clean vial and frozen. Cortisol concentrations in frozen plasma are stable for long periods. Hemolysis or storage of samples at warm temperatures for short periods has little effect on assay results.[51]

Plasma Aldosterone Assays. Various commercially available kits for aldosterone assays are valid for samples from dogs and cats. There are few situations, however, in which this information is necessary to the diagnosis of hyperadrenocorticism. When specific aldosterone-related disorders are suspected, it is reasonable to assess plasma aldosterone concentrations.

Endocrine Testing

The evaluation of an animal suspected of having hyperadrenocorticism proceeds through two basic steps (Fig. 118–18). The first stage is to confirm or deny the presence of Cushing's. The second stage consists of differentiating PDH from adrenal tumor–dependent hyperadrenocorticism.

Screening Tests

Urinary Corticosteroids

24-Hour Collection and Assay. Traditionally, an aliquot of urine from a sample collected over 24 hours provides an integrated assessment of the amount of hormone produced over time. This has been the gold standard used in the diagnosis of humans with hyperadrenocorticism for decades, and it continues to be the most reliable means of confirming a diagnosis. Despite the advantages recognized as inherent with this diagnostic tool, the cumbersome nature of collecting urine for this test has made it rarely used in dogs and cats. When used, the testing is reliable.

Urine Cortisol-Creatinine Ratio. Studies have demonstrated that the ratio of cortisol to creatinine concentration from a single, randomly obtained voided urine sample provided information that aided in identifying people with hyperadrenocorticism.[52, 53] Similar studies in dogs revealed that measurement of the urine cortisol-creatinine (C/C) ratio had potential as a screening test for hyperadrenocorticism.[54] There is general agreement that the urine C/C ratio readily distinguishes between apparently healthy dogs and those with hyperadrenocorticism[55] but that the test lacks specificity; that is, it was abnormal in dogs with Cushing's, but it was also abnormal in dogs with diabetes mellitus, diabetes insipidus, pyometra, hypercalcemia, and liver failure (Fig. 118–19).[56, 57]

Choosing a screening test for hyperadrenocorticism is important because that test may determine whether or not a dog is treated. Routinely used screening tests include ACTH stimulation, low-dose dexamethasone, and urine C/C ratio. Recommendations regarding treatment should be based on the history, physical examination, and data base results as well as the results of a screening test. No screening test is perfect.

Resting (Basal) Plasma Cortisol Concentrations. Basal (morning) plasma cortisol determination is, by itself, of little diagnostic value. The mean resting plasma cortisol concentration in dogs with Cushing's is significantly above that of normal dogs, but individual test results usually are within the normal range (see Fig. 118–5). Both ACTH and cortisol are secreted episodically. Dogs with hyperadrenocorticism have a greater frequency of cortisol bursts as well as increased amounts of cortisol in each surge. For the most part, these bursts result in cortisol concentrations in the plasma that overlap with normal. During any 24-hour period, however, this hormonal profile creates a relative excess in the amount of cortisol secreted. Over a period of months or years, the clinical syndrome of Cushing's results from this chronic and unrelenting pattern of cortisol excess.

ACTH Stimulation Test

History. The ACTH stimulation test has commonly been used for the diagnosis of hyperadrenocorticism. The test is safe, simple, relatively inexpensive, and not time-consuming. Results of the ACTH stimulation test have undergone critical studies that have revealed the test's weaknesses and strengths.

Theory. Dogs and cats with pituitary-dependent Cushing's have adrenal hyperplasia secondary to chronic excessive stimulation by ACTH. These hyperplastic adrenals have a capacity to synthesize excessive amounts of cortisol. Dogs with functioning adrenocortical tumors (adenomas and car-

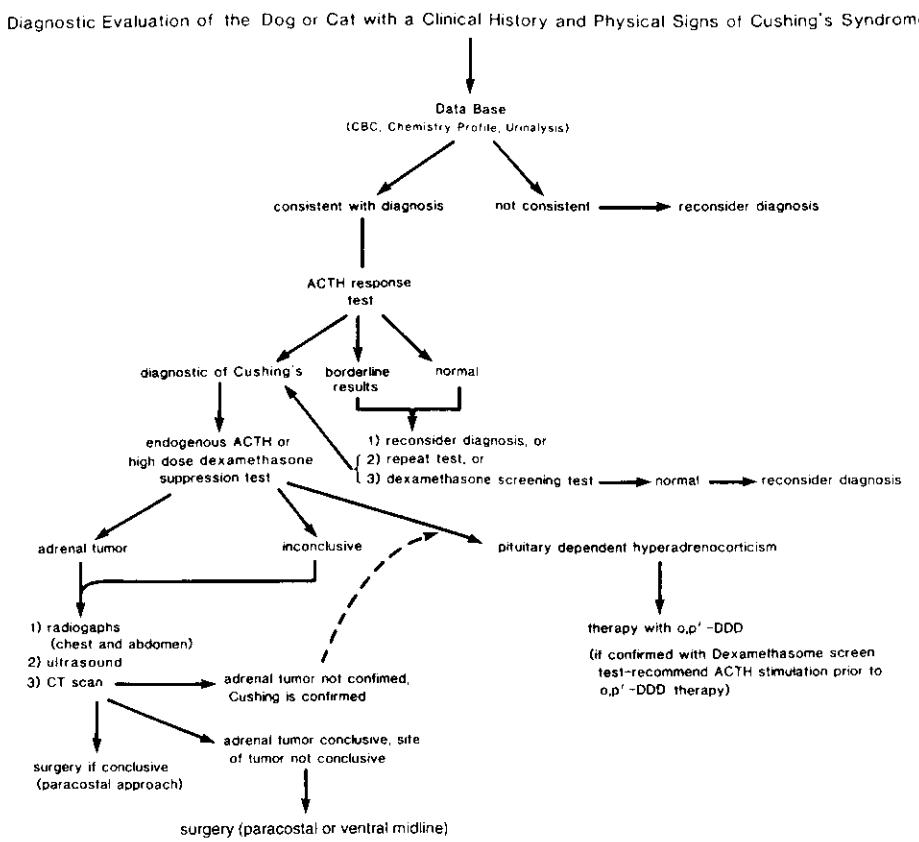

Figure 118–18. Diagnostic evaluation of a dog or cat with suspected hyperadrenocorticism. (From Feldman EC and Nelson RW: Canine and Feline Endocrinology and Reproduction. Philadelphia, WB Saunders, 1987, p 160.)

cinomas) have similar abnormal capacities to synthesize cortisol. These animals with pituitary- or adrenocortical-dependent Cushing's have the potential for an exaggerated response to ACTH. If this is true and if the adrenals in both disorders maintain ACTH responsiveness, dogs or cats with Cushing's syndrome can be distinguished from non-Cushing's animals.

Protocol. Reliable results are obtained when using porcine aqueous gelatin ACTH (Cortigel-40 repository corticotropin injection USP) at a dose of 1 IU/lb (2.2 IU/kg) of body weight IM, with plasma samples obtained before and 2 hours after injection. Alternatively, synthetic ACTH (cosyntropin [Cortrosyn]; 0.25 mg per dog [one vial] IM, with samples obtained before and 1 hour after administration) provides reliable results. In cats, 0.125 mg (one-half vial) is administered IM, with plasma samples obtained before and 30 and 60 minutes after administration. The 0.25-mg dose caused vomiting in some cats.[58]

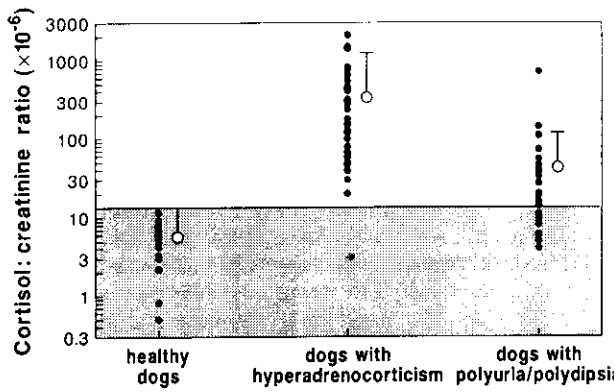

Figure 118–19. Urine cortisol-creatinine (C/C) ratios from healthy dogs, dogs with naturally occurring hyperadrenocorticism, and dogs with polyuria and polydipsia caused by disorders other than hyperadrenocorticism. These values show that the C/C ratio is a sensitive test for Cushing's syndrome but that it is not specific and should not be used as the sole test in confirming a diagnosis.

Results—Normal Dogs. Normal values must be established by each laboratory. Most laboratories, however, have reasonably similar results for plasma cortisol concentrations. Reference ranges for baseline cortisol concentrations are between 0.5 and 6.0 μg/dl, and the normal poststimulation cortisol concentration is between 6 and 17 μg/dl (Fig. 118–20). Poststimulation values between 17 and 22 μg/dl are considered borderline, and those greater than or equal to 22 μg/dl are consistent with a diagnosis of hyperadrenocorticism. It is important to emphasize that ratios and percentages change; comparing the basal with the poststimulation cortisol is not informative, and only the absolute values should be evaluated.

Results—Hyperadrenocorticism. ACTH stimulation test results are abnormal in 80 to 85 per cent of dogs with PDH, making the test useful but not absolutely reliable. Test results from dogs with PDH are not distinguishable from those of dogs ultimately shown to have functioning adrenocortical tumors. Suppression of endogenous ACTH in dogs or cats with adrenocortical tumors results in atrophy of all normal adrenocortical tissue. Despite their autonomous function, these neoplastic cells retain surface ACTH receptors and the intracellular pathways integral to a response caused by ACTH. Most dogs with hyperadrenocorticism caused by functioning adrenocortical tumors have abnormally exaggerated ACTH stimulation test results. A significant percentage (20 to 40 per cent) have normal response tests. Failure to

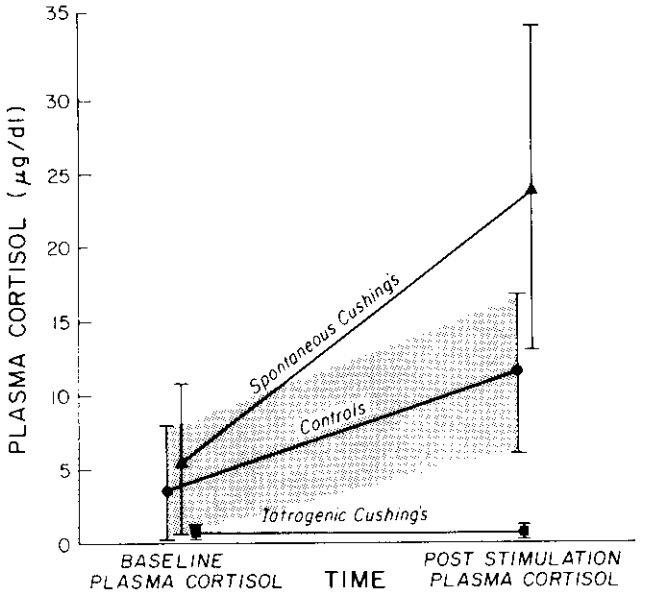

Figure 118–20. Mean radioimmunoassay plasma cortisol concentrations (±2 SD) determined before and 1 hour after administration of synthetic ACTH in control dogs, dogs with spontaneous hyperadrenocorticism, and dogs with iatrogenic hyperadrenocorticism.

respond to ACTH is unusual but possible in dogs with adrenocortical tumors. No consistent difference has been noted comparing ACTH responsiveness in dogs with adrenal adenomas versus those with carcinomas.

Results—Diabetes Mellitus. Confusion regarding whether individual dogs with diabetes mellitus also have Cushing's syndrome is common. Dogs with well-regulated diabetes have normal endocrine test results.[59] It is possible, however, for chronic illness to alter adrenocortical test results. Therefore, the non-Cushing's dog with poorly regulated diabetes can have misleading test results. The diagnosis of hyperadrenocorticism in this situation must be supported by abnormal endocrine test results and clinical signs of Cushing's. Insulin resistance is nonspecific and should not be the sole reason to treat for Cushing's syndrome.

Iatrogenic Cushing's Syndrome. A dog with clinical signs and routine laboratory test features of Cushing's syndrome with a low-normal baseline cortisol concentration and little or no response to exogenous ACTH is likely to have iatrogenic Cushing's syndrome (see Fig. 118–20). All other test results are identical to those of dogs with spontaneous hypoadrenocorticism. No other screening test differentiates naturally occurring hyperadrenocorticism from iatrogenic Cushing's syndrome.

o,p'-DDD Therapy. *o,p'*-DDD and ketoconazole (Nizoral) commonly are used in the treatment of hyperadrenocorticism. In either case, there is only one means of satisfactorily monitoring therapy: ACTH stimulation. This is the only test that can assess adrenocortical reserve and provide reliable information regarding adequacy of therapy.

Anticonvulsant Medication. Diagnosis of dogs with signs of Cushing's syndrome that are receiving anticonvulsant medication can be confusing. Such medication (primidone, phenytoin, phenobarbital) can cause polydipsia, polyuria, polyphagia, lethargy, increased serum liver enzyme values, and abnormal plasma cortisol concentrations. The clinician must be cautious when establishing a diagnosis in dogs taking these medications (see Table 118–6).

Dexamethasone Screening Test (Low-Dose Dexamethasone Test)

Theory

NORMAL. Pituitary ACTH, under hypothalamic control, stimulates adrenocortical synthesis and secretion of glucocorticoids. Increasing plasma cortisol concentrations, by way of negative feedback, suppress continued secretion of ACTH (see Fig. 118–3). Communication between the pituitary and the adrenal cortex is constantly functioning. The result is maintenance of plasma cortisol concentrations in the physiologic range necessary for normal metabolic homeostasis.

Dexamethasone, a potent synthetic glucocorticoid, administered in small doses inhibits pituitary secretion of ACTH and, in turn, decreases endogenous cortisol secretion within 2 to 3 hours, and they remain suppressed for 24 to 48 hours. Dexamethasone does not cross-react with cortisol assays, allowing documentation of effect. Therefore, normal pituitary-adrenal axis function could be demonstrated by administering dexamethasone and noting reduction in plasma cortisol concentrations 8 hours later (Fig. 118–21).[60]

ADRENOCORTICAL TUMOR. Functioning adrenocortical tumors secrete cortisol autonomously. The cortisol, secreted in excess and causing clinical signs of Cushing's, suppresses endogenous ACTH secretion. These tumors function independent of ACTH control, and administration of dexamethasone would not have a demonstrable effect on plasma cortisol concentration. Thus, dexamethasone administration to these animals would not affect plasma cortisol concentrations (see Fig. 118–21).[60]

PITUITARY-DEPENDENT CUSHING'S. Functioning ACTH-secreting pituitary tumors cause adrenocortical hyperplasia because of the chronic and excessive stimulation of the adrenal cortex. This abnormal pituitary, logically, must be somewhat resistant to the negative feedback action of cortisol. If this were not true, the excess cortisol would suppress ACTH secretion and PDH would never develop. Administration of a small dose of dexamethasone to an animal with PDH would not decrease the plasma cortisol concentration 8 hours later because the pituitary tumor is relatively resistant to the effects of this hormone (see Fig. 118–21).[60]

DIABETES MELLITUS. Dogs with well-controlled diabetes mellitus usually have normal adrenocortical endocrine test results. Dogs with poorly controlled diabetes may have abnormal results. Therefore, the diagnosis of Cushing's should be based first on clinical signs of Cushing's and then on endocrine test results.

