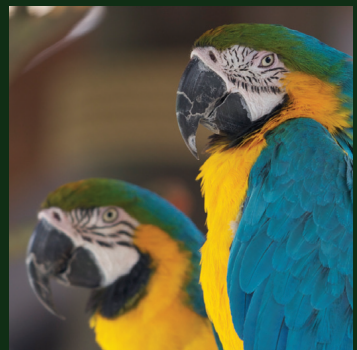




# Clinical Endocrinology of Companion Animals

**JACQUIE RAND** EDITOR

Ellen N. Behrend, Danièle Gunn-Moore and Michelle L. Campbell-Ward  
SECTION EDITORS



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# Clinical Endocrinology of Companion Animals



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Edited by  
**Jacquie Rand**



**WILEY-BLACKWELL**

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# Dedication

This book is dedicated to the important people who shaped my life and goals.

My parents, Geoff and Moira, who inspired me to be the best I could be, to never accept mediocrity from myself, and to always remain optimistic about achieving my goals. They are not here to see the book published, but their legacy remains.

My husband, Tom, who is my greatest supporter, through the challenging times and the good times in life, always there, encouraging me to follow my dreams and be happy.

My daughter, Lisette, who reminds me to maintain a balance in my life and inspires me to be a better role model.

Merlin, our characterful Burmese cat, who has lived a full life despite many twists and turns—surrendered to a municipal animal facility and, on death row, acquired as one of my research cats, identified as insulin resistant and predisposed to diabetes, adopted into our family—and who sat beside me or on my desk as I wrote and edited chapters for this book.

Thank you all for your inspiration.



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## Preface

The inspiration for the format of *Clinical Endocrinology of Companion Animals* was from teaching students in the clinic and consulting with busy veterinarians in busy practices. There was clearly a need for a quick reference guide that had detailed information, but in a format designed to easily find that information. My hope is that this book will provide valuable assistance for clinicians in diagnosing and managing endocrine cases in practice, as well as for students wishing to quickly find information to help with a case or learn in greater depth the details of diseases of the endocrine system. My aim is that this book be a quick reference book for practical use, to be referred to in the consulting room and in the field.

I thank the section editors, Ellen Behrend, Danielle Gunn-Moore, and Michelle Campbell-Ward, for their absolute dedication to making this a quality publication with the most current information known in veterinary science on endocrine diseases of the various companion animal species. I also thank the many contributors for the richness of their contributions, which represents the sum of many decades of combined knowledge.

I found it fascinating learning of the susceptibility of some exotic companion species to certain endocrine diseases. I hope you also enjoy and find useful the breadth of this book across the common, and not so common, companion animals that veterinarians see in practice.



# CHAPTER 1

## Hypoadrenocorticism in Dogs

Patty Lathan

### Pathogenesis

- Primary hypoadrenocorticism results from the destruction of >90% of the adrenal cortex.
- Most cases are presumed to be due to an immune-mediated process.
- Combined glucocorticoid and mineralocorticoid deficiency occur most frequently, but isolated glucocorticoid deficiency (“atypical hypoadrenocorticism”) is probably underdiagnosed.

### Classical Signs

- Young to middle-age dogs are predisposed, as are poodles, West Highland White Terriers, and Great Danes.
- Addison’s disease is known as the “Great Pretender” because nonspecific signs such as lethargy, decreased appetite, and weight loss predominate.
- Gastrointestinal signs such as vomiting and diarrhea are also common.
- Patients may present in hypovolemic shock or following collapse.

### Diagnosis

- ACTH stimulation test demonstrates minimal cortisol response.

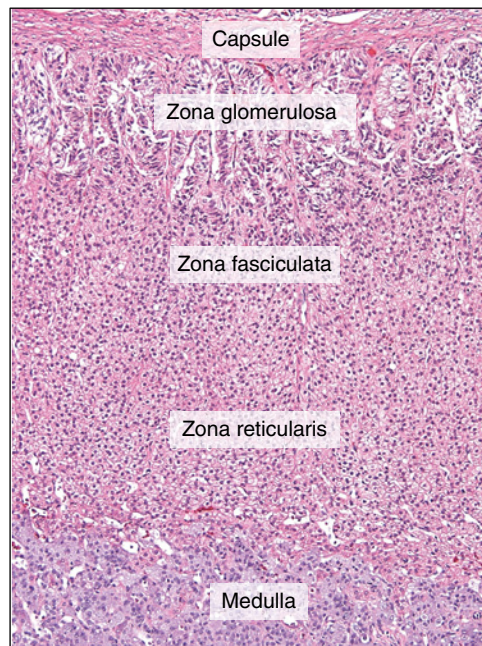
### Treatment

- Glucocorticoid and mineralocorticoid supplementation, ± intravenous fluids and supportive therapy.

### I. Pathogenesis

#### A. Pathophysiology:

1. Most patients with naturally occurring hypoadrenocorticism (“Addison’s disease”) suffer from combined glucocorticoid and mineralocorticoid deficiency:



**Figure 1.1** The adrenal cortex is made up of three layers—the zona glomerulosa, zona fasciculata, and zona reticularis. The zone glomerulosa is responsible for mineralocorticoid synthesis, whereas the inner two layers are responsible for glucocorticoid and sex hormone synthesis. (Image provided by Dr. Jim Cooley.)

