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,

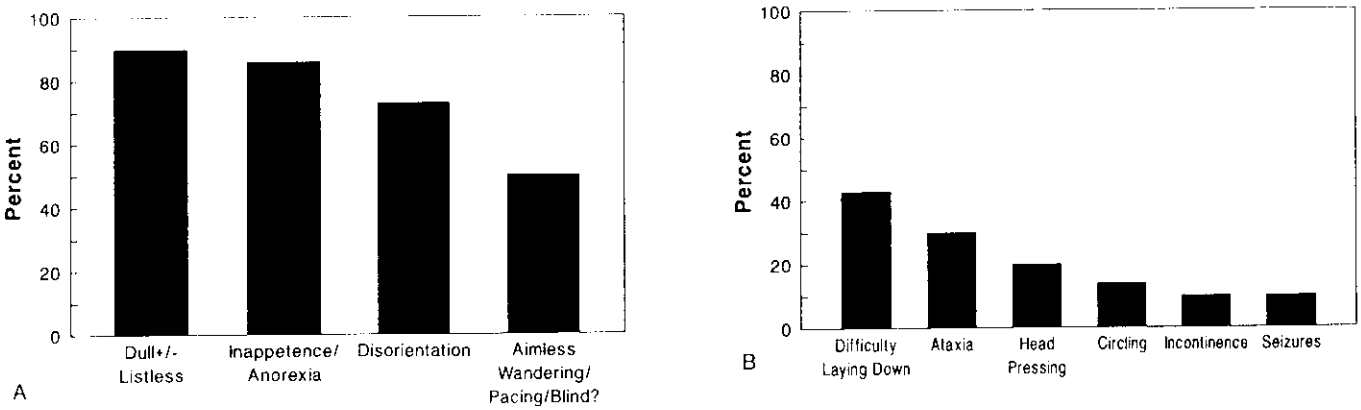

Figure 118–17. Common clinical signs observed by owners and veterinarians in dogs with large pituitary tumors that are causing CNS signs.

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-

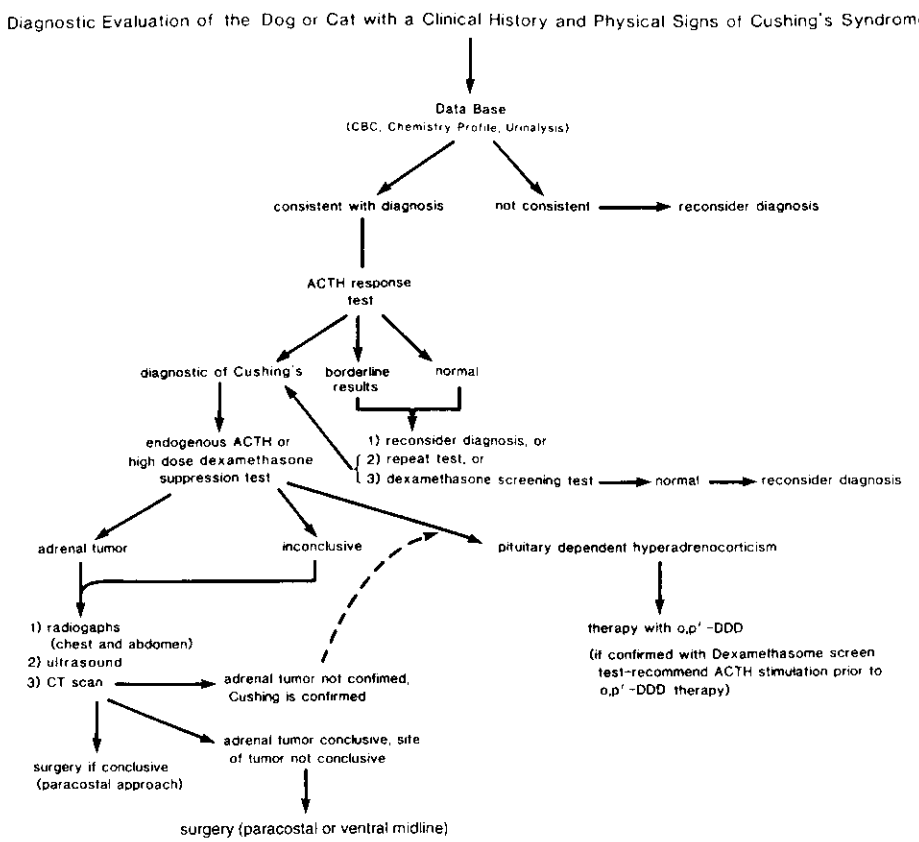

Figure 118–18. Diagnostic evaluation of a dog or cat with suspected hyperadrenocorticism. (From Feldman EC and Nelson RW: Canine and Feline Endocrinology and Reproduction. Philadelphia, WB Saunders, 1987, p 160.)