RAPID DEXAMETHASONE CLEARANCE. In addition to dexamethasone resistance, an explanation for the failure of plasma cortisol concentrations to decrease normally in dogs with Cushing's syndrome is the clearance rate of the hormone. Seventy-five per cent of dogs with Cushing's syndrome clear dexamethasone from their plasma within a 3- to 5-hour period.[61] Plasma dexamethasone concentrations in healthy dogs persist for more than 12 hours. This concept explains the suppression seen in many dogs with PDH 4 hours after dexamethasone administration but not at 8 hours.[60a]

Protocol. A morning baseline plasma sample is obtained for cortisol determination and then 0.01 mg/kg (or 0.15 mg/kg) of dexamethasone is administered IV. Dexamethasone sodium phosphate or dexamethasone in polyethylene glycol (Azium) may be used.[61] Samples should be obtained 4 and 8 hours later for cortisol determination. If suppression is not seen at 8 hours but is documented at 4 hours, it is likely that the dog has PDH and not an adrenocortical tumor. Some dogs with PDH also fail to suppress at 4 hours.

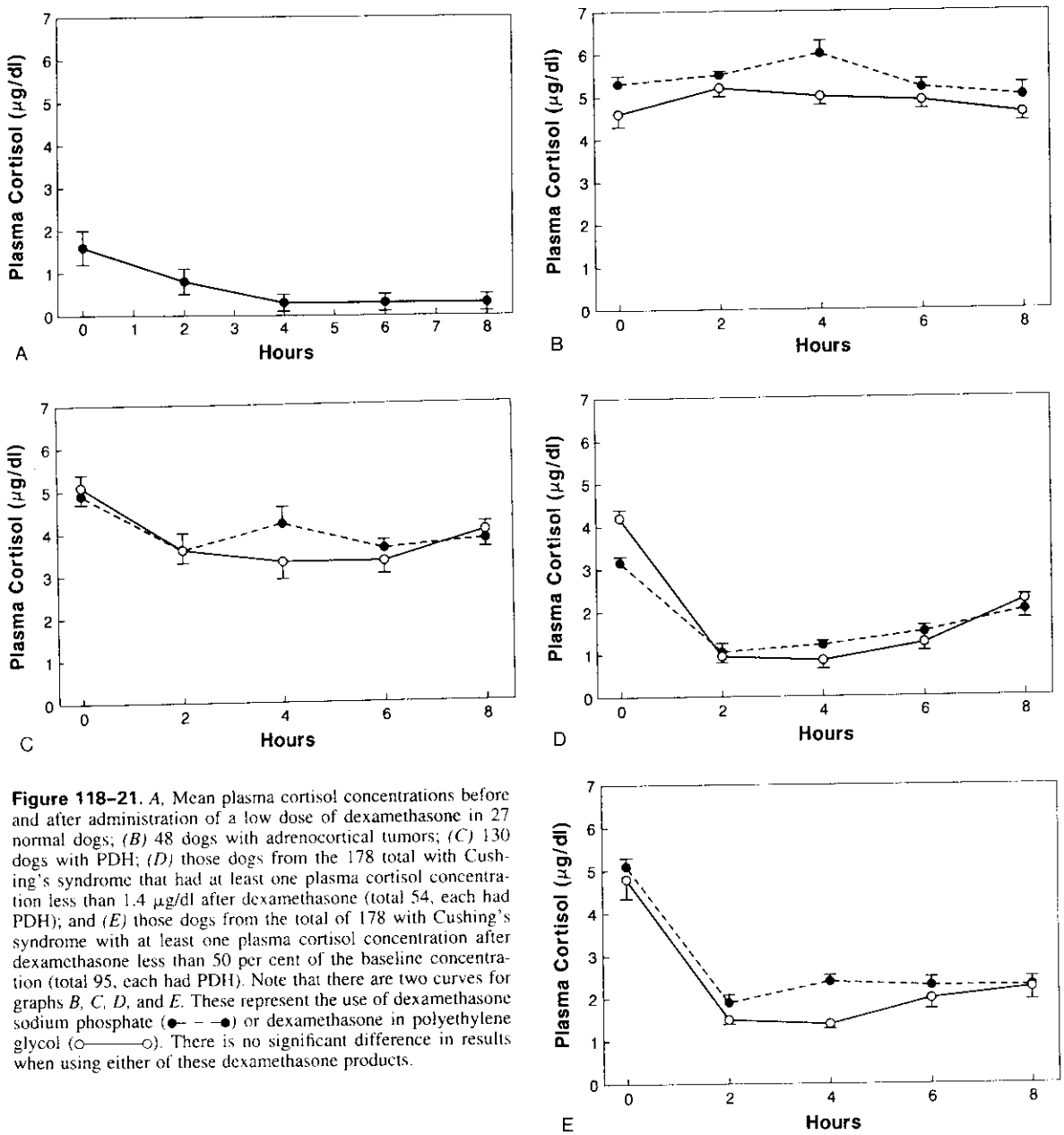

Figure 118–21. *A,* Mean plasma cortisol concentrations before and after administration of a low dose of dexamethasone in 27 normal dogs; *(B)* 48 dogs with adrenocortical tumors; *(C)* 130 dogs with PDH; *(D)* those dogs from the 178 total with Cushing's syndrome that had at least one plasma cortisol concentration less than 1.4 μg/dl after dexamethasone (total 54, each had PDH); and *(E)* those dogs from the total of 178 with Cushing's syndrome with at least one plasma cortisol concentration after dexamethasone less than 50 per cent of the baseline concentration (total 95, each had PDH). Note that there are two curves for graphs *B, C, D,* and *E.* These represent the use of dexamethasone sodium phosphate (●– – –●) or dexamethasone in polyethylene glycol (○————○). There is no significant difference in results when using either of these dexamethasone products.

Test Results—PDH. Normal dogs have plasma cortisol concentrations less than 1.0 μg/dl 4 and 8 hours after dexamethasone administration (see Fig. 118–21).[60] Several response patterns to the low dose of dexamethasone have been identified in dogs with hyperadrenocorticism (see Fig. 118–21). Complete suppression of plasma cortisol concentrations 8 hours after dexamethasone administration (less than 1 μg/dl) does not occur in dogs with adrenocortical tumors or in dogs with PDH. Dogs with functioning adrenocortical tumors tend to have little fluctuation in plasma cortisol concentration during the low-dose test.

Misleading Results. As with the ACTH stimulation test results, dexamethasone screening test results can be misleading. Anticonvulsant medications can cause dogs to have abnormal plasma cortisol concentrations. The stress of bathing, hospitalization, illness, and numerous other factors may interfere with the suppressive effects of dexamethasone. Iatrogenic steroids may remain in the blood for long periods, causing an apparent failure to respond to dexamethasone because cortisol assays measure endogenous and iatrogenic glucocorticoids (not dexamethasone). The most important initial screening tests are the history and physical examination.

Miscellaneous Screening Tests

Alkaline Phosphatase Isoenzyme. See Alkaline Phosphatase.

High-Performance Liquid Chromatography and Free Cortisol Concentrations in Plasma. These assays are not widely available, are expensive and difficult to perform as compared with commercially available kits, and do not offer significant advantages over the more traditionally available tests.

Combined Dexamethasone Suppression and ACTH Stimulation. The goal of this procedure was to provide information concerning both pituitary gland and adrenal gland activity in a single, brief, relatively inexpensive trial. The test is no longer recommended. It is recognized to have combined

two imperfect tests, with the result being a test less reliable than either of its component parts.[62, 63]

Liver Biopsy. Abnormal liver enzymes and abnormal liver function tests are common in hyperadrenocorticism. For this reason, patients with vague clinical features of hyperadrenocorticism may be tentatively diagnosed as having a primary hepatopathy. With the increasing use of percutaneous liver biopsies, liver tissue from dogs with Cushing's will be submitted to pathologists. Dogs with naturally occurring hyperadrenocorticism or those given exogenous glucocorticoids usually have histologic evidence of glucocorticoid-induced or steroid hepatopathy. This hepatopathy is histologically characterized by centrilobular vacuolization, perivacuolar glycogen accumulation within hepatocytes, and focal centrilobular necrosis. These histologic findings are observed regardless of whether the Cushing's is naturally occurring or iatrogenic. Other disadvantages to the routine use of liver biopsy as a screening test include the complications of infection and inadequate healing after the procedure because of the systemic effects of hyperadrenocorticism. Steroid hepatopathy is unique to the dog.

Discrimination Tests

Discrimination tests differentiate between pituitary-dependent and adrenocortical tumor hyperadrenocorticism.

Low-Dose Dexamethasone Test

Protocol. The protocol for this test is the same as that previously described.

Results. About 35 per cent of dogs with PDH have a 4-hour cortisol concentration less than 1 μg/dl and an 8-hour value above 1.4 μg/dl. No dog with an adrenocortical tumor demonstrates 4-hour suppression of this magnitude. An additional 35 to 40 per cent of dogs with PDH (a total of 70 to 75 per cent of dogs with PDH) have a 4-hour cortisol concentration less than 50 per cent of the baseline value and an 8-hour value that is consistent with hyperadrenocorticism. Dogs with an adrenocortical tumor should not demonstrate 4-hour suppression of this magnitude. Note that 25 to 30 per cent of dogs with PDH and 100 per cent of adrenocortical tumor dogs fail to demonstrate significant suppression at any time during low-dose testing (Fig. 118–21).[60]

Dogs with a history, physical examination, data base, and 8-hour low-dose dexamethasone test result consistent with hyperadrenocorticism have the disease. Further, those that demonstrate suppression at 4 hours have PDH. This can be further supported with other discrimination tests, but additional testing probably is not needed. Dogs that meet all the criteria above for establishing the diagnosis of hyperadrenocorticism but fail to demonstrate suppression of their plasma cortisol concentration at 4 hours of a low-dose dexamethasone test must be considered candidates for either PDH or adrenocortical tumor.[60a]

Endogenous ACTH Concentrations

Theory. Adrenocortical tumors suppress ACTH secretion, and pituitary-dependent Cushing's syndrome is the result of excessive ACTH secretion. Assays for ACTH concentration are not used to diagnose hyperadrenocorticism because a large number of test results are within the reference range. In addition, iatrogenic glucocorticoid administration can suppress ACTH concentrations. Assaying the plasma endogenous ACTH level is a valuable aid, however, in distinguishing patients with adrenocortical tumors from those with pituitary-dependent disease.

Protocol. To diminish the variables of stress and time of day, the blood sample should be obtained between 8 and 9 A.M., after the dog has been hospitalized for a night. To avoid erroneous values, blood samples should be centrifuged immediately, with the plasma quickly transferred to a clean plastic vial. Samples should not be allowed to stand at room temperature for even short periods. Contact with glass must be avoided during collection, separation, and storage because it is known that plasma ACTH adheres to glass. Plasma ACTH levels can be effectively preserved by storing them at −20°C for not longer than a month.[64]

As endogenous ACTH assays have gained acceptance, their use in humans has increased dramatically. A number of RIA kits for human ACTH are commercially available. Several kits for human ACTH have excellent cross-reactivity in dogs and cats.[65, 66] ACTH assays can be moderately expensive. Any assay used by veterinarians must be validated for the species being studied.

Results—Adrenocortical Tumors. The mean baseline plasma ACTH concentration in healthy dogs is 45 pg/ml (reference range, 20 to 100 pg/ml). Endogenous ACTH concentrations less than 10 pg/ml in a dog with naturally occurring hyperadrenocorticism are strongly suggestive of a functioning adrenocortical tumor (Fig. 118–22). Sixty-two endogenous ACTH concentrations were evaluated from 41 dogs with Cushing's due to adrenocortical tumors. In 36 (58 per cent), the ACTH concentration was undetectable. The remaining 26 samples had values of 20 to 44 pg/ml.[12] If a dog with iatrogenic Cushing's is evaluated, its plasma endogenous ACTH concentration probably would be undetectable, but the ACTH stimulation test results should reveal the underlying disorder (see Fig. 118–20).

Results—PDH. ACTH concentrations greater than or equal to 45 pg/ml are consistent with a diagnosis of pituitary-dependent bilateral adrenal hyperplasia. Again, appropriate screening tests must be used first to obtain a diagnosis of hyperadrenocorticism. The endogenous ACTH concentration is greater than 45 pg/ml in 85 to 90 per cent of dogs with PDH (Fig. 118–22). About 35 per cent of dogs with PDH have endogenous ACTH concentrations greater than 100 pg/ml and 55 per cent have concentrations of 45 to 100 pg/ml. Only 10 to 15 per cent of the dogs with PDH we have evaluated have had endogenous ACTH concentrations less than 45 pg/ml, values that are considered nondiagnostic. Dogs with PDH have not had endogenous ACTH concentrations less than 20 pg/ml.

Nondiagnostic Results. Dogs with hyperadrenocorticism that have endogenous ACTH concentrations greater than 20 pg/ml but less than 45 pg/ml have nondiagnostic results (Fig. 118–22). In these dogs, results of a repeated ACTH concentration, abdominal ultrasonography, and low- and high-dose dexamethasone test should define the cause.

High-Dose Dexamethasone Suppression Test

Theory. The 8-hour low-dose dexamethasone test (screening test) is used to distinguish dogs that do not have Cushing's from those with naturally occurring Cushing's syndrome. Regardless of the dose, dexamethasone should not suppress cortisol secretion from an adrenocortical tumor. However, administering larger doses of dexamethasone does suppress pituitary ACTH and then cortisol secretion in most dogs with PDH. Thus, most pituitary tumors retain cortisol receptors but are more resistant to feedback than normal.

