

# The Great Mimic: Canine Addison's Disease

Debbie Stafford, CVT



Most dogs with Addison's disease can live a normal life and have a normal life span.

The endocrine disorder hypoadrenocorticism is uncommon in dogs and rare in cats. The term *Addison's disease* (AD) is also used to identify this syndrome, which was first described in humans in 1855 by Thomas Addison. The first canine case was reported in 1953.<sup>1</sup> AD is one of the most diagnostically and therapeutically challenging, confusing, and frustrating veterinary diseases. Signs may be vague and mimic those of many other common illnesses. A good history and appropriate laboratory work are extremely beneficial in making a diagnosis, and technicians play an important role in both.

The disease can be primary or secondary. Primary AD is more common; it is associated with diseases of the adrenal gland that result in deficiencies of both glucocorticoids and mineralocorticoids. Secondary AD is associated with deficiencies of glucocorticoids only; it is caused by lack of stimulation of the adrenal glands, usually as a result of inflammation, tumor, trauma, or congenital defects of the hypothalamus or pituitary gland.<sup>1</sup> Because of the low incidence of secondary AD and the rarity of feline AD in general, only canine primary AD is discussed in this article.

## Background

Primary AD is most commonly classified as an idiopathic (see the Glossary) disease, generally with bilateral adrenal atrophy. Other causes include infections (coccidioidomycosis, blastomycosis, or tuberculosis), hemorrhagic infarctions, metastatic neoplasia, trauma, and amyloidosis; AD may also be the end result of an immune-mediated process. Iatrogenic AD may occur following administration of the adrenocortolytic drug *o,p'*-DDD (mitotane), which is used to treat hyperadrenocorticism (Cushing's disease).<sup>2</sup> Ketoconazole and megestrol acetate are two other therapeutic agents that may interfere with adrenocortical function, albeit only with glucocorticoid synthesis.<sup>1</sup> Genetic influences may play a role in some dog breeds; the standard poodle, Labrador retriever, rottweiler, and Portuguese water spaniel are the only breeds with a well-documented possible genetic predisposition for AD.<sup>1</sup>

## Anatomy and Physiology

The adrenal glands are essential for life; they secrete a number of hormones re-

## KEY POINTS

- Primary hypoadrenocorticism (*Addison's disease*) is most commonly classified as an idiopathic disease, generally with bilateral adrenal atrophy.
- Because signalment and history are very important in identifying *Addison's disease*, technicians' initial and follow-up questioning of clients are critical in helping veterinarians diagnose this condition.
- Corticotropin stimulation testing is the only definitive diagnostic test for *Addison's disease*; thus technicians must perform this test properly.

## Glossary

**Addisonian**—Referring to Addison's disease (hypoadrenocorticism)

**Atrial fibrillation**—Rapid, irregular contractions of the heart

**Hilum**—An indentation in an organ where the nerves and vessels enter

**Hyponatremia**—Deficiencies of sodium in the blood

**Hyperkalemia**—Abnormally high potassium concentration in the blood

**Iatrogenic**—Caused by treatment or diagnostic procedure

**Idiopathic**—Without a known cause

**Pathognomonic**—A sign or symptom linked to a disease or condition

**Retroperitoneal**—Referring to organs that are closely attached to the stomach and intestine walls and partly covered by the peritoneum rather than those organs that are held up by that lining

**Sinoatrial standstill**—A heart rhythm that is characterized by pauses in complexes that are more than twice the normal R-R interval

**Stress leukogram**—A hemogram characterized by mature neutrophilia, eosinopenia, lymphopenia, and monocytosis

**Ventricular premature contraction**—An electrocardiographic pattern in which the QRS complexes are typically wide and bizarre and the P waves are dissociated from the QRS complexes