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]

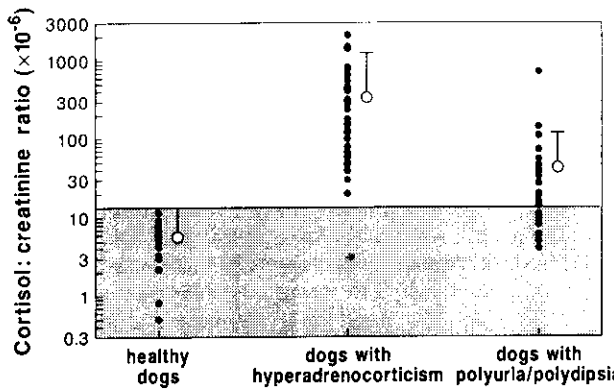

Figure 118–19. Urine cortisol-creatinine (C/C) ratios from healthy dogs, dogs with naturally occurring hyperadrenocorticism, and dogs with polyuria and polydipsia caused by disorders other than hyperadrenocorticism. These values show that the C/C ratio is a sensitive test for Cushing's syndrome but that 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

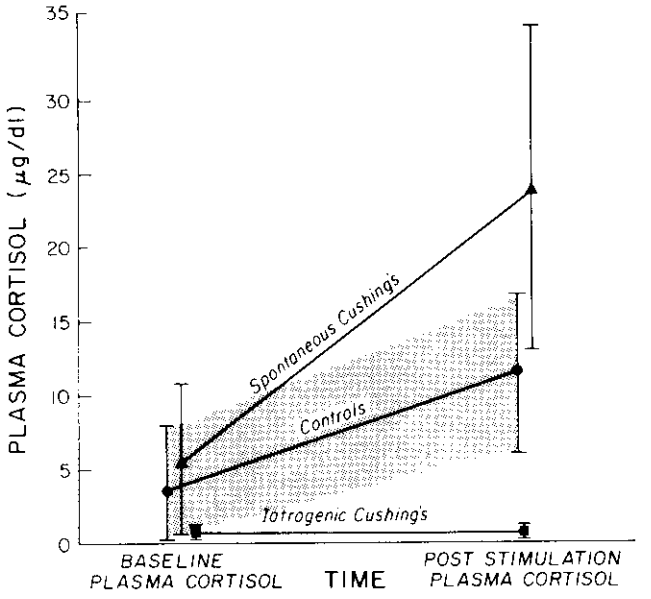

Figure 118–20. Mean radioimmunoassay plasma cortisol concentrations (±2 SD) determined before and 1 hour after administration of synthetic ACTH in control dogs, dogs with spontaneous hyperadrenocorticism, and dogs with iatrogenic hyperadrenocorticism.

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.