Protocol. The high-dose dexamethasone suppression protocol commonly used includes the collection of heparinized

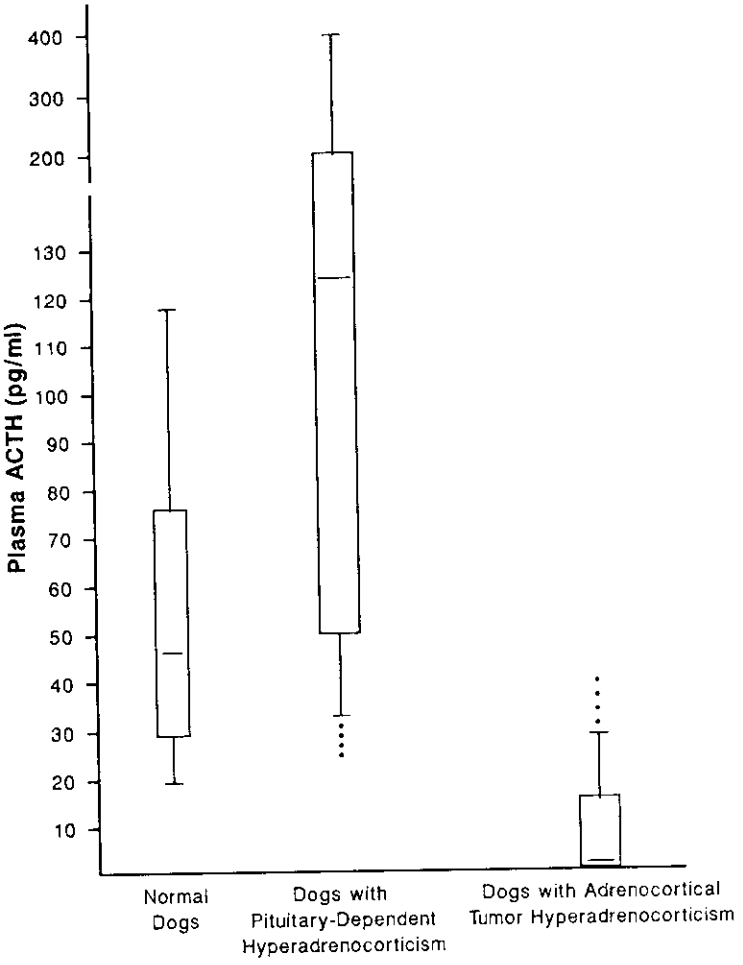

Figure 118–22. Endogenous plasma ACTH concentrations from clinically normal dogs, dogs with PDH, and dogs with functioning adrenocortical carcinomas or adenomas.

blood samples before and 8 hours after 0.1 mg/kg IV dexamethasone.[19] Suppression is defined as an 8-hour plasma cortisol concentration less than 50 per cent of the baseline concentration.

Results—Adrenocortical Tumors. Adrenocortical tumors function autonomously (independent of ACTH control). As expected, administration of a high dose of dexamethasone does not result in cortisol suppression (Fig. 118–23 and see Fig. 118–21).[19] However, in any animal, cortisol levels fluctuate, and a suppressed plasma cortisol concentration may be encountered by chance. This would be extremely unusual in a dog with an adrenocortical tumor.

Results—PDH. About 75 to 80 per cent of dogs with PDH have plasma cortisol concentrations less than 50 per cent of the baseline concentration 8 hours after administration of a high dose of dexamethasone (Fig. 118–23 and see Fig. 118–21). The percentage is not much different in dogs tested with the 1.0 mg/kg dose. Dogs with naturally occurring Cushing's that suppress on the high dose have PDH. Among the dogs with Cushing's that fail to demonstrate suppression are 20 to 30 per cent of dogs with PDH and 100 per cent of dogs with adrenocortical tumors.[19, 62]

It is not known why some dogs with PDH are extremely resistant to dexamethasone suppression, whereas others suppress completely after administration of a high dexamethasone dose. Some pituitary tumors arise from the pars intermedia, which may account for decreased dexamethasone sensitivity because this area of the pituitary gland is under neural control versus hormonal control of the pars distalis.[2] There has been an impression that the larger the pituitary tumor, the less likely the dog will suppress after receiving any dose of dexamethasone, but results have not been consistent (Fig. 118–24).[8, 17, 50, 66–69]

Multiple Samples? The literature neither supports nor rejects the need for samples to be obtained at 2, 3, 4, or 6 hours or at other times after administration of a high dexamethasone dose. There is uniform agreement that the 8-hour sample is important and that samples other than the pretest and that obtained after 8 hours seldom are informative.

Radiographs. See previous section.

Abdominal Ultrasonography. See previous section.

Computed Tomography

Adrenals. CT is a noninvasive method of visualizing the anatomy of almost any area of the body. In Cushing's, it has been successful in distinguishing dogs and cats with normal adrenals from those with one large adrenal and those with two large adrenals.[70] Abdominal radiography is not as sensitive as CT scanning, but ultrasonography is comparable for detecting adrenocortical tumors in dogs.[38, 41]

Pituitary. The pituitary region of normal dogs can be visualized by CT scanning. Many pituitary tumors are relatively small, are contained within the normal pituitary, and can be difficult to discern by CT scanning, accounting for the low 39 per cent accuracy in people with PDH.[71] Most dogs with PDH considered for pituitary CT scanning have significant clinical signs suggestive of a large intracranial mass. In this population of dogs (and cats), CT scan results have been satisfactory because the clinician is attempting to determine whether a large tumor is the cause of clinical signs. If such a

dog has a small tumor that CT failed to detect, the diagnosis of large tumor is still adequately rejected. CT is extremely accurate for visualization of large pituitary tumors or cerebral ventricular dilatation secondary to a pituitary or hypothalamic mass.

Magnetic Resonance Imaging

Background. MRI has become an essential tool for the diagnosis of central nervous system (CNS) disorders. MRI frequently is compared with and has several advantages over CT: superior tissue contrast, ability to obtain images in multiple planes, absence of artifacts caused by bone, vascular imaging capability, absence of ionizing radiation, and safer contrast media. The disadvantages include a longer scanning time, which makes MRI more sensitive to motion artifacts and less practical for patients whose condition is unstable. Gadolinium-enhanced T_1-weighted images are preferred for the diagnosis of intracranial tumors. MRI is superior to CT in the detection of associated tumor features: edema, cysts, vascularity, hemorrhage, and necrosis.[72] Several reports of MRI scans in dogs have demonstrated that MRI is both sensitive and accurate.[17, 50, 73]

Protocol. The MRI scans that we have performed on dogs and cats were at local human hospitals. Dogs were sedated with an IV mixture of ketamine and diazepam, allowing intubation and thereby decreasing movement associated with respiration. No acute or long-term problems have been associated with this mode of sedation, even in severely debilitated dogs with massive intracranial tumors.

Dogs with Untreated PDH and No CNS Signs. About 50 per cent of dogs with untreated PDH and no signs suggestive of an intracranial mass have easily visualized pituitary tumors measuring 3 to 13 mm at greatest vertical height (Fig. 118–25). Most masses extend beyond the dorsal confines of the sella turcica and are contrast-enhancing. Dilation of the lateral ventricles, seen in several dogs, is considered an age-related change rather than an indication of obstructive hydrocephalus.[17]

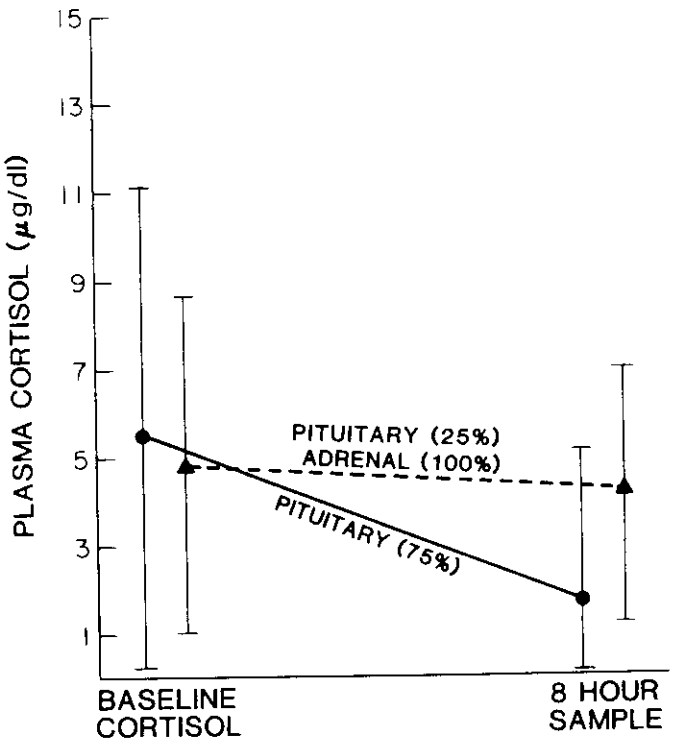

Figure 118–23. Pattern of plasma cortisol responses during high-dose dexamethasone suppression in dogs with PDH or adrenal tumor hyperadrenocorticism. Note that suppression is diagnostic of pituitary dependency; lack of suppression included all adrenal tumor cases and 20 to 30 per cent of PDH cases.

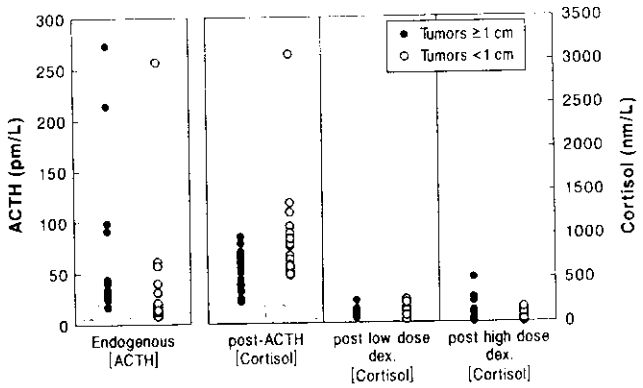

Figure 118–24. Basal plasma endogenous ACTH concentrations and plasma cortisol concentrations after administration of ACTH, after a low dose of dexamethasone, and after a high dose of dexamethasone in dogs with PDH attributed to pituitary tumors greater than or equal to 1 cm and less than 1 cm in diameter.

Dogs with PDH and Signs of an Intracranial Tumor. Dogs with PDH that have signs of an intracranial tumor have a mean age of 9.5 years (younger than the mean for all dogs with PDH) and a mean body weight of 24 kg (larger than the average dog with PDH). MRI was definitive in demonstrating the size and nature of the tumor in each dog. Masses were better visualized after administration of the contrast agent (gadolinium DTPA), measuring 8 to 24 mm at greatest vertical height (Fig. 118–25*D*). All tumors had expanded dorsally beyond the limits of the sella turcica. Some masses elevated the floor of the third ventricle, and some appeared to compress the hypothalamus. Obstructive hydrocephalus was suspected in 2 of 13 dogs. Tumor-associated necrosis or hemorrhage was not apparent on any scans.[50]

CRH Stimulation Test. A single IV dose of CRH produced increases in plasma ACTH and cortisol concentrations in normal dogs as well as in those with PDH. No significant rise in plasma ACTH or cortisol was demonstrated in dogs with adrenocortical tumors. The CRH stimulation test may have value as a discriminating study in the evaluation of dogs with hyperadrenocorticism.[74]

Radioisotope Imaging of the Adrenals. Gamma camera imaging of the adrenal glands can aid in distinguishing normal glands from hyperplastic glands and functioning adrenal tumors. Use of radioactive substances and gamma cameras plus the sensitivity and reliability of ultrasonography, CT, and MRI restrict the use of this diagnostic test.

Metyrapone Testing. Metyrapone is an enzyme blocker that inhibits the action of 11β-hydroxylase in steroid synthesis. Thus, in normal dogs, plasma cortisol concentrations decline, whereas 11-desoxycortisol accumulates as ACTH stimulation continues. The suggested dosage of metyrapone is 25 mg/kg PO every 6 hours for four treatments, with plasma collected before beginning the test and 6 hours after the final dose. Samples are assayed for both cortisol and 11-desoxycortisol. If metyrapone results in a decrease in the plasma cortisol concentration and a concomitant increase in plasma 11-desoxycortisol level, a diagnosis of PDH can be made. If plasma cortisol and 11-desoxycortisol concentrations both decline after the four metyrapone doses, an adrenal tumor is the likely cause of the hyperadrenocorticism.[75] Use

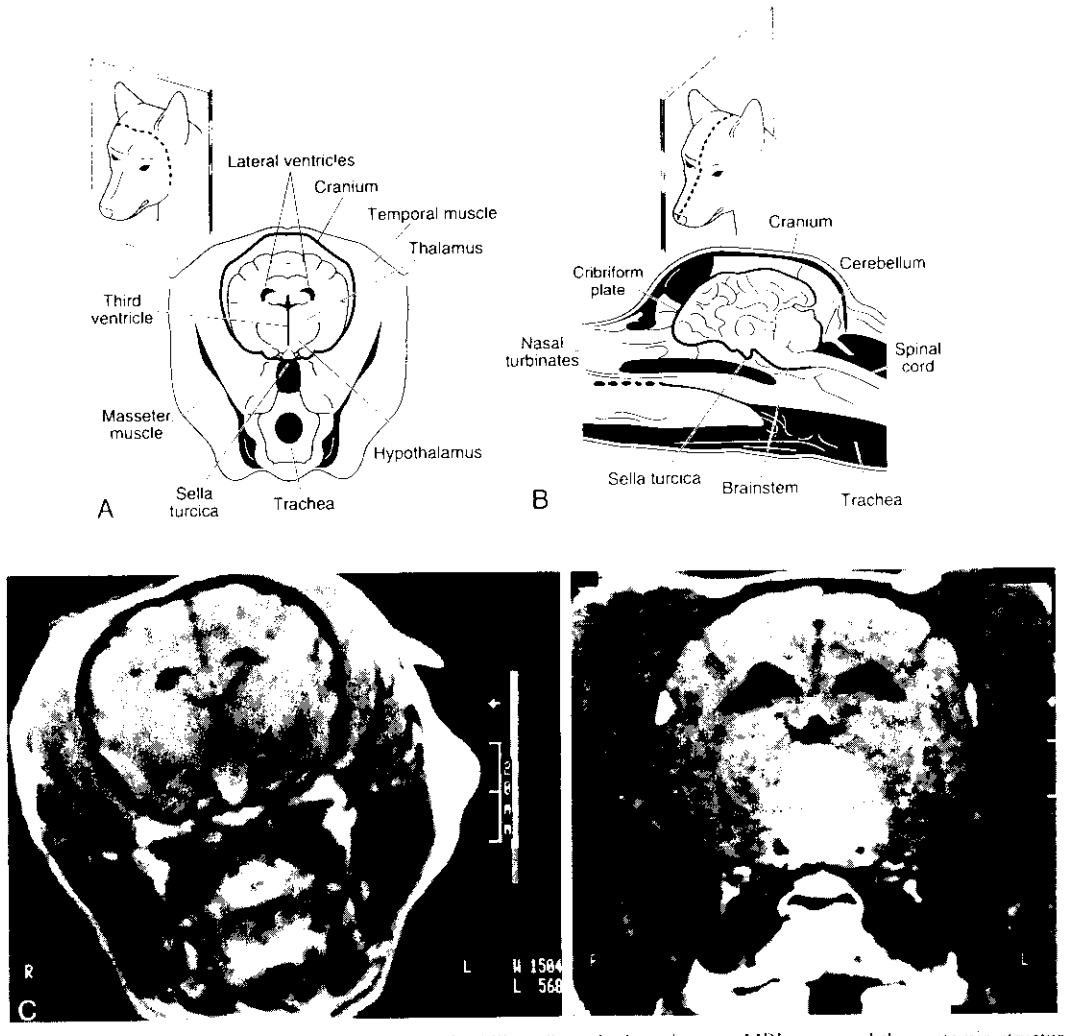

Figure 118–25. Orientation of the transverse *(A)* and midline *(B)* sagittal sections on MRI scans and the anatomic structures seen on each view. *C*, MRI scan of a dog with PDH and a relatively small (7 mm) pituitary mass *(arrow)*. *D*, MRI scan of a dog treated for PDH with *o,p'*-DDD and that subsequently developed CNS signs caused by a large (2.6 cm) pituitary tumor.

of this drug is briefly reviewed in the treatment section on feline Cushing's.[76]

TREATMENT—BACKGROUND

Excellent rapport between veterinarian and owner is valuable during the long-term management of a dog or cat that has been diagnosed as having hyperadrenocorticism. The surgical and medical options should be discussed in detail, including what is expected of the owner. One hopes to return such dogs to a normal endocrine state, but this is not always possible, and all complications must be discussed. These dogs may have endocrine excesses or deficiencies after treatment, and the prepared owner can better accept these setbacks. Time spent explaining the pathophysiology in lay terms is well worth the effort to improve client understanding and to establish a good basis for communication.

