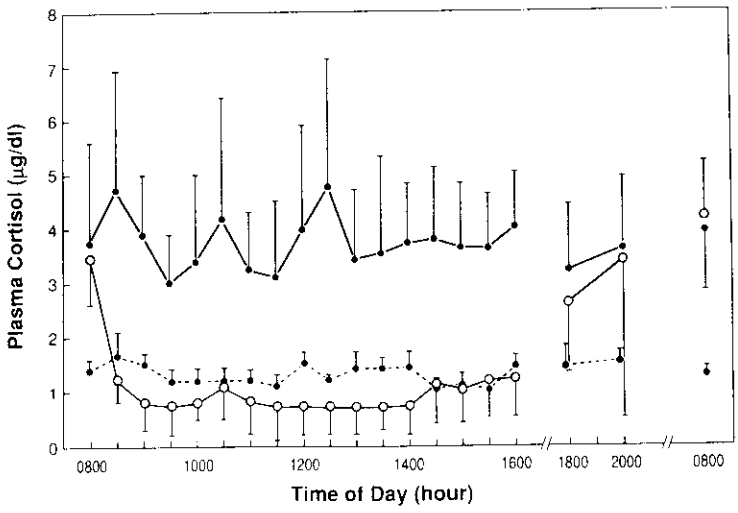

Figure 118–29. Mean plasma cortisol concentrations over a 24-hour period from 15 normal dogs (●– – –●), 18 dogs with untreated hyperadrenocorticism (9 with PDH and 9 with adrenocortical tumors; (●————●), and those 18 dogs after their first dose of ketoconazole (○————○), showing the potent and rapid effect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