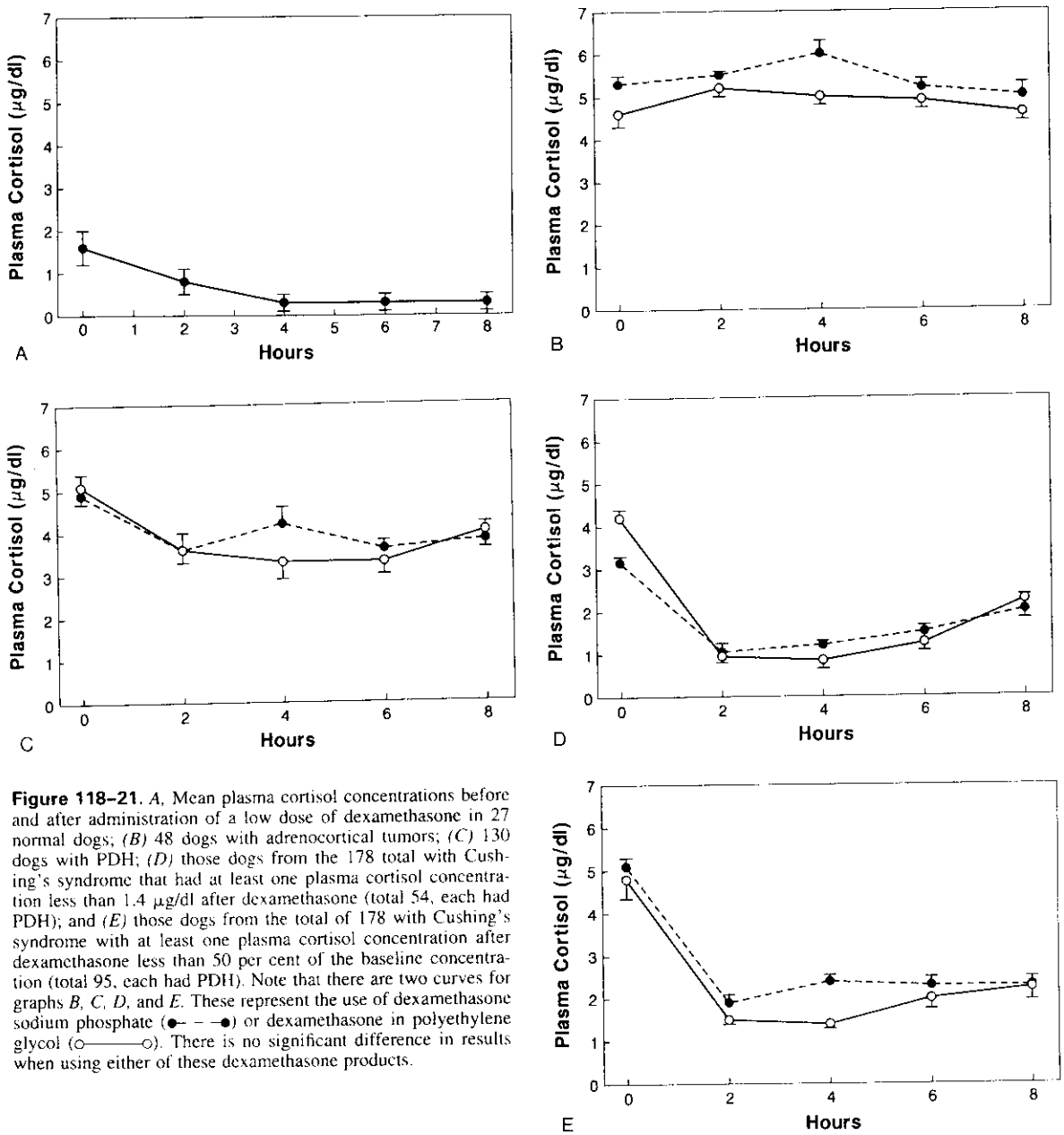

Figure 118–21. *A,* Mean plasma cortisol concentrations before and after administration of a low dose of dexamethasone in 27 normal dogs; *(B)* 48 dogs with adrenocortical tumors; *(C)* 130 dogs with PDH; *(D)* those dogs from the 178 total with Cushing's syndrome that had at least one plasma cortisol 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