TREATMENT—SURGERY

Adrenal Tumor Hyperadrenocorticism

Preoperative Evaluation. Once the diagnosis of Cushing's syndrome and the presence of an adrenal tumor are confirmed, the clinician should attempt to localize the tumor and rule out metastasis. Thoracic radiographs aid in determining metastases to the lungs. Abdominal ultrasonography is the preferred tool for localizing tumors and defining metastasis (especially to the liver) and vessel or organ invasion or compression. Abdominal surgery should not be considered without prior ultrasound evaluation.

Screening tests, such as radiographs, ultrasound, and CT and MRI scans, may also provide valuable information regarding the size of the tumor present. Small tumors are much more likely to be benign and easily removed than tumors as big as or bigger than a normal kidney. The preoperative evaluation should also be directed at determining whether a particular dog is a reasonable surgical candidate. If not, because of Cushing's-related debilitation, treating the dog for 1 to 3 months with ketoconazole or *o,p'*-DDD could be beneficial. This time can also be used to treat other concurrent problems (infection) before surgery.

Surgical Approach. The recommended surgical approaches are paracostal or ventral midline laparotomy. A ventral midline celiotomy provides excellent exposure of both adrenal glands and an opportunity to evaluate the abdominal contents, especially the liver, for metastasis and/or other problems.[77] A specimen of abnormal tissue can be removed for biopsy or the tissue can be excised. Problems

associated with wound healing in tissues that have been exposed to high concentrations of corticosteroids are exaggerated by a ventral weight-bearing incision. In addition, the large amount of abdominal fat found in patients with Cushing's syndrome, coupled with the location of the adrenals dorsal and medial to the kidneys, makes the ventral midline approach difficult.

The paracostal retroperitoneal approach to adrenalectomy provides adequate exposure of the adrenal gland on that side of the abdomen. This approach avoids the wound-healing problems on a weight-bearing ventral midline incision as well as the difficulties of traversing an abdomen filled with fat. Also, the adrenals, which are dorsolateral to the vena cava and aorta, are more accessible by way of the paracostal approach. Marked disadvantages of the paracostal approach include only being able to explore one adrenal bed (exploration of the opposite side requires closure of the first incision and a second surgical procedure) and inability to evaluate the liver and the balance of the abdomen for metastasis.

Regardless of the surgical approach, an attempt should be made to remove an adrenal tumor as one mass. This is not always possible because of mass friability, and care must be taken to remove small tumor pieces. If a tumor is deemed to be inoperable at surgery, an attempt should be made to debulk the mass as much as possible. Such attempts have resulted in patient improvement.

Patient Management During Surgery. At the time of anesthesia, IV fluids (saline or Ringer's solution) should be administered at a maintenance rate. When the adrenal tumor is recognized by the surgeon, dexamethasone is placed in the IV infusion bottle at a dose of 0.05 to 0.1 mg/lb of body weight.[39, 78] This dose is given over a 6-hour period and repeated four times a day for 2 days before beginning oral prednisone therapy. Alternatively, an infusion of hydrocortisone hemisuccinate can be used (625 μg/kg/h). The hydrocortisone should have both glucocorticoid and mineralocorticoid effects, although we have not been impressed that hydrocortisone provides adequate mineralocorticoid effect. The blood pressure and BUN, serum electrolytes, and blood glucose concentrations should be closely monitored. Adrenal tumors cause decreased secretion of pituitary ACTH, and this causes some atrophy of all three zones of the adrenal cortex. When an adrenal tumor is excised, acute hypoadrenocorticism may result. If hyperkalemia and/or hyponatremia is identified, desoxycorticosterone pivalate (DOCP; 1 mg/lb IM) or oral fludrocortisone acetate (0.01 mg/lb) should be administered.

Although some investigators have recommended treating surgical patients with corticosteroids for 1 or 2 days before the procedure, this protocol is unnecessary and actually potentially harmful. The iatrogenic steroids predispose the patient to fluid balance problems (overhydration) and an increased risk of thromboembolic episodes.

Once the dog is eating and drinking on its own, it should receive 1 mg/lb of prednisone PO twice a day for 2 days. The dosage is then tapered over a period of 2 to 4 months. Fludrocortisone acetate or DOCP is continued if the serum electrolyte concentrations (hyperkalemia ± hyponatremia) indicate that it is needed (40 per cent of the dogs have needed this medication). Its dosage is then tapered similar to that of the glucocorticoid. Glucocorticoid and mineralocorticoid medication must meet individual requirements; "cookbook" approaches must be avoided. ACTH stimulation tests can be used as adjuncts to therapy in determining when to discontinue medication. Any time a patient becomes listless, anorectic, or ill during the tapering process, the glucocorticoid dose may need to be raised and serum electrolytes monitored. If the dog has a normal ACTH stimulation test result, medication is no longer needed.

Results (Prognosis). Of 102 dogs we have diagnosed with functioning adrenocortical tumors, 98 had a unilateral tumor and 63 of those underwent surgery. Four dogs were euthanized at surgery with an inoperable mass. Eighteen dogs died during surgery or soon after as a result of direct complications from the surgery (hemorrhage) or postoperative problems of sepsis or thromboembolism. Forty-one dogs underwent successful surgery—24 had carcinomas and 17 had adenomas. The dogs that underwent successful surgery have a good prognosis if metastasis has not occurred and if they survive the 1- to 4-week postsurgical period. Medical therapy was used in some of the dogs that had surgery (because of recurrence) as well as in those not undergoing surgery. The average life expectancy after surgery is about 46 months. Dogs with adenomas, logically, have a better prognosis. Although the dogs with adenomas do live longer as a group, the tumors in some dogs have been misdiagnosed (adenomas ultimately diagnosed as carcinomas and vice versa). As previously discussed, endocrine tumors are notorious for being difficult to correctly identify and classify. This makes rigid statements to owners unwise.

Inoperable Mass, Poor Anesthetic Risk, or Obvious Metastasis. Surgery cannot be considered for some dogs with Cushing's that have adrenocortical tumors. The reasons for avoiding surgery include finding a large, obviously inoperable mass on radiographs, ultrasound, or CT scan; finding metastatic lesions in the lungs, liver, or other tissue; having a patient that is so debilitated that surgery probably would be harmful; and having an owner who refuses surgery. In these dogs, medical therapy should be considered.

Pituitary-Dependent Hyperadrenocorticism

Hypophysectomy. Surgery to remove the pituitary gland, and thus the source of ACTH in PDH, has been successfully performed in the dog. The procedure has been described,[79-81] but it is not commonly performed.

Adrenalectomy. Removal of both adrenals results in complete resolution of signs attributed to Cushing's. This surgery involves the risk of putting an ill animal with a compromised immune system and poor wound healing through a difficult procedure. As with hypophysectomy, experience minimizes these risks, but such dogs must be permanently treated for hypoadrenocorticism. Because "medical adrenalectomy" is relatively easy to accomplish in dogs with *o,p'*-DDD, the risk of surgery seems unwarranted.

TREATMENT—MEDICAL MANAGEMENT OF CUSHING'S USING *o,p'*-DDD

Pituitary-Dependent Hyperadrenocorticism

Initial Chemotherapy Using *o,p'*-DDD

Background. Since the treatment protocol first suggested by Schechter and others in 1973, chemotherapy with *o,p'*-DDD has become the most common method of treating PDH in dogs. The systemic effects of *o,p'*-DDD, a chemical derived from the insecticide DDT, were first reported in 1949 by Nelson and Woodard. The drug causes severe, progressive necrosis of the zona fasciculata and zona reticularis. Subsequent studies by Kirk and Jensen in 1975 also demonstrated partial or complete necrosis of the zona glomerulosa. The only other major pathologic processes involved the liver,

including moderate to severe fatty degeneration, moderate centrolobular atrophy, and congestion.

Normal dogs given *o,p'*-DDD appear clinically resistant to the adrenocorticolytic effects of the drug. In the 1940s study, four dogs received 50 mg/kg 5 days per week. Two of the four died after 20 and 21 months of therapy, respectively. The third dog was euthanized after 21 months of therapy, and the fourth dog was alive after 38 months on the drug. In the 1975 study, 10 dogs were treated at a dosage of 50 mg/kg/day. One dog died after 124 consecutive days of treatment, and a second died after 147 days. The remaining eight dogs were clinically healthy at the time of euthanasia, after 36 to 150 consecutive days of drug therapy. These dogs, however, had biochemical evidence of decreased adrenocortical reserve and adrenocortical destruction after only 3 to 10 days of therapy. These reports should remind veterinarians of the potent effects of *o,p'*-DDD, that the drug must not be used indiscriminately, and that dogs with Cushing's are more sensitive to the drug than are normals.

A dog diagnosed as having PDH, requiring more than 21 consecutive days of *o,p'*-DDD therapy, must be carefully reevaluated. Possible explanations for resistance are the dog is not receiving or absorbing the drug (it should be administered after meals); the dog has an adrenocortical tumor; the diagnosis is incorrect; and the dog may have a resistant form of PDH.

Initiating Therapy—Loading-Dose Phase. Therapy is begun at home with the owner administering *o,p'*-DDD at a dosage of 50 mg/kg/day, divided and given twice a day (Fig. 118–26). The drug must be administered immediately after the meal has been consumed to enhance absorption.[82] Glucocorticoids are not advised, but the owner should have a small supply of prednisone tablets if an emergency should arise. During this phase of treatment, the dog should be fed one-third of its normal intake twice daily. This decrease in food allotment should enhance the dog's excessive appetite and make it easier for the owner to monitor the pet. The owner should receive thorough instructions on the actions of *o,p'*-DDD and have specific instructions on when the drug should be discontinued. *o,p'*-DDD administration should be stopped when the dog demonstrates reduction in appetite (this might mean just pausing slightly during meal consumption, stopping to drink some water, or stopping in response to the owners voice); the polydipsic dog consumes less than 60 ml/kg/day of water; vomiting occurs; diarrhea occurs; or the dog is unusually listless.[19] The first two indications for stopping the medication are strongly emphasized because they are common. The occurrence of any of these signs strongly indicates that the end point in therapy has been achieved.

Because of the potency of *o,p'*-DDD, the veterinarian is encouraged not to rely on the instructions given to an owner. An owner should not be provided with more than an 8 day supply of *o,p'*-DDD initially. This drug is highly successful in eliminating the signs of Cushing's because of its potency coupled with close communication between owner and veterinarian. Either the veterinarian or a technician should call the owner every day during the loading-dose phase, beginning with the second day of therapy. In this way, the owner will be impressed with the veterinarian's concern and will observe the animal closely. It is wise for the owner to feed the dog two small meals each day, as previously described. The dog's appetite should be observed before each administration of *o,p'*-DDD. If food is rapidly consumed (with or without polydipsia), medication is warranted. If food is consumed slowly or not at all, medication should be discontin-

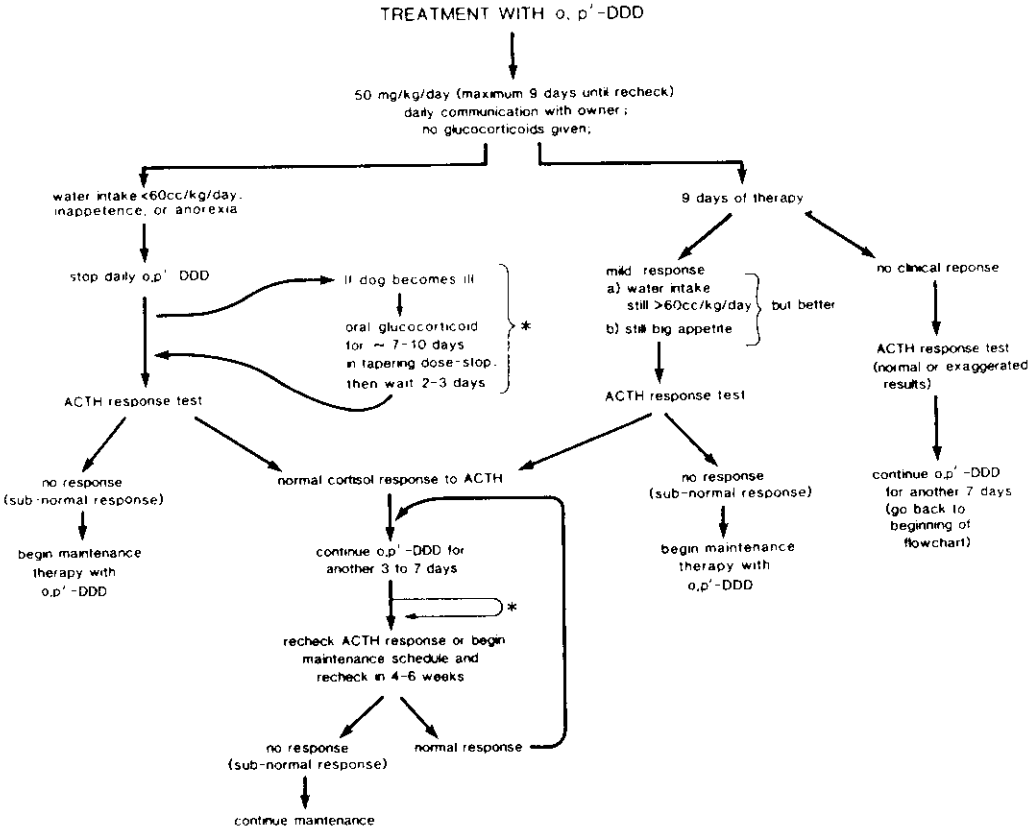

Figure 118–26. Flow chart for the management of hyperadrenocorticism using *o,p'*-DDD. Asterisks indicate similar treatment protocols.

ued until the veterinarian is consulted. The initial loading-dose phase usually is complete when a reduction in appetite is noted or after water intake approaches or falls below 30 ml/lb/day.

If a dog diagnosed with Cushing's syndrome is not polyphagic, the diagnosis and the advisability of treatment must be questioned. The most important monitoring guide in these dogs is their appetite. We do not treat dogs that fail to exhibit excellent to ravenous appetites. Reduction in appetite in a dog receiving *o,p'*-DDD is an indication that overdosage is imminent.

The water intake in polydipsic dogs may decrease to the normal range (less than 30 ml/lb/day) in as few as 2 days or in as long as 35 days (average, 5 to 16 days). Owners should continue to monitor water intake daily until it falls to or below this level. Water intake usually begins to diminish within days of initiating *o,p'*-DDD treatment, but it usually does not become normal until after some reduction in appetite is obvious.