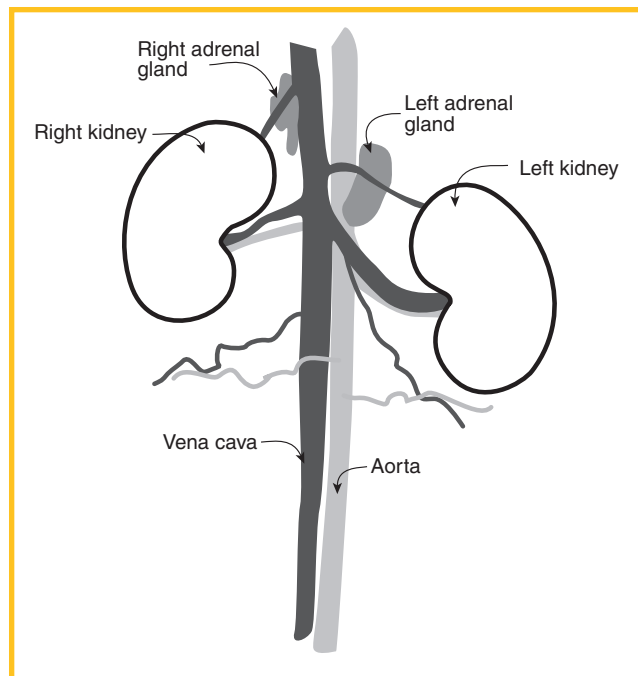


Figure 1—Anatomic illustration showing the location of the adrenal glands.

quired for normal function and for survival during periods of stress. Adrenal glands are composed of several layers of tissue, each with a separate function.<sup>4</sup> The innermost part is the medulla, or heart of the gland; its role is to modulate the nervous system's reaction to stress by secreting the catecholamines epinephrine and norepinephrine.

The adrenal cortex comprises several separate layers that, in combination, form the major steroid-producing organ of the body. The outer zona glomerulosa of the cortex is primarily involved with the synthesis and secretion of the mineralocorticoid aldosterone. The middle zona fasciculata synthesizes and secretes glucocorticoids; cortisol is the most important glucocorticoid in mammals. The inner zona reticularis primarily secretes adrenal sex hormones.<sup>1</sup>

The left adrenal gland is the larger of the two glands and is positioned retroperitoneally, near the craniomedial border of the left kidney. The right adrenal gland, also retroperitoneal in position, is near the hilum of the right kidney (Figure 1). Both glands lie in a generous bed of retroperitoneal fat.<sup>4</sup> AD is associated with the adrenal cortex and the major steroids it produces. These steroids are classified as glucocorticoids (cortisol) and mineralocorticoids (primarily aldosterone). An estimated 90% of corti-

cal function must be compromised before clinical signs of AD become evident.<sup>3</sup>

Mineralocorticoids control sodium, potassium, and water homeostasis. They promote reabsorption of these agents as well as excretion of potassium in many epithelial cells. The main site of action is in the renal tubules, where sodium and chloride are absorbed and sodium and potassium are exchanged. In patients with AD, the lack of aldosterone secretion results in an impaired ability to conserve sodium and excrete potassium, which leads to hyponatremia and hyperkalemia.<sup>2</sup>

Glucocorticoids affect almost every tissue in the body. They promote a general sense of well-being, stimulate appetite, help maintain normal serum calcium levels, have antiinflammatory and immunosuppressive effects on leukocytes, and stimulate erythrocytosis. They also protect against shock and maintain blood pressure. A lack of glucocorticoid secretion may result in gastrointestinal signs, mental changes (e.g., depression, lethargy), and impaired tolerance to stress.

## Clinical Findings

Signalment and history are very important in diagnosing AD. Through appropriate initial and follow-up questioning of clients, technicians play an invaluable role in helping veterinarians diagnose this frustrating disease.

Addison's disease is primarily a disease of young to middle-aged female dogs. Studies indicate that 70%

to 85% of cases occur in females, the majority of which are younger than 7 years of age.<sup>1</sup> Typically, these pets are presented with vague, nonlocalized clinical signs that reflect mineralocorticoid and glucocorticoid deficiencies. Common signs include depression, lethargy, weakness, anorexia, and weight loss. Gastrointestinal (vomiting and diarrhea) or renal (polyuria and polydipsia) signs are also often seen<sup>2</sup> (see Common Clinical Signs of Addison's Disease).