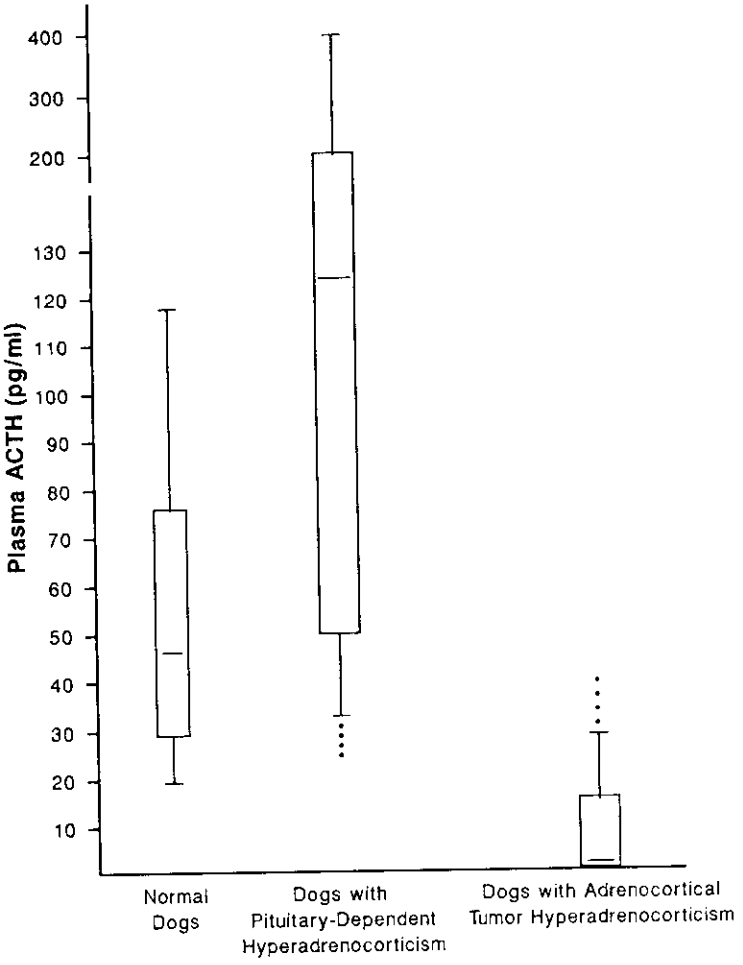

Figure 118–22. Endogenous plasma ACTH concentrations from clinically normal dogs, dogs with PDH, and dogs with functioning adrenocortical carcinomas or adenomas.

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]

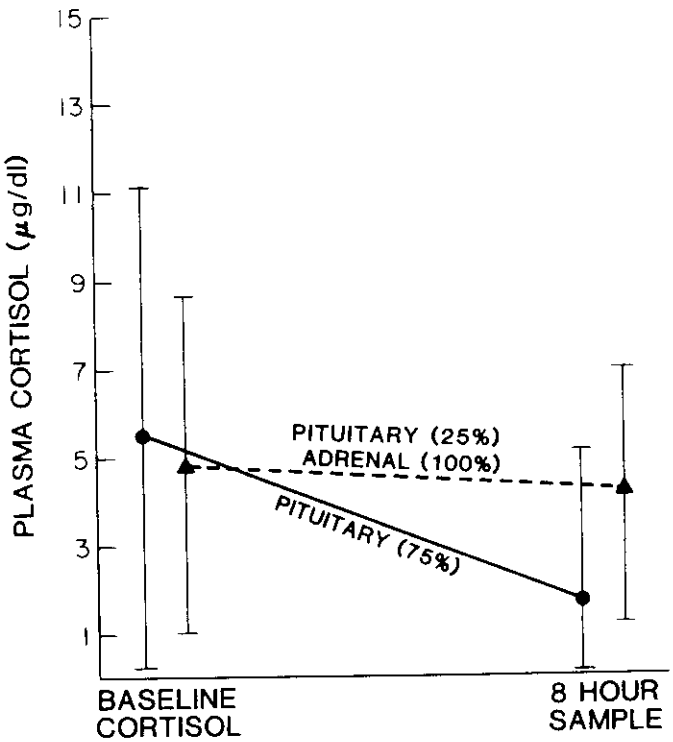

Figure 118–23. Pattern of plasma cortisol responses during high-dose dexamethasone suppression in dogs with PDH or adrenal tumor hyperadrenocorticism. Note that suppression is diagnostic of pituitary dependency; lack of suppression included all adrenal tumor cases and 20 to 30 per cent of PDH cases.

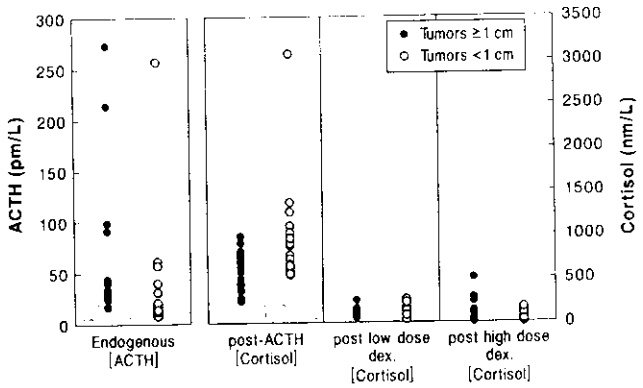

Figure 118–24. Basal plasma endogenous ACTH concentrations and plasma cortisol concentrations after administration of ACTH, after a low dose of dexamethasone, and after a high dose of dexamethasone in dogs with PDH attributed to pituitary tumors greater than or equal to 1 cm and less than 1 cm in diameter.