A small percentage of dogs demonstrate mild gastric irritation or systemic signs of illness from the *o,p'*-DDD 1 to 3 days after medication has been started. These signs, in addition to anorexia, include vomiting, diarrhea, weakness, and lethargy. If any of these signs are observed, the medication should be discontinued until the veterinarian can evaluate the dog. If the signs are the result of drug sensitivity and not because the treatment is complete, dividing the dose further may be helpful; discontinuing the medication for a few days may be necessary. It is recommended that *o,p'*-DDD treatment be initiated on a Sunday, so that if illness develops after just a few days, the veterinarian should be available during a regular work week.

Veterinary Monitoring. In addition to making daily telephone calls, the veterinarian should see the dog 8 to 9 days after beginning therapy. At this time, a thorough history and physical examination should be performed and a recheck of the ACTH response test obtained. A recheck of the BUN, serum sodium, and potassium concentrations may be warranted, although these test results are seldom abnormal. Regardless of the clinical response, *o,p'*-DDD should be withheld until the ACTH response test results can be evaluated (see Fig. 118–26).

Goal of Therapy. The goal of therapy is to achieve an ACTH response test result suggestive of hypoadrenocorticism. In our laboratory, successful response to *o,p'*-DDD is indicated by pre- and post-ACTH plasma cortisol concentrations less than 5 μg/dl. Whenever the appetite has declined or the water intake declines below 30 ml/lb/day, the ACTH response test results typically correspond by being dramatically improved.

A dog that has a normal or exaggerated response to ACTH before therapy and a normal response to ACTH after the initial phase of therapy is likely to continue exhibiting some clinical evidence of Cushing's. This is due to the continuing presence of an abnormal pituitary-adrenal axis (see Fig. 118–5). *o,p'*-DDD therapy has no effect on the pituitary abnormality. Mild to severe excesses in ACTH secretion continues, causing the excess cortisol secretion for much of each 24-hour period.[65]

To Continue or Not Continue o,p'-DDD at the Loading Dose. If the dog with Cushing's has a normal or exaggerated response to ACTH after the initial 8 to 9 days of *o,p'*-DDD therapy, medication should be continued. It usually is continued for 3 to 7 additional consecutive days, the shorter period being used for dogs that have shown some significant (albeit inadequate) response. Repeat ACTH response tests are continued every 7 to 10 days until a low post-ACTH plasma cortisol response is achieved. Numerous repeat tests usually are not necessary because most dogs have responded during the initial 5 to 9 days of medication and almost all have responded by the 14th day of therapy.

Average Duration of Daily Loading-Dose o,p'-DDD Therapy. Most dogs with PDH respond within 5 to 9 days (average, 6.4 days). Some dogs respond in as little as 2 or 3 days, and a few have required more than 21 consecutive days of therapy. More than 80 per cent of our patients respond in the initial 5-to-9-day period. Each dog must be treated as an individual. There is no reliable method of predicting the length of time a dog will need to respond or the amount of *o,p'*-DDD necessary to destroy enough of the adrenal cortex for response to be seen.

Concomitant Glucocortoids During the Loading-Dose Phase. The veterinary literature recommends two distinct protocols for the induction or loading-dose phase of *o,p'*-DDD therapy: no concomitant glucocorticoids versus administration of both glucocorticoids and *o,p'*-DDD. Neither method is wrong, and there are advantages and disadvantages with each.

NO GLUCOCORTICOIDS. The advantages of not administering glucocorticoids are as follows: (1) Close communication between veterinarian and client, plus an understanding of when to discontinue medication, clinically, has been successful. (2) If a dog receives glucocorticoids, it is not possible for an owner or a veterinarian to know if and when an adequate amount or too much *o,p'*-DDD has been administered. (3) Because the end point cannot be seen clinically, the clinician must rely on the ACTH stimulation test. To perform this test, all glucocorticoid therapy must be withdrawn for 1 or 2 days to avoid having the cortisol assay detect the oral rather than the dog's glucocorticoid concentrations. (4) If glucocorticoids are needed because of *o,p'*-DDD overdosage, a crisis may develop after their withdrawal. (5) Simultaneous administration of glucocorticoids did not eliminate clinical signs of cortisol deficiency in many dogs treated with both drugs. (6) It seems easier to determine if glucocorticoid therapy is needed during treatment. The incidence of *o,p'*-DDD overdosage with clinical signs is less in dogs that do not receive simultaneous glucocorticoids than in dogs that do receive the drug because the owners can appreciate mild clinical changes early in therapy and stop the medication before the problem becomes severe. Transient need for glucocorticoids has occurred in only 5 per cent of our dogs (versus 35 per cent in glucocorticoid-treated dogs) and permanent Addison's, in only 2 per cent of our dogs (versus 5.5 per cent of glucocorticoid-treated dogs). If signs of cortisol deficiency do develop, the clinician can be certain that the end point in therapy has been achieved. An ACTH response test may be performed immediately and the dog then placed on glucocorticoids. Response to glucocorticoid medication would also be diagnostic of surpassing the desired end point of therapy.[79,83]

GLUCOCORTICOIDS. The advantages of using glucocorticoids are as follows: (1) Use of both glucocorticoids and *o,p'*-DDD has been quite successful. (2) The number of dogs with one or more adverse effects to *o,p'*-DDD is significant, and administration of glucocorticoids minimizes or eliminates these signs. (3) Resolution of clinical signs was obvious to owners despite the glucocorticoid therapy. (4) Oral glucocorticoids do not interfere with assays if discontinued the day of testing.[83]

Need for Glucocorticoids. If signs of anorexia, vomiting, diarrhea, weakness, or listlessness develop, glucocorticoid therapy is warranted. If the dog has received no glucocorticoids during the initial phase of *o,p'*-DDD therapy, they

should be started. If the dog has been treated with glucocorticoids, the dose needs to be increased. This is true during the maintenance phase of therapy and if the well-controlled dog undergoes major stress (e.g., illness, trauma, elective surgery). Prednisone is administered at 1 mg/lb/day for 2 days. If signs have developed as a result of *o,p'*-DDD overdosage, the dog usually shows clinical improvement within hours of initiating prednisone therapy. If oral therapy is not possible because of vomiting, parenteral steroids are warranted. After 2 days of therapy, the prednisone dosage is tapered over 1 to 3 weeks and then stopped. Recurrence of signs demands reinstitution of therapy or raising the dosage.

Planned Induction of Permanent Hypoadrenocorticism. Favorable results associated with accidental induction of permanent hypoadrenocorticism have prompted the suggestion that all dogs with hyperadrenocorticism undergo a treatment schedule aimed at the complete destruction of the adrenal cortices. Substitution therapy for the ensuing adrenocortical insufficiency would continue for the life of the dog. The treatment protocol involves 25 consecutive days of *o,p'*-DDD in a dose of 50 to 75 mg/kg daily and as much as 100 mg/kg daily for toy breeds. The daily *o,p'*-DDD dosage is divided into three or four administrations per day with food to minimize neurologic complications and ensure good intestinal absorption. Lifelong cortisone (0.5 mg/lb twice a day) and mineralocorticoid (Chapter 119) substitution is begun on the 3rd day of *o,p'*-DDD administration. The cortisone dosage should be tapered after the 25-day *o,p'*-DDD schedule has been completed.[84, 85]

There are several disadvantages to this protocol. First, about 33 per cent of dogs so treated relapse with Cushing's within the first year alone, suggesting that periodic ACTH stimulation testing is necessary, just as with traditional modes of treatment. This treatment protocol would be considerably more expensive than long-term treatment with *o,p'*-DDD because treatment of Addison's disease is usually expensive. Finally, the dog with well-controlled Cushing's receiving *o,p'*-DDD several times a week or month is not in danger if medication is not given, whereas the dog with hypoadrenocorticism must receive its medication to live.

Need for Both Glucocorticoids and Mineralocorticoids. *o,p'*-DDD is reported to spare the zona glomerulosa and, therefore, mineralocorticoid secretion. Dogs that develop signs of weakness, anorexia, and/or vomiting without electrolyte imbalances require immediate glucocorticoid therapy. Electrolyte disturbances suggestive of deficient mineralocorticoids (hyperkalemia and/or hyponatremia) have resulted from *o,p'*-DDD administration; these dogs require both glucocorticoid and mineralocorticoid therapy (Chapter 119). This finding is extremely rare (seen in less than 2 per cent of our closely monitored dogs). Glucocorticoid deficiency usually is transient in *o,p'*-DDD–treated dogs. Addison's disease (deficiency of both glucocorticoids and mineralocorticoids) in *o,p'*-DDD–treated dogs usually is permanent.

Time Sequence for Improvement in Signs and Biochemical Abnormalities. Dogs with *o,p'*-DDD–treated PDH usually respond quickly. The most obvious and rapid response is the reduction in appetite, water intake, and urine output seen during the first 5 to 9 days of therapy. Many owners comment that they see an increase in activity during the 1st or 2nd week of treatment. Other signs take longer to dissipate. Muscle strength improves within weeks, as does reduction in the potbellied appearance.

Alopecia, thin skin, acne, calcinosis cutis, and panting often take 3 to 6 months for significant improvement to be noted. Dogs with hair coat abnormalities may go through a phase of severe seborrhea associated with a terrible hair coat or worsening alopecia and pruritus that may last for 1 or 2 months before the hair coat shows significant improvement. Some dogs go through a phase of "puppy hair coat" before the normal adult coat returns. A few dogs have dramatic changes in coat color after successful therapy (Fig. 118–27). Female dogs may begin an estrous cycle within 1 or 2 months of completing successful treatment.

The external appearance of a dog with Cushing's syndrome improves with therapy before internal changes are noted. The liver enzymes and cholesterol may take 6 to 18 months to improve. These two parameters may not improve, however, because of the mild but continuing effects *o,p'*-DDD has on the liver (resulting in abnormal serum enzyme activities) and because in people, *o,p'*-DDD has been demonstrated to cause increases in serum cholesterol concentration.[86, 87] Six to 18 months may be required for return of normal blood pressure. Urinary tract infections may resolve quickly or linger because of pyelonephritis, bladder retention of urine, calculi, or other problems.

Failure to Respond to o,p'-DDD. It is uncommon for *o,p'*-DDD to fail to help a dog with PDH. The drug is potent, and its effect on destroying the zona fasciculata and zona reticularis is consistent. There are several reasons for apparent treatment failures. (1) A dog thought to have PDH may indeed have an adrenocortical tumor (adenoma or carcinoma). Adrenocortical tumors are relatively resistant to the cytotoxic effects of *o,p'*-DDD. (2) The drug itself may not be potent, and replacing the owner's tablets with *o,p'*-DDD obtained from a new or different bottle may solve an appar-

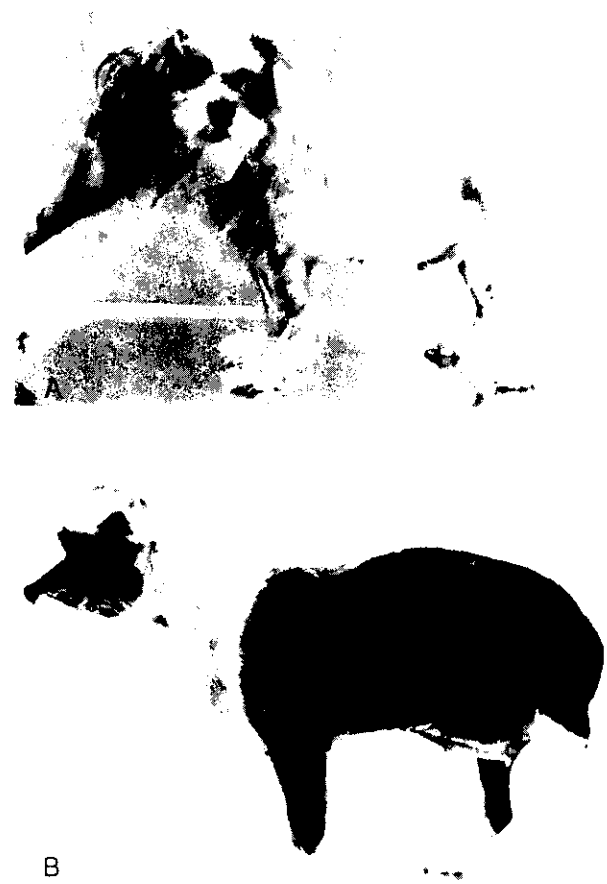

Figure 118–27. Small mixed-breed dog with PDH before therapy (*A*) and 2 months after *o,p'*-DDD therapy, showing dramatic hair coat color change (*B*).

ent treatment failure. (3) The drug may not be given with food, and absorption may be adversely effected (fatty meals improve absorption the most, but when given with any food, absorption is enhanced). (4) There may be concern about a treatment failure after 14 days without response, but a small percentage of dogs require 30 to 60 consecutive days of therapy, or 100 to 150 mg/kg/day rather than the usual initial dosage of 50 mg/kg/day. (5) Dogs that are diagnosed incorrectly fail to respond. (6) The dog may have iatrogenic Cushing's syndrome.

The various causes of an apparent treatment failure must be considered before abandoning the use of *o,p'*-DDD. If treatment failure has occurred, the 25-day induction of hypoadrenocorticism, ketoconazole therapy, or bilateral adrenalectomy should be considered. Other medical therapies can also be considered (each is described later in this chapter).

Therapy of Concurrent Diabetes Mellitus and Cushing's Syndrome

INITIAL DIAGNOSIS AND TREATMENT. If both diagnoses are suspected at initial examination, insulin therapy should be initiated while completing the diagnostic evaluation for Cushing's. Most of these dogs require large doses of insulin. Those that need a conservative or low dose of insulin are the best candidates for no longer needing insulin after *o,p'*-DDD therapy. Attempts at extremely good control of the diabetes should not be undertaken until the Cushing's is controlled or until that diagnosis is refuted.

o,p'-DDD DOSAGE. These dogs should be treated in the same manner as any dog with PDH (*o,p'*-DDD at 50 mg/kg/day and no glucocorticoids). It is recognized, however, that Cushing's results in insulin antagonism. Therefore, successful reduction in the circulating cortisol concentrations should reduce insulin requirements. Failure to recognize this effect could result in hypoglycemic reactions.

TREATMENT AND MONITORING PROTOCOL. The complicated nature of treating this combination of diseases should be carefully explained to the owner. Both owner and veterinarian must be aware that as the dog receives *o,p'*-DDD, the Cushing's should progressively resolve, and the diabetes management usually changes as well. Owners should be asked to catch a small amount of urine for glucose monitoring at least three times daily from their pet during the loading-dose phase of *o,p'*-DDD therapy. Any time a urine sample is found to be negative for glucose, the subsequent insulin dose should be reduced by at least 10 to 20 per cent. The hyperadrenocorticism in most of these dogs is controlled in the expected 5 to 9 days.

The ACTH stimulation test should be rechecked within 7 days of initiating the *o,p'*-DDD to recognize the end point and to avoid overdosage. The recheck protocol for these dogs should proceed as follows: (1) owner feeds pet at home; (2) dog brought to veterinary hospital in the morning (7 to 9 A.M.); (3) blood glucose measured and owner observed as he or she administers insulin; (4) blood glucose monitored every hour throughout the day; (5) 1 to 2 hours before owner is to pick up the pet in the late afternoon, ACTH stimulation test is begun and completed. This protocol provides an opportunity to answer two critical questions: What effect has *o,p'*-DDD therapy had on diabetes control (blood glucose, insulin dosage), and what effect has it had on the hyperadrenocorticism?