Owners do not always recognize the waxing and waning of these signs, but a full history can be obtained through careful questioning and follow-up. No set of clinical signs is pathognomonic for AD, and the associated signs are common in a variety of disease processes. The majority of dogs examined are presented for chronic progressive problems, but dogs in "acute" adrenal crisis may be a true medical emergency (Figure 2). The situation may appear acute to owners, but often the history will reveal a trend of signs that wax and wane with response to nonspecific treatment and supportive care (e.g., parenteral fluid administration, cage rest).<sup>3</sup>

### Laboratory Findings

Diagnosis of AD requires a thorough history, careful physical examination, and complete laboratory screening (full chemistry profile [including electrolytes], complete blood count, and complete urinalysis). Although patients may be stressed, they may not have a stress leukogram at presentation. The lack of adequate cortisol (glucocorticoid) prevents the body

### Common Clinical Signs of Addison's Disease<sup>a</sup>

■ Depression (95%)	■ Dehydration (45%)
■ Anorexia (90%)	■ Diarrhea (40%)
■ Vomiting (75%)	■ Polydipsia (25%)
■ Weakness (75%)	■ Polyuria (25%)
■ Weight loss (50%)	■ Bradycardia (18%)

<sup>a</sup>Numbers in parentheses indicate the percentage of patients with that sign on presentation.<sup>3</sup>



Figure 2—This patient was presented with vomiting, weakness, depression, and dehydration. Serum analysis revealed hyponatremia, hypochloremia, and mild hyperkalemia. A diagnosis of Addison's disease was confirmed with a corticotropin stimulation test.

**TABLE I**  
Laboratory Findings in Dogs with Addison's Disease

Parameter	Normal	Change from Normal
Sodium	136–150 mEq/L	↓
Potassium	3.5–5 mEq/L	↑
Na <sup>+</sup> :K <sup>+</sup> ratio	≥27:1	↓
Blood urea nitrogen	9–25 mg/dl	↑
Calcium	8.8–11 mg/dl	↑ <sup>a</sup>
Glucose	70–110 mg/dl	↓ <sup>a</sup>
Total carbon dioxide	18–24 mmol/L	↓ <sup>a</sup>
Urine specific gravity	>1.030	↓ <sup>a</sup>

<sup>a</sup>May or may not be present.

from responding normally to stress conditions, thus explaining the lack of a stress leukogram.

Abnormalities may be present in all commonly reported electrolytes (Na<sup>+</sup>, K<sup>+</sup>, Ca<sup>+</sup>, Cl<sup>-</sup>, and P). Typically, a presumptive diagnosis of AD is based on the presence of hyponatremia, hypochloremia, hyperkalemia, and an Na<sup>+</sup>:K<sup>+</sup> ratio of less than 27:1 (normal, 27:1 to 40:1; mean, 30:1). Most dogs with adrenal insufficiency have Na<sup>+</sup>:K<sup>+</sup> ratios below 20:1.<sup>1</sup> Regardless of the cause, the presence of hyperkalemia and an abnormal Na<sup>+</sup>:K<sup>+</sup> ratio warrants therapy to prevent the development of life-threatening cardiac arrhythmias.

Approximately 10% of dogs will have normal potassium levels at presentation. Calcium levels are increased (hypercalcemia) in about one third of Addisonian dogs that have hyperkalemia at presentation. Mild to moderate metabolic acidosis (total carbon dioxide below 15 mEq/L [normal, 18 to 24 mEq/L]) is another classic finding in affected dogs (Table I).

Elevations in blood urea nitrogen and creatinine levels and a reduction in renal concentrating ability (low urine specific gravity) are also common in dogs with AD and may be confused with acute renal failure. Creatinine levels tend to be less elevated than are blood urea nitrogen levels. Even if a patient has

all of the laboratory findings listed, the only definitive way to diagnose AD is with a corticotropin (ACTH) stimulation test (see the Corticotropin Stimulation Testing section).