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

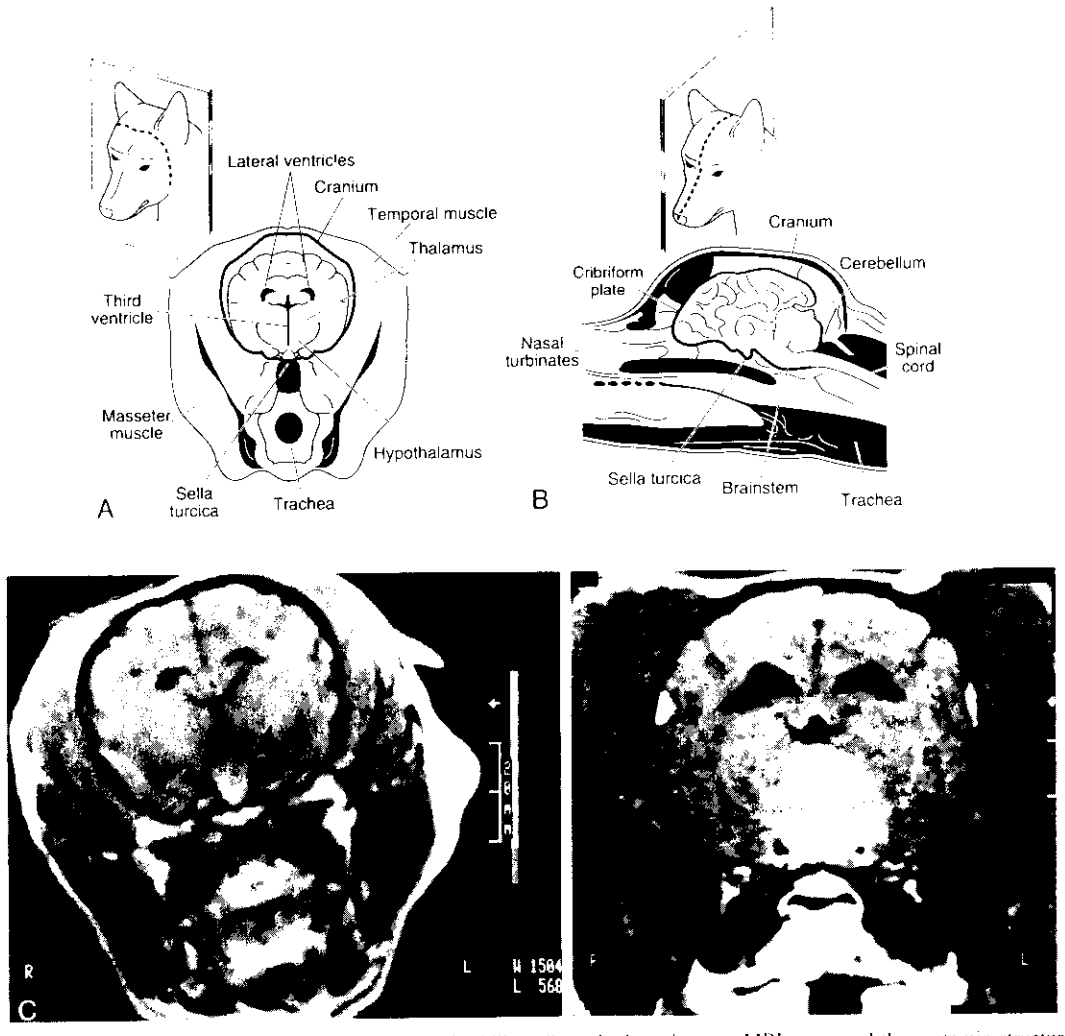

Figure 118–25. Orientation of the transverse *(A)* and midline *(B)* sagittal sections on MRI scans and the anatomic structures seen on each view. *C*, MRI scan of a dog with PDH and a relatively small (7 mm) pituitary mass *(arrow)*. *D*, MRI scan of a dog treated for PDH with *o,p'*-DDD and that subsequently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