PROGNOSIS. About 10 per cent of these dogs require no insulin after successful therapy. An additional 60 to 70 per cent require significantly less insulin and their diabetes mellitus is easier to control. The insulin requirement in the remaining dogs may not be reduced by control of the PDH, but that insulin should be more effective in lowering blood glucose concentrations. If none of these three results are observed, the original diagnosis of hyperadrenocorticism must be questioned.

o,p'-DDD Therapy of Dogs with Functioning Adrenocortical Tumors

Background. The ideal treatment for a dog with a functioning adrenocortical tumor causing hyperadrenocorticism is surgical removal of the tumor, curing the dog. It is appreciated, however, that some of these dogs have inoperable tumors, some have metastases at the time of diagnosis, some are too debilitated for this type of major surgery, and some have owners who will not allow surgery for any of a variety of reasons. *o,p'*-DDD treatment of dogs with PDH was compared with that in dogs with adrenocortical tumors. Using similar doses of *o,p'*-DDD (50 mg/kg/day initially), it was demonstrated that dogs with adrenocortical tumors were relatively resistant to the adrenocorticolytic effects of the drug (Fig. 118–28).[88] Some dogs with adrenocortical tumors, however, respond to the traditional doses, and those that appear resistant often respond to higher dosages.[89]

Protocol. The recommended treatment of dogs with adrenocortical tumors with *o,p'*-DDD would be to follow the protocol for PDH, using the same initial dose of 50 mg/kg/day. If, after the initial 7 to 10 days of treatment, the ACTH response test result demonstrates improvement but not values in the ideal less than 5 μg/dl range, the original 50 mg/kg/day schedule should be continued. This second 7-to-10-day phase should again be assessed with an ACTH stimulation test.

Lack of significant improvement in ACTH response testing after the initial 7-to-10-day loading-dose phase would indicate a need for continuing the *o,p'*-DDD at twice the dosage for an additional 7 to 10 days. Duration of the loading-dose phase and dosage requirement would then be determined on an individual basis.

Results. Using this protocol, 43 per cent of 32 dogs had abnormally exaggerated ACTH response test results after the first 10 to 14 days. Despite concurrent glucocorticoid therapy, 60 per cent suffered adverse effects sometime during treatment as a result of direct drug toxicity associated with high-dose *o,p'*-DDD or low cortisol concentrations or both. More than 60 per cent of the *o,p'*-DDD–treated dogs with adrenocortical tumor were considered to have a good to excellent response.[89]

***o,p'*-DDD Resistance and Histologic Evaluation.** There is little doubt, from clinical response to therapy, that adrenocortical tumors are relatively resistant to *o,p'*-DDD compared with the adrenocortical hyperplasia associated with PDH. This concept is supported with review of histologic findings from these two groups of dogs. Histologically, the adrenal cortices, specifically the zona fasciculata, of dogs with *o,p'*-DDD–treated PDH demonstrates collapse, necrosis, and hemorrhage, with fibrosis, atrophy, and degeneration in dogs that received the drug chronically. In the latter group, hyperplastic nodules occasionally are noted. In many, adrenocortical destruction is noted and hyperplasia is presumed to have been present.

Dogs with adrenocortical tumors similarly treated with *o,p'*-DDD, by contrast, usually have a clear description of tumor histology. The pathologist usually provides an impression with respect to the malignant potential of the tumor (adenoma or carcinoma).[88, 89] Most of these evaluations con-

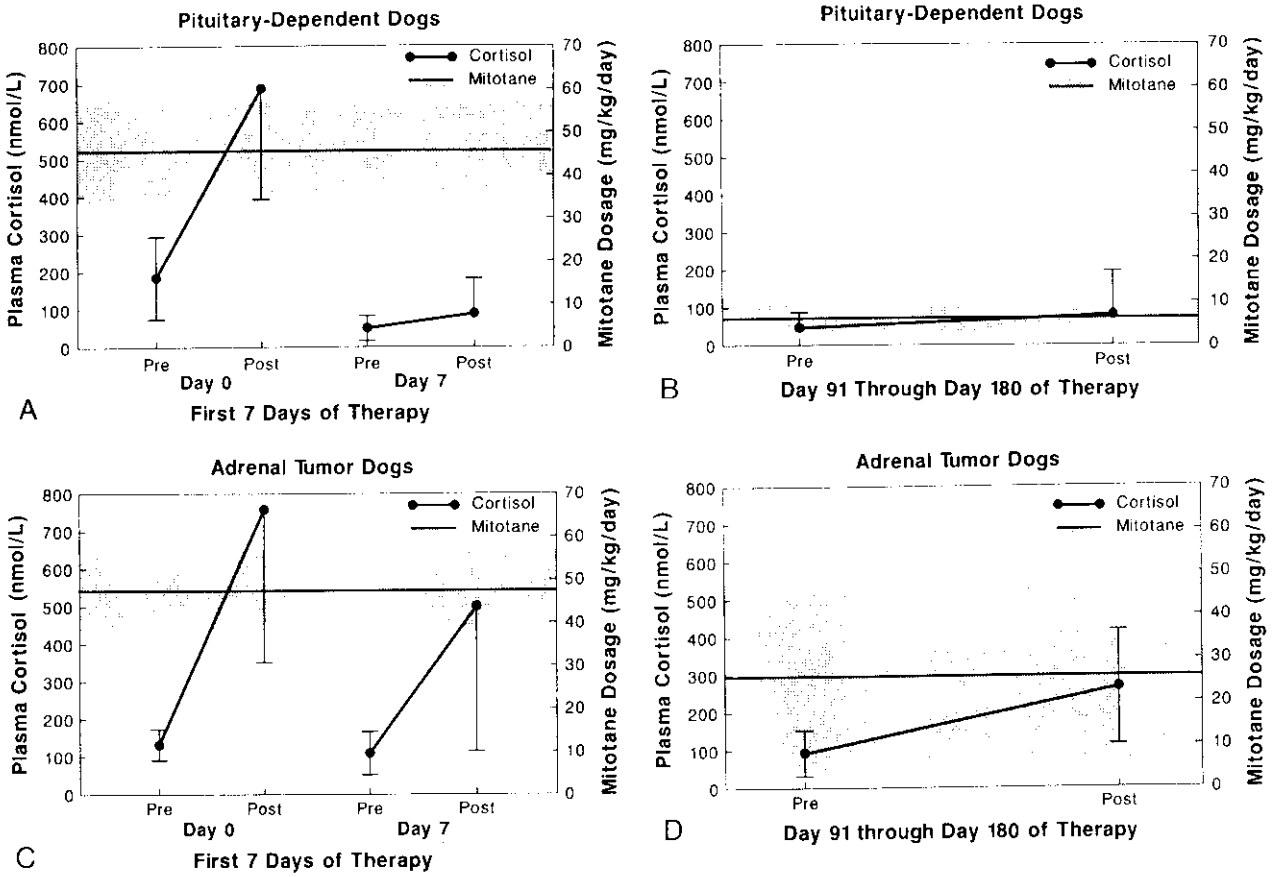

Figure 118–28. ACTH response test results from a group of 12 dogs with PDH before and after 7 days of *o,p'*-DDD treatment (*A*) and again after 180 days of treatment (*B*) compared with results of the same tests from a group of 12 dogs with hyperadrenocorticism resulting from adrenocortical tumors that were matched for age, body weight, and dose (*C* and *D*). The results show that dogs with PDH are more sensitive to *o,p'*-DDD than are dogs with adrenocortical tumors.

tain no mention of adrenal destruction or necrosis, support to the concept that these tumors are more resistant to the lytic effects of the drug.

Maintenance (Long-Term) Therapy with o,p'-DDD

Background. Once the initial daily protocol with *o,p'*-DDD completes adequate destruction of the adrenal cortex, as determined by clinical signs (reduced appetite and water intake) and/or ACTH stimulation test results, maintenance therapy should begin. In dogs with PDH, *o,p'*-DDD has not affected the abnormal pituitary, and excessive ACTH secretion continues or becomes exaggerated.[65] Failure to continue *o,p'*-DDD therapy will result in regrowth of the adrenal cortices and return of clinical signs. This exacerbation of the disease usually occurs within 3 to 24 months of stopping therapy, although some dogs demonstrate recurrence within weeks.

Protocol. Maintenance therapy involves choosing a regimen and altering that regimen as required. Dogs that respond to daily *o,p'*-DDD therapy within 9 days or that have a post-ACTH plasma cortisol concentration less than 2 μg/dl are classified as sensitive and begin a maintenance schedule of 25 mg/kg of *o,p'*-DDD every 7 days. Those that initially require more than 10 days of therapy or with a post-ACTH plasma cortisol concentration greater than 5 μg/dl are classified as resistant and receive 50 mg/kg every 7 days. In either situation, the dosage is divided into two to four treatments per week.

An ACTH response test is performed 1 and 3 months after beginning the maintenance therapy. If the plasma cortisol concentration after ACTH administration begins to rise to or above 4 to 5 μg/dl, the *o,p'*-DDD dosage is increased. Some dogs remain stable for months or years on conservative dosages, whereas others receive rather large doses. It is important to tailor treatment to the needs of each dog. Return of clinical signs suggestive of hyperadrenocorticism should be managed by performing an ACTH stimulation test to confirm disease exacerbation, followed by raising the dose of *o,p'*-DDD. Obvious recurrence of Cushing's should be managed with daily *o,p'*-DDD after ruling out other diseases with signs that mimic Cushing's, such as kidney disease and diabetes mellitus (see Table 118–6).

Long-Term Monitoring. Many dogs treated with *o,p'*-DDD remain stable on maintenance treatment. It is recommended that these dogs be rechecked with an examination and an ACTH response test every 3 to 4 months. Test results allow the veterinarian to adjust maintenance dosages if subclinical problems are occurring. Whenever the post-ACTH plasma cortisol concentration exceeds 5 μg/dl, the dose of *o,p'*-DDD should be increased. Whenever listlessness and anorexia are associated with low plasma cortisol results, the *o,p'*-DDD should be transiently discontinued or the dose should be reduced.

Stress or Illness. Dogs receiving *o,p'*-DDD and undergoing stress (illness, trauma, elective surgery) should be treated with glucocorticoids. The adequately treated dog with PDH has sufficient adrenal reserve for day-to-day living but not enough to handle major stress.

o,p'-DDD Overdosage

Overdosage with *o,p'*-DDD is common. Most overdosed dogs (20 to 50 per cent of treated dogs) have mild and transient signs, especially after glucocorticoid treatment. A minority of dogs (less than 2 per cent) develop permanent Addison's disease. Permanent disease usually is associated with hyperkalemia, hyponatremia, and low plasma cortisol concentrations before and after ACTH. Most of these dogs require both mineralocorticoid and glucocorticoid treatment for life.

In the more typical and mild forms of overdosage, the *o,p'*-DDD–treated dog becomes weak, anorectic, lethargic, ataxic, or develops vomiting and/or diarrhea. Serum chemistry profiles, CBC, and urinalysis from these dogs often are unremarkable. The easiest method of confirming the diagnosis is to treat the dog with prednisone. Clinical improvement in 1 to 3 hours (sometimes 6 to 12 hours are required) confirms that an overdosage of *o,p'*-DDD has occurred. Treatment with *o,p'*-DDD is withheld. The prednisone is initially administered to effect (to eliminate all signs). The prednisone dose is then slowly tapered over 2 to 6 weeks. As long as the dog needs prednisone, *o,p'*-DDD is withheld. When the prednisone is discontinued and the dog is stable on no treatment for an additional 2 to 4 weeks, *o,p'*-DDD should again be given but at a lower dosage.

Prognosis—o,p'-DDD–Treated Dogs with PDH

Pituitary-dependent hyperadrenocorticism is a serious disorder. We have been able to monitor more than 500 treated dogs. Of the dogs that have died, the life expectancy averaged 29.7 months. These included dogs that lived only days and several that lived longer than 10 years. It appears that good owner observation improves the prognosis. Relapses were common. More than 40 per cent of the dogs had at least one period in which signs of hyperadrenocorticism recurred, requiring a brief repeat of daily *o,p'*-DDD therapy or an increase in the maintenance dose. Forty-five per cent of the dogs that died had a problem that could have been or was related to the hyperadrenocorticism (e.g., thromboembolism, congestive heart failure, infection, pancreatitis, diabetic ketoacidosis, growing pituitary tumor). Episodes of *o,p'*-DDD overdosage were also common. Five per cent of the dogs were mildly overdosed during the induction phase of therapy. A total of 32 per cent were overdosed sometime during therapy. Death from overdosage was seen in less than 2 per cent of the dogs.

TREATMENT—MEDICAL MANAGEMENT WITH KETOCONAZOLE

Background

Ketoconazole (Nizoral), an imidazole derivative, is an orally active broad-spectrum antimycotic drug. At high dosages, the drug also affects steroid biosynthesis. The endocrine potencies of the substance result from an interaction of the imidazole ring with the cytochrome P-450 component of various steroidogenic enzyme systems. *In vivo*, the administration of low doses of ketoconazole leads to a significant reduction in serum androgen concentrations, whereas at higher doses, cortisol secretion is suppressed.[90] This inhibitory effect of ketoconazole on steroid biosynthesis has led to its therapeutic use in the treatment of advanced prostatic cancer, hirsutism, precocious puberty, and Cushing's syndrome.[91]

Protocol in Canine Cushing's Syndrome

The drug is administered initially at a dose of 5 mg/kg twice daily for 7 days. If no problems with appetite or icterus are noted, the dose is increased to 10 mg/kg twice daily. After 14 days, an ACTH response test should be completed, in addition to a complete history and physical examination. If the Cushing's is not controlled, the dosage is increased to 15 mg/kg twice daily. We have not used larger doses. Some dogs can be maintained at the 10 mg/kg, b.i.d., dose and others at the 15 mg/kg dose indefinitely. Dose requirement is determined from owner opinion, physical examination results, blood chemistries, and ACTH stimulation test monitoring. The goal in ACTH stimulation results are pre- and post-ACTH plasma cortisol concentrations less than 5 μg/kg. Most dogs do not achieve clinical remission at doses less than 30 mg/day.

Results

We have evaluated the use of this drug in more than 50 dogs with naturally occurring hyperadrenocorticism, including dogs with pituitary-dependent disease as well as dogs with adrenocortical tumors. Laboratory data demonstrate that about 80 per cent of treated dogs have a rapid reduction in serum cortisol concentration and cortisol responsiveness to ACTH (Fig. 118–29). In the dogs treated for more than 2 months, there has been significant improvement in their clinical condition, as evidenced by a reduction in water intake, urine production, appetite, panting, and other signs. Regrowth of hair and return of muscle strength are also noted. Signs of toxicity seldom have developed. Signs of overdosage usually are due to hypocortisolism.[92]

It appears that 20 to 25 per cent of dogs fail to respond to the drug as a result of poor intestinal absorption. Although this is true for some dogs that fail to improve, other explanations must be entertained because some dogs demonstrate a paradoxical increase in pre- and post-ACTH plasma cortisol concentrations when receiving ketoconazole. Plasma cortisol concentrations return to pretreatment levels when the drug is discontinued. The major drawbacks (Table 118–7) to the use of this drug are its expense and failure to respond and the fact that it must be administered twice daily indefinitely.