## **Electrocardiographic Findings**

Hyperkalemia associated with mineralocorticoid deficiency can have a profound effect on myocardial contractility. Hyperkalemia primarily affects electrical conduction through the myocardium and the strength of contractions.<sup>1</sup> Electrocardiography (ECG) should be performed on all dogs with marked hyperkalemia (potassium levels above 6.5 mEq/L), especially if bradycardia is present. ECG changes tend to parallel the severity of the serum potassium concentration.<sup>1</sup> In general, an ECG of a patient with mild hyperkalemia will reveal a “peaking” of the T wave. As hyperkalemia progresses and increases, the P–R interval becomes prolonged and the P wave ultimately disappears. The QRS complex widens, and R–R intervals become irregular.<sup>2</sup> Sinoatrial standstill is by far the most common arrhythmia, whereas ventricular premature contractions and atrial fibrillation occur occasionally.<sup>1</sup>

## **Acute Adrenal Crisis**

Patients with clinical, biochemical, and electrolyte abnormalities compatible with acute AD should be treated as if they have the disease until they respond appropriately or the diagnosis is refuted. Patients with nonadrenal causes for their hyperkalemia will not be harmed by therapy. If a diagnosis of AD is being considered, it is important to collect laboratory samples before initiating fluid therapy unless the patient is also considerably dehydrated (see the Corticotropin Stimulation Testing section); this applies to collecting the initial sample for ACTH stimulation testing as well as to the administration of ACTH for the test. Death from adrenal crisis usually occurs secondary to vascular collapse and shock, not from profound hyperkalemia.<sup>1</sup>

The primary goals in the treatment of acute adrenal crisis are to replace glucocorticoid deficiencies and correct hypovolemia, hypotension, electrolyte abnormalities, hypoglycemia, and acidosis. Thus immediate intravenous (IV) fluid therapy is lifesaving. The fluid of choice for treating adrenal crisis is 0.9% sodium chloride (NaCl) because (1) sodium and chloride deficits are present and (2) it has no potassium, which is often present in excess in acutely ill patients.

Fluids may be started at a rate of 60 to 80 ml/kg/hour for the first 1 to 2 hours.<sup>3</sup> Fluid administration increases vascular volume and blood pressure, improves renal perfusion, and dilutes extracellular potassium. By rapidly decreasing hyperkalemia, the risk of a patient developing, or continuing to have, possibly fatal arrhythmias is reduced. A 5% dextrose solution may be used in hypoglycemic patients until hypoglycemia is corrected.<sup>1</sup>

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Glucocorticoid replacement therapy may be started immediately or preferably delayed for 1 or 2 hours until the post-ACTH stimulation sample has been obtained (see the Corticotropin Stimulation Testing section). However, steroid treatment should not be delayed for patients in adrenal crisis because this is a life-threatening emergency that requires immediate intervention. Blood samples should be collected before initiating therapy, and this can be easily done at the time of catheter placement.

Fluid therapy is usually sufficient for the first hour or two (i.e., until the ACTH stimulation test is completed).<sup>5</sup> If glucocorticoid therapy is initiated immediately, dexamethasone sodium phosphate (0.25 to 1.0 mg/lb IV) must be used because its effects interfere the least with the ACTH stimulation test. Prednisolone sodium succinate (2 to 10 mg/lb IV over 2 to 4 minutes) is an alternative rapid-acting glucocorticoid that also has some mineralocorticoid activity; however, it will cross-react with the ACTH stimulation test. The ideal glucocorticoid to use in acute hypoadrenal crisis is hydrocortisone sodium phosphate (which is not available in a veterinary-approved product). This agent possesses glucocorticoid and mineralocorticoid activity, thus helping to replace both substances in the crisis patient. These medications are usually readministered in 2 to 8 hours depending on the drug used and patient response.<sup>1</sup> Rapid-acting parenteral mineralocorticoid preparations are no longer available.

In animals with severe hyperkalemia (i.e., hyperkalemia that cannot be controlled via rapid volume expansion), additional strategies to volume expansion and glucocorticoid and mineralocorticoid replacement therapy alone must be considered; without these additional treatments (which are rarely needed), potassium's effects on the heart may cause irreversible damage. Such strategies include IV glucose, glucose plus regular insulin, sodium bicarbonate therapy, and 10% calcium gluconate.<sup>1</sup>

Intravenous glucose is useful in managing hyperkalemia because as glucose enters cells, potassium follows, thus lowering the extracellular concentration of potassium. Regular insulin can be administered subcutaneously or IV at 0.03 to 0.06 U/lb to promote potassium uptake by cells. If insulin is administered, supplemental glucose (20 ml of 10% dextrose for every unit of insulin<sup>1</sup>) must also be provided to avoid severe hypoglycemia.

Alkalosis also promotes the transcellular movement of potassium into cells, thereby reducing the cardiotoxic effects of hyperkalemia. Administration of sodium bicarbonate as a slow IV bolus at 0.25 to 0.5 mEq/lb has been recommended.<sup>1</sup> Calcium gluconate is known to protect the myocardium against the effects of hyperkalemia; a 10% solution can be administered at 0.2 to 0.5 mg/lb IV

over 10 to 20 minutes. If calcium gluconate is used, a continuous ECG must be monitored; the infusion should be stopped if any new arrhythmias are noted.

These additional therapies can have drastic effects, and patients need to be monitored closely if any are initiated. Excess administration of sodium bicarbonate can cause severe metabolic alkalosis rather than correcting the hyperkalemia. If calcium gluconate is used, ECG monitoring for any new arrhythmias is a must; if any occur, calcium gluconate therapy must be stopped immediately.

As stated, the most important factors in the treatment of acute adrenal crisis are proper collection of laboratory specimens, initiation of fluid therapy, and replacement of glucocorticoids. Patients generally improve significantly within a few hours without additional medications; vomiting and diarrhea cease within 24 to 48 hours in patients with these signs. Gradual reintroduction of oral food, water, and medications can be done safely at this point. A rapid reversal of severe renal compromise, hypercalcemia, hyponatremia, and hyperkalemia lends further support to the diagnosis of AD if the results of the ACTH stimulation testing are pending.

## Corticotropin Stimulation Testing

Because only an ACTH stimulation test can definitively identify AD, this procedure is of special importance to technicians—the quality of the results is only as good as the quality of the testing protocol. Technicians can easily collect the specimens and conduct the test (see Corticotropin [ACTH] Stimulation Testing Procedures). The sample-handling instructions from the laboratory that will perform the assay must be observed.

A plasma or serum sample, which should be collected before and 1 or 2 hours after the ACTH stimulation test (depending on type of ACTH used), is generally recommended for hormone measurement; under no circumstance should whole or clotted blood be submitted. Plain red-topped tubes are recommended for collecting serum; after the sample has been centrifuged in a plain red-topped tube, serum must be removed from the clot immediately. For plasma samples, EDTA (purple-topped) tubes should be used and the specimen centrifuged within 15 minutes of collection.<sup>5</sup> Samples should not be mailed in glass and should be well protected to avoid breakage or spillage. Tubes should be pre-labeled with the patient's name and the type of sample (i.e., pre- or post-ACTH stimulation test) to prevent later confusion.

Cortisol in serum or plasma samples is generally stable for as long as 5 days at room temperature; degradation may be significant after this time.<sup>2</sup> Most laboratories, however, request that all samples be refrigerated or frozen

## Corticotropin (ACTH) Stimulation Testing Procedures

- Obtain resting plasma or serum sample<sup>a</sup> (check with testing laboratory to determine which should be submitted).
- Administer 1 IU/lb ACTH gel intramuscularly or one vial (0.25 mg) cosyntropin intravenously.
- Obtain a post-ACTH sample 2 hours later if ACTH gel is used or 1 hour later if cosyntropin is used.
- Package samples and keep refrigerated until sent to the laboratory.