Indications

Ketoconazole, with its low incidence of toxicity and negligible effects on mineralocorticoid production, may be an attractive (albeit expensive) alternative in the medical management of canine hyperadrenocorticism (see Table 118–7). Ketoconazole is readily available, and because effect is a result of enzyme blockage, it is completely reversible. It may be used as an alternative to *o,p'*-DDD in the medical management of dogs with malignant, large, or invasive adrenal tumors if surgical intervention is not an option but palliative therapy is desired. We use ketoconazole most frequently in the preoperative stabilization and improvement of surgical candidates. Some dogs (extremely rare in our experience) do not tolerate *o,p'*-DDD at any dose, and ketoconazole can be tried. Despite the number of screening tests for hyperadrenocorticism, the clinician may use response to therapy as a diagnostic aid. In this situation, ketoconazole is an enzyme blocker with no long-term effects. One can assess its effect without causing tissue damage.

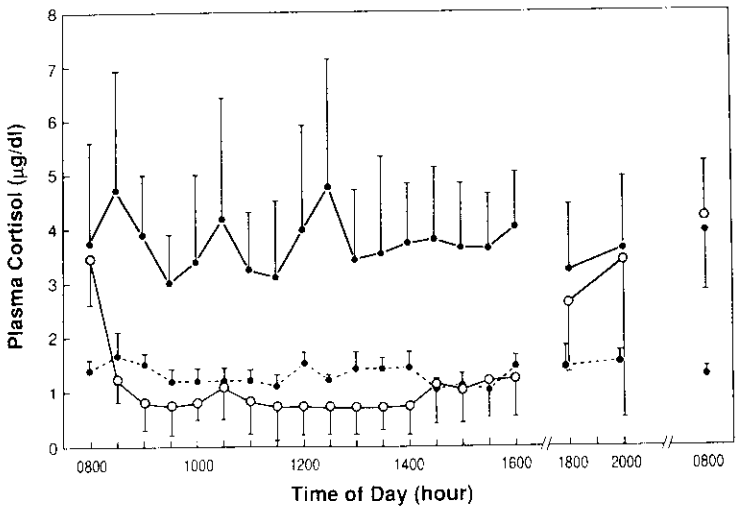

Figure 118–29. Mean plasma cortisol concentrations over a 24-hour period from 15 normal dogs (●– – –●), 18 dogs with untreated hyperadrenocorticism (9 with PDH and 9 with adrenocortical tumors; (●————●), and those 18 dogs after their first dose of ketoconazole (○————○), showing the potent and rapid effect this drug has on preventing cortisol synthesis.

TREATMENT—OTHER MEDICATIONS

Cyproheptadine

Increased CNS serotonin concentrations may be associated with excess pituitary secretion of ACTH and, therefore, increased adrenal secretory activity. Cyproheptadine (Periactin), a drug with antiserotonin, antihistamine, and anticholinergic effects, has been used with limited success in treating humans and dogs with PDH.[1, 23] Although a few well-documented cases of remission have been reported, cyproheptadine causes sedation, increased appetite, and weight gain. It usually is ineffective in treating individuals with ACTH-secreting pituitary tumors.[1]

Bromocriptine

Bromocriptine (Parlodel), a dopamine agonist, seldom lowers plasma ACTH concentrations and seldom produces remission in people with PDH. The recommendation is that the drug be reserved for people with hyperprolactinemia as well as Cushing's. Bromocriptine is not recommended for use in dogs or cats with Cushing's syndrome because of its relative ineffectiveness.[93]

Metyrapone

Metyrapone, an 11β-hydroxylase inhibitor, has been used to reduce cortisol hypersecretion. Its use may be accompanied by increased ACTH levels that may overcome the enzyme inhibitory properties, and it may cause gastrointestinal adverse effects in people. Several reports on the use of metyrapone as the sole therapy for people with Cushing's syndrome demonstrate effectiveness.[94, 95] Metyrapone has been used successfully in the management of a cat with hyperadrenocorticism.[96] This drug is not consistently available.

TABLE 118–7. KETOCONAZOLE THERAPY

Indications
1. Prepare a dog for surgery
2. Alternative therapy for a dog that has metastasis or any other reason that it is not a surgical candidate
3. Alternative to dogs that cannot tolerate *o, p'*-DDD
4. Diagnostic aid—improvement points toward Cushing's syndrome
5. Sole mode of therapy
Drawbacks
1. Must be given twice daily indefinitely
2. Expensive
3. 20–25% of treated dogs fail to respond (fail to absorb the drug?)
4. Overdosage problems can occur

L-Deprenyl

L-Deprenyl is approved for use in humans with Parkinson's disease. It acts as an inhibitor of the enzyme monoamine oxidase type B, thereby promoting normalization of dopamine. ACTH secretion is controlled in part by hypothalamic CRH secretion by way of positive feedback. It is hypothesized that ACTH is also controlled by way of a negative feedback mechanism mediated by dopamine and that pituitary-dependent Cushing's may be caused by a lack of this negative suppression of ACTH, allowing excess synthesis and secretion of the hormone. L-Deprenyl, by enhancing dopamine concentrations, may downregulate ACTH and control Cushing's. The initial pilot project involved the treatment of seven dogs with PDH with 2 mg/kg PO once daily. Five of the seven demonstrated partial to complete resolution of the PDH within a 2-month period.[97]

RU486—Mifepristone

RU486 is a 19-norsteroid that inhibits glucocorticoid binding at the receptor. The result is blockage of the feedback effect of cortisol on ACTH secretion as well as blockage of the systemic effects of cortisol. People treated with 4 to 6 mg/kg have increases in both plasma ACTH and cortisol concentrations, but they are prone to developing signs of cortisol deficiency (weakness, nausea, vomiting). Serum cortisol concentrations increase because it is the binding that is inhibited, not hormonal synthesis or secretion. Treatment with mifepristone ameliorates the clinical manifestations of hypercortisolism in more than 50 per cent of people with Cushing's syndrome caused by adrenocortical tumor or in whom the source of ACTH is other than the pituitary (ectopic; not reported in dogs or cats). By contrast, people with pituitary-dependent Cushing's do not respond with consistency to mifepristone because their excesses in ACTH, and then cortisol, overwhelm the receptor blockade.[98, 99]

TREATMENT—LARGE PITUITARY TUMORS (PITUITARY MACROTUMOR SYNDROME)

Background

The clinical signs, endocrine testing, and diagnostic evaluation of dogs with the macrotumor syndrome have been

reviewed in the pathology, medical complications (CNS signs), and MRI sections of this chapter. The macrotumor syndrome is being recognized with increasing frequency because of improved diagnostic capabilities (CT and MRI) and an increasing index of suspicion. Conservatively, 10 to 15 per cent of dogs with PDH develop clinical problems as a result of this condition. The primary mode of treating these dogs is photon irradiation. Success has been limited. Most of the dogs undergoing irradiation have significant clinical signs and extremely large intracranial masses. Response to treatment will improve as our ability to identify these dogs earlier in the course of their disease improves, so that the radiation is directed at smaller tumors or in dogs less debilitated by the condition.

Diagnosis

The specific antemortem diagnosis of a pituitary macrotumor is made with results of CT or MRI scans. Because these studies involve facilities that are not widely available, require anesthesia, and can be expensive, patient selection becomes of paramount importance (see previous section in this chapter).

Treatment

Modes of Therapy. Modes of therapy are limited. Most dogs with CNS signs have masses much too large for safe surgical extirpation. Success in resolving some to all of the clinical signs has been achieved with the use of cobalt-60 photon irradiation or with the use of linear accelerator photon irradiation.

Dose. Treatment usually involves delivery of a predetermined total dose of radiation given in fractions over a period of several weeks. Current doses include 40 to 48 Gy given in 4-Gy doses three times per week for 3 to 4 weeks. Alternatively, 3 Gy may be delivered 5 days per week with a total dose of 45 to 60 Gy. Irradiation has successfully reduced tumor size and caused a reduction in or elimination of the CNS clinical signs.[69] Reduction of the secretory nature of the pituitary tumors is variable, and secretion may increase despite a confirmed reduction in tumor size. Therefore, *o,p'*-DDD or an alternative form of medical therapy may be necessary in addition to pituitary irradiation.

Results. There are few reports in the veterinary literature, and those reports each include rather small numbers of dogs. Response to radiation can be categorized into those dogs that fail to respond or die during radiation treatment (about 33 per cent); dogs that demonstrate some response and that survive for a few months (about 33 per cent); and dogs in which a complete resolution of signs and years of survival are noted (about 33 per cent). If the dogs were first categorized according to tumor size and clinical signs, those with the subtlest signs and smallest tumors have the best response to treatment and those with the most worrisome clinical signs and largest tumors probably should not be treated.

Success

We are convinced that treatment success is not dependent on the source of photons (cobalt-60 versus linear accelerator), the dose per day, or the total dose of radiation delivered to the pituitary tumor. Although these factors are important, the most critical parameter is probably the time of diagnosis. A dog with severe clinical signs and a huge tumor (greater than 2 cm in diameter) carries a much poorer prognosis than a dog with subtle signs and a small tumor (0.5 to 1.5 cm in diameter). There is little doubt that brain CT or MRI scanning of all dogs with PDH, with subsequent radiation of all visible pituitary tumors, could be of potential value but is not practical. We recommend radiation therapy of any tumor greater than or equal to 7 mm in diameter.

The problem lies in identifying dogs that are most likely to have visible masses. Use of age, sex, breed, and endocrine test results has not been consistent.[8, 17, 50] Clinical signs associated with Cushing's have not proved informative. Clinical signs of a large intracranial tumor are probably observed too late in many dogs.

SPONTANEOUS REMISSION OF CUSHING'S SYNDROME

Spontaneous remission of Cushing's syndrome is a documented phenomenon in humans. It is possible for a dog with PDH to undergo spontaneous remission as well. We have had five dogs with a history, physical examination, and endocrine testing consistent with PDH. Treatment was withheld in each of these dogs because the owners believed that their pets were already improving. Subsequent evaluations demonstrated resolution of all evidence supporting the diagnosis of PDH. It has been hypothesized that these dogs embolized their pituitary microadenomas, resulting in return of a normal state.

HYPERADRENOCORTICISM IN CATS

The incidence of this condition in cats is rare. A complete description of the endocrinopathy is not presented here. The 34 cats with hyperadrenocorticism we have had over the past 10 years are reviewed. In the same time span, we have evaluated more than 700 dogs with Cushing's syndrome, illustrating the relative frequency of diagnoses in the two species.

SIGNALMENT

Cats with Cushing's syndrome have been middle-aged or older (average, 10 to 11 years) and usually of mixed breeding. About 70 per cent of the cats have been female, and no breed predilection has been noted.

HISTORY AND PHYSICAL EXAMINATION

The most common clinical signs of feline hyperadrenocorticism are polydipsia, polyuria, and polyphagia (Table 118–8). These signs frequently are observed because the incidence

TABLE 118–8. HISTORY AND PHYSICAL EXAMINATION FINDINGS IN CATS WITH HYPERADRENOCORTICISM

History	*Physical Examination*
Polydipsia and polyuria	Potbellied appearance
Polyphagia	Unkempt (rough) hair coat
Patchy alopecia	Thin, fragile skin (bruises easily)
Weight gain, abdominal enlargement	Muscle wasting
Inactivity, muscle weakness	Hepatomegaly
Poor hair coat, not grooming	Patchy alopecia
Skin infections	Skin infections
Weight loss	

of diabetes mellitus is extremely high. In most cats, Cushing's syndrome is diagnosed after documentation of insulin-resistant diabetes mellitus. Therefore, these signs develop as a result of the hyperglycemia and glycosuria rather than from hypercortisolism. Consistent with this concept are the low incidence of similar signs in cats receiving exogenous glucocorticoids and the common finding of concentrated urine (greater than 1.020) in most cats with hyperadrenocorticism.

A pot belly (pendulous abdomen); unkempt hair coat; thin, easily bruised, fragile, pigmented skin; and muscle wasting are also common signs. Symmetric endocrine alopecia involving the trunk and flanks has been observed in a few cats. Normal feline grooming behavior or lifting the skin to administer a subcutaneous injection may result in severe lacerations. These cats may be described as listless or depressed. Dermatologic infections (including demodicosis) and hepatomegaly are common. Less common but reported sites of infection include facial abscesses, bacterial and fungal cystitis, pyothorax, wet feline infectious peritonitis, bronchitis, and rhinitis.

Data Base Evaluation

Complete Blood Count

The CBC from cats with hyperadrenocorticism was not contributory to the final diagnosis. The red and white blood cell counts were consistently within normal limits. One-half of the cats tested have had circulating eosinophils, and 75 per cent had normal lymphocyte counts. As in the dog, the white blood cell differential is not a reliable screening test for predicting the presence of hyperadrenocorticism in the cat.

Urinalysis

Seventy-five to eighty per cent of cats with Cushing's syndrome have had randomly obtained urine specific gravities greater than 1.020. More than 80 per cent of cats with Cushing's syndrome had diabetes mellitus with hyperglycemia and glycosuria. Only 5 to 15 per cent of dogs with Cushing's syndrome have glycosuria.

Serum Biochemistry Profile

The most frequently observed abnormalities are hyperglycemia, hypercholesterolemia, and a mild increase in ALT. Each of these alterations could be attributed to poorly regulated diabetes mellitus. Indeed, more than 80 per cent of cats diagnosed with hyperadrenocorticism have had concurrent diabetes mellitus. Steroid-induced ALP is unique to dogs, as is steroid hepatopathy.

Radiographs

Radiographically, most (more than 70 per cent) of these cats have had hepatomegaly, and several were thought to have a pendulous abdomen. No other radiographic abnormalities were common. Abdominal ultrasonography has proved to be more valuable and reliable than radiographs in evaluation of the presence and size of adrenals.

Establishing the Diagnosis

ACTH Stimulation

Protocol. The ACTH stimulation test in cats is performed by obtaining plasma before and 1 and 2 hours after 1 U ACTH gel/lb IM (repository corticotropin injection USP). Alternatively, plasma is obtained before and 30 and 60 minutes after 0.125 mg of synthetic ACTH per cat IM (Cortrosyn). Increases in plasma cortisol occur more rapidly in cats than in dogs. Two post samples are recommended because the peak effect is less consistent in cats, and the two values allow results to be cross-checked.

Results. The normal values for cats may be slightly lower than those for dogs. Laboratories are encouraged to establish their own reference values and to avoid using canine or incorrect reference values. Using our plasma cortisol assay, a post-cortisol level greater than or equal to 15 μg/dl was consistent with hyperadrenocorticism and one between 13 and 15 μg/dl was borderline.[58] About 60 per cent of cats with hyperadrenocorticism have abnormally exaggerated test results, and dexamethasone testing is more sensitive and specific.

Low-Dose Dexamethasone Test

Protocol. The dexamethasone screening test is performed as in dogs (0.01 to 0.015 mg/kg IV; determination of plasma cortisol concentration before and 8 hours after administration). During the 8 hours after dexamethasone administration, other procedures should not be performed and the cat should be kept as quiet as possible in its cage. Post-dexamethasone plasma cortisol concentrations less than or equal to 1 μg/dl are consistent with a diagnosis of hyperadrenocorticism.[58] Because 15 to 20 per cent of normal cats fail to demonstrate suppression after this low dose of dexamethasone (or they escape transiently from the suppressive effects of dexamethasone), it is recommended that cats suspected of having Cushing's also be tested with the 0.1 mg/kg dose. Failure to suppress on both these doses is strongly consistent with a diagnosis of hyperadrenocorticism.

Results. About 90 to 95 per cent of cats with Cushing's syndrome have failed to demonstrate normal suppression in plasma cortisol concentrations on any of the low-dose dexamethasone test protocols (0.01; 0.015; 0.1 mg/kg).

Urine Cortisol:Creatinine Ratio

The use of the C:C ratio as a screening test for canine Cushing's syndrome has gained significant support. It is likely that this test has screening test value for Cushing's syndrome in cats.

Abdominal Ultrasonography

Ultrasonography is an excellent tool in distinguishing pituitary-dependent from adrenocortical tumor Cushing's syndrome. In cats, results have also been used as a screening test. If one obviously enlarged or misshapened adrenal is seen, the clinician should be suspicious of an adrenocortical tumor. With obvious bilateral adrenal enlargement, the probability of PDH is enhanced. It must be remembered that ultrasonography, perhaps more than any other tool, is remarkably operator dependent. In other words, ultrasonography is only as sensitive and reliable as the individual conducting and interpreting the study.

Discrimination Testing

High-Dose Dexamethasone Test

Protocol. The high-dose dexamethasone test is performed by collecting blood (plasma) samples before and 8 hours

after IV administration of 1 mg/kg. As with low-dose tests, the cat should be kept quiet and should not be disturbed during the 8-hour testing period.

Results. Arbitrarily, post-dexamethasone plasma cortisol concentrations less than 50 per cent of baseline are indicative of suppression. If the result is greater than or equal to 1 μg/dl and less than 50 per cent of baseline, the interpretation would be Cushing's of pituitary origin. Lack of suppression supports the diagnosis of Cushing's but is not specific for adrenocortical tumor.

Plasma Endogenous ACTH

Plasma endogenous ACTH is used in the dog as a discriminatory tool. The endogenous ACTH test should aid in distinguishing between PDH and adrenocortical tumors. Using canine and human values, a result greater than 40 pg/ml is consistent with PDH, and one less than 20 pg/ml is consistent with an adrenocortical tumor (normal, 20 to 100 pg/ml). In 11 of our cats diagnosed with Cushing's syndrome and 5 from the literature, the results were correct for the final diagnosis. Three cats with an adrenal tumor had a low endogenous plasma ACTH concentration, and the 13 cats with PDH had ACTH values that ranged from 66 to more than 1000 pg/ml. As in dogs and humans, this test can only be interpreted reliably after the diagnosis has been confirmed with acceptable screening test results.

TREATMENT

Background

Hyperadrenocorticism is remarkably debilitating in cats. Although therapy is difficult and the prognosis guarded, an attempt usually is made to control the disease because of the deteriorating clinical condition of afflicted cats.

Medical Therapy

Presurgical Preparation. Transient resolution of hyperadrenocorticism could be extremely beneficial to cats in which surgery is planned. Cats with Cushing's syndrome are prone to infection and heal poorly. Complications from these problems can be catastrophic. These complications can be minimized by presurgical management of the Cushing's. Therapeutic options include the use of the adrenocorticolytic drug *o,p'*-DDD, blocking cortisol synthesis with ketoconazole or metyrapone, and destruction of the pituitary source of ACTH by means of radiation.

***o,p'*-DDD.** When *o,p'*-DDD was administered to clinically normal cats, only 50 per cent had adrenocortical suppression.[19, 100] Several cats with Cushing's treated with *o,p'*-DDD failed to demonstrate improvement, including two cats treated daily for longer than 90 days. Response was demonstrated in one cat treated with 100 mg/kg/day for 21 days, after 14 days at 50 mg/kg/day.

Ketoconazole. The response to ketoconazole has been inconsistent at best. After ketoconazole administration to five cats with hyperadrenocorticism, three responded moderately well but not completely, one had no response, and one developed severe thrombocytopenia, necessitating discontinuing therapy.[101, 104]

Metyrapone. Reports of four hyperadrenal cats treated with metyrapone have been published. Subjective clinical improvement was observed in one cat lost to follow-up after 10 months of therapy.[102] One of two others was described as having slight improvement.[105] One cat had demonstrated reductions in baseline and ACTH-stimulated cortisol concentrations, amelioration of clinical signs, and subsequent successful adrenalectomy.[96] The dose in which the best results were described was 65 mg/kg PO twice daily. This latter cat was also diabetic and suffered from a severe hypoglycemic reaction after metyrapone treatment was initiated. Successful resolution of hypercortisolism should reduce insulin antagonism and reduce or eliminate the need for exogenous insulin in some of these cats. Appropriate monitoring, anticipating this effect, should minimize the risk associated with this beneficial effect.

Radiation. Cobalt-60 radiation therapy of several cats with visible pituitary tumors was not successful in resolving hypercortisolism.[19]

Presurgical Management. Food usually is withheld for the 12-hour period preceding surgery. Conservative volumes of IV fluids are recommended plus parenteral antibiotics. Intermediate-acting insulin should be administered to those cats with diabetes mellitus at 50 per cent the usual morning dose. A continuous IV infusion of hydrocortisone (625 μg/kg/h) is recommended from the time of anesthetic induction until 24 to 48 hours after surgery is completed. Oral prednisone (2.5 mg per cat twice daily) should be given to all cats. Mineralocorticoids should be administered to those cats undergoing bilateral adrenalectomy or in which hyperkalemia and/or hyponatremia is documented. Serum electrolyte concentrations should be evaluated twice daily for several days after surgery. Fludrocortisone acetate (0.1 to 0.3 mg per cat) or desoxycorticosterone pivalate (DOCP; 1 mg/lb SC every 25 days) can be administered as needed.

Surgery. Two of ten cats undergoing surgery for Cushing's syndrome were diagnosed as having adrenocortical tumors (one adenoma and one adenocarcinoma). These two cats were among the three that lived the longest after surgery (12 and more than 30 months, respectively).[106] Although surgical procedures are well described elsewhere, the surgeon must be prepared to make decisions regarding removal of one or both adrenals at surgery.

Postsurgical Management. Postoperative complications that contribute to death or euthanasia include sepsis, pancreatitis, thromoembolic phenomena, wound dehiscence, and adrenal insufficiency. Sepsis was identified in 50 per cent of our most recently treated cats. Preoperative management of the Cushing's syndrome and administration of anticoagulants may be extremely beneficial. Two of our cats that survived bilateral adrenalectomy subsequently (2 and 14 months later, respectively) developed signs consistent with large intracranial masses. Both were euthanized, and necropsy in one cat demonstrated a 12-mm pituitary mass.

PROGNOSIS

Hyperadrenocorticism must be considered a serious disease with a guarded to grave prognosis. Medical therapies have had limited success, and surgery has been difficult to perform because of the debilitated condition of these cats. The longest surviving cats are those that have had an adrenocortical adenoma or carcinoma removed surgically.

PRIMARY MINERALOCORTICOID EXCESS—PRIMARY HYPERALDOSTERONISM

Human Beings

Physiopathology. In humans, the increased production of aldosterone by abnormal zona glomerulosa tissue (ade-

noma or hyperplasia) initiates a series of events that result in primary aldosteronism. Aldosterone excess leads to increased sodium retention, expansion of the extracellular fluid volume, and increased total body sodium content. The expanded extracellular fluid and plasma volumes are registered by stretch receptors at the juxtaglomerular apparatus, and sodium retention is registered at the macula densa. With primary increases in aldosterone production, the renin system is suppressed. This is the hallmark of the disorder. Primary aldosteronism is a disease of the zona glomerulosa. Cells of this zone do not have the capacity to make cortisol. There are no abnormalities in cortisol production, plasma cortisol concentration, or cortisol metabolism.

In addition to sodium retention, potassium depletion develops, decreasing the total body and plasma concentrations of potassium. The extrusion of potassium from its intracellular position results in the intracellular movement of hydrogen ions, increased renal secretion of hydrogen ions, and systemic alkalosis. Moderate potassium depletion decreases carbohydrate tolerance, and resistance to ADH (vasopressin) occurs. Severe potassium depletion blunts baroreceptor function. Because aldosterone biosynthesis is intensified, the entire biosynthetic pathway becomes activated. Increased concentrations of precursor steroids (desoxycorticosterone, corticosterone, 18-hydroxycorticosterone) are present in humans with aldosterone-producing adenomas.

Clinical Signs. Humans with primary hyperaldosteronism require medical attention because they develop symptoms of hypokalemia. The medical history reveals no specific symptoms but often only nonspecific complaints of tiredness, loss of stamina, weakness, nocturia, and lassitude—all symptoms of potassium depletion. If potassium depletion is severe, alkalosis, thirst, and polyuria develop. Unsuspected hypertension may be diagnosed during the course of physical examination. Blood pressure in patients with primary aldosteronism can range from normal to severe hypertension.

Diagnostic Testing. Assessment of the serum potassium concentration is an important initial screening procedure in humans with hypertension. Care must be taken to assess the state of sodium intake or balance in the patient before serum electrolytes are obtained. The serum potassium concentration is dependent to a great extent on the sodium chloride intake. A low-sodium diet, by sparing potassium loss, can correct serum potassium abnormalities and mask depletion of potassium. As the amount of sodium ion available for reabsorption is reduced, potassium secretion is retarded in the distal renal tubule. In the presence of normal renal function and aldosterone excess, salt loading will reveal hypokalemia. Normokalemic hyperaldosteronism under these conditions has been reported but is probably rare. A normal to increased serum sodium concentration (142 to 156 mEq/L) in the presence of hypokalemia and a reduced hematocrit (caused by increased extracellular fluid and plasma volume from sodium retention) is presumptive evidence of mineralocorticoid excess. Clues toward the diagnosis of primary hyperaldosteronism, in addition to the hypokalemia, are failure to concentrate urine, an abnormal glucose tolerance test, and alkalosis.

If hypokalemia is documented, the renin-angiotensin system must be assessed. This is accomplished in humans by measurement of random plasma renin activity. If plasma renin activity is normal or high in a patient who has been off diuretic therapy for 3 weeks, it is unlikely that primary aldosteronism is present. If the random plasma renin activity is suppressed, primary aldosteronism is a likely diagnosis.

Assessment of aldosterone production can best be accomplished by measurement of urinary aldosterone excretion over a 24-hour period under conditions of adequate sodium intake. Measurement of either the 18-glucuronide or the tetrahydroaldosterone metabolite is sufficient to assess the rate of total production. Plasma samples must be obtained under proper conditions to yield reliable diagnostic information. Although the value obtained for plasma aldosterone concentration is the aldosterone level only at a given moment, in the properly prepared patient, it can provide an excellent assessment of mineralocorticoid production. Both plasma and urinary aldosterone measurements should be performed while the patient is taking a high-salt diet with sodium chloride supplementation. This is crucial because with any diminution of salt intake, plasma aldosterone concentration and aldosterone production normally increase. Although urinary measurements have been adequate for detecting abnormal production of aldosterone (and in fact superior to plasma aldosterone concentration measurements), it has not been possible to use daily excretion of aldosterone to discriminate between adenoma and hyperplasia.

It is important to distinguish between adenoma and hyperplasia because surgery is indicated in the former but not in the latter. Plasma aldosterone concentrations in humans provide not only diagnostic information concerning the hyperaldosteronism but also differential diagnostic information about the pathologic process. After at least 4 days of sodium intake exceeding 120 mEq daily and after overnight (at least 6 hours) recumbency, the 8 A.M. plasma aldosterone concentration can be used to distinguish humans with an aldosterone-secreting adrenal adenoma from those with hyperplasia. A plasma aldosterone concentration greater than 20 ng/dl indicates adenoma; a concentration less than 20 ng/dl indicates hyperplasia.

After 2 or 4 hours in the upright posture (which normally activates the renin system with a rise in plasma aldosterone concentrations), plasma aldosterone concentration shows no significant change or diminution in 90 per cent of humans with adenoma, but it almost always increases in humans with adrenocortical hyperplasia. This important differential maneuver is extremely accurate in identifying the specific disorder. The difference is due to the profound suppression of the renin system by excessive aldosterone production caused by an adrenal adenoma. In humans with adrenocortical hyperplasia, increased sensitivity of the hyperplastic gland to minute but measurable increases in renin that occur with assumption of the upright posture leads to an increased aldosterone level.

Treatment. Treatment depends, for the most part, on the precision of diagnosis. In humans with an aldosterone-producing adrenal adenoma and no contraindication to surgery, unilateral adrenalectomy is recommended. The degree of reduction of blood pressure and correction of hypokalemia achieved with spironolactone provide a surprisingly close approximation to the actual response to surgery; in fact, greater reduction often occurs postoperatively, presumably because of a greater reduction of extracellular fluid. The surgical cure rate of hypertension associated with adenoma is excellent—more than 50 per cent in several series—with reduction of hypertension in the remainder.

In humans with aldosteronism of indeterminate type, spironolactone alone usually is effective in controlling both the hypertension and the potassium-depleted state. Because of the effectiveness of spironolactone in these patients, other antihypertensive medications often can be discontinued.

Pathology. A number of pathologic abnormalities are associated with primary aldosteronism. More than 50 per cent of patients with the diagnosis who have undergone surgery have had unilateral adenoma. Bilateral tumors are rare. The characteristic adenoma is readily identified by its golden

yellow color. In addition, small satellite adenomas often are found, and distinction from micronodular or macronodular hyperplasia frequently is difficult. In patients with adenoma, the contiguous adrenal gland can show hyperplasia throughout the gland. Hyperplasia is also present in the contralateral adrenal gland but is not associated with aldosterone abnormalities after removal of the primary adenoma. Causes of secondary hyperaldosteronism include heart and/or kidney failure and severe hepatocellular dysfunction.

Dogs

We have had experience with three dogs that have been diagnosed as having primary hyperaldosteronism. Each of these dogs was 8 years of age or older at the time of diagnosis (8, 9, and 11 years of age, respectively). The breeds included a beagle, poodle, and Doberman pinscher. The primary owner concern in each dog was episodic weakness, and each dog, on initial data base blood evaluation, had a serum potassium concentration less than 3 mEq/L. Two of the three dogs have had extensive laboratory studies, including assessment of plasma aldosterone concentrations. These concentrations were consistently extremely increased (greater than 3000 pmol/L) until surgical tumor removal, after which the hormone values decreased dramatically. Each dog had an adrenal tumor: one adenoma and two adenocarcinomas. One dog was euthanized before an attempt at treatment and two became clinically and biochemically normal after surgery. One has been normal for longer than 24 months (this dog had an adenoma) and one suffered a recurrence 24 months later, at which time widespread metastasis was recognized. Both of these dogs are alive more than 3 years after surgery.

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