<sup>a</sup>Hemolyzed or lipemic samples should be avoided if at all possible.

to prevent questionable results. Most synthetic glucocorticoids interfere with test results; thus if it is necessary to administer glucocorticoids before samples are obtained, only dexamethasone should be used.

Tests may be conducted using animal-origin ACTH gel or synthetic ACTH (cosyntropin). In dogs with marked dehydration, it is advisable to delay ACTH stimulation testing until initial fluid replacement has been accomplished. Decreased tissue perfusion may impede absorption of the ACTH preparations. If testing must be conducted while the patient is still markedly dehydrated, IV cosyntropin should be used.<sup>3</sup>

In dogs with AD, resting ACTH levels are typically in the low range and fail to increase following ACTH administration. Poststimulation values are often similar to or below resting (i.e., pretesting) values. Poststimulation cortisol values in dogs with AD are consistently below 50 ng/ml (5.0 µg/dl; normal, 80 to 200 ng/ml [8 to 20 µg/dl]).

## Maintenance of Addisonian Patients

Both glucocorticoid and mineralocorticoid replacement therapy are needed initially in most animals with primary AD. Oral glucocorticoid replacement therapy is generally continued for 3 to 4 weeks after the crisis has ended. Prednisone or prednisolone may be administered at an initial dose of 0.25 to 0.5 mg/lb/day in divided doses every 12 hours. The glucocorticoid is gradually tapered (decreased by 50% each week) until it is discontinued entirely.<sup>1</sup>

Approximately half of affected dogs will do well on replacement mineralocorticoid therapy alone after the first few weeks if fludrocortisone acetate (Florinef® Acetate, Apothecon, a Bristol-Myers Squibb Company, Princeton, NJ) is used. This medication has both glucocorticoid and mineralocorticoid activity. If signs of glucocorticoid deficiency (anorexia, lethargy, depression) occur, low-dose glucocorticoid therapy can be restarted. Daily maintenance prednisone doses are approximately 0.1 mg/lb/day.

In times of stress, prednisone may need to be restarted or the current dose increased.

Fludrocortisone acetate is generally administered at 0.1 mg/10 lb body weight in divided doses every 12 hours.<sup>1</sup> Doses are normally adjusted based on normalization of serum sodium and potassium concentrations. One drawback to treatment with fludrocortisone acetate is the occasional occurrence of Cushing's disease-like signs in large dogs.

Another option that is once again available is desoxycorticosterone pivalate (DOCP; Percorten®, Novartis Animal Health, Greensboro, NC). DOCP, which has no glucocorticoid activity, can be considerably less expensive than is fludrocortisone acetate for maintenance of large dogs. DOCP is administered as a subcutaneous injection every 25 days versus the twice daily dosing needed with fludrocortisone.

Sodium and potassium levels should be monitored every 4 to 7 days for the first 2 weeks of therapy (or until levels have stabilized in the normal range) and then every 3 to 4 months for the first year. Most patients develop an increased need for medication after the first 18 months of treatment and then stabilize.

One of the most common client complaints is the cost of treatment using fludrocortisone acetate. Costs can be controlled if the goal of fludrocortisone acetate treatment is to maintain potassium levels in the high-normal range.

Patients will occasionally continue to be hyponatremic despite normal potassium levels; most dogs, however, can live a normal life and have a normal life span after being stabilized, if good patient-client-veterinarian relationships are maintained. Owners must communicate with their veterinary team frequently to achieve this normal life for their dogs. Technicians are an important link in such communications, and their expertise and compassion for clients and patients help maintain open lines of communication between clients and veterinarians.

### About the Author

Ms. Stafford is Head Technician at the Fox Valley Animal Referral Center. This 24-hour referral, emergency, and critical care facility is located in Appleton, Wisconsin.

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