**a.** Aldosterone is a mineralocorticoid secreted in the outermost layer of the adrenal cortex, the zona glomerulosa (Figure 1.1). The major action of aldosterone is the conservation of sodium and water, and excretion of potassium and hydrogen ions (acid), from the distal renal tubule. In normal dogs, secretion of aldosterone is stimulated by hypovolemia and hyperkalemia and is primarily regulated by the renin-angiotensin-aldosterone system (RAAS). In patients with hypoadrenocorticism and subsequent **aldosterone deficiency**, **hyponatremia**, **hyperkalemia**, and **hypovolemia** are common.

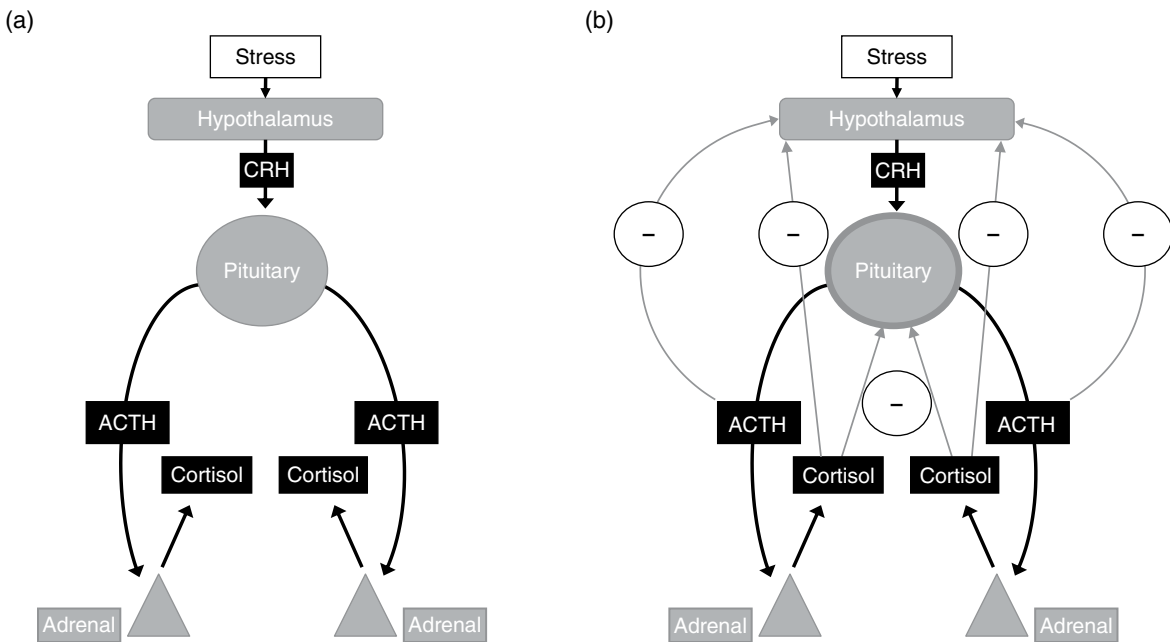
**b.** Cortisol is a glucocorticoid produced in the inner-most layers of the adrenal cortex, the zonae fasciculata and reticularis. Cortisol has activity in almost every cell in the body. Functions include stimulation of gluconeogenesis and erythropoiesis, maintenance of gastrointestinal mucosal integrity, and suppression of the inflammatory response. Additionally, cortisol has important roles in the maintenance of blood pressure and contractility of the heart. Cortisol requirements increase during times of stress. Cortisol release from the adrenal cortex is controlled by adrenocorticotropic hormone (ACTH) (Figure 1.2). Cortisol deficiency in dogs with hypoadrenocorticism may result in gastrointestinal signs, lethargy, hypoglycemia, hypotension, and anemia.

**2.** Some patients with hypoadrenocorticism suffer from isolated glucocorticoid deficiency. In these cases, aldosterone secretion is preserved, and electrolyte abnormalities are **not** present. Patients with **isolated glucocorticoid deficiency** are often said to have “**atypical hypoadrenocorticism**” or “**atypical Addison’s disease**.”

**B.** Etiology:

**1. Primary hypoadrenocorticism** results from the destruction of greater than 90% of the adrenal cortex. Most cases of naturally occurring hypoadrenocorticism in dogs are idiopathic, most likely due to immune-mediated destruction of the adrenal cortex. Rarely, infiltration of the adrenal cortex by fungal disease, amyloidosis, or neoplasia has been reported. Trauma, hemorrhage, and infarction may also lead to hypoadrenocorticism.

**2. Drug-induced adrenocorticolysis** can also result in hypoadrenocorticism in dogs being treated for hyperadrenocorticism:



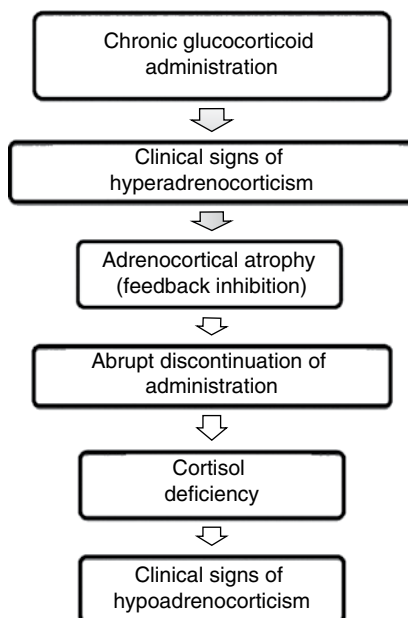
**Figure 1.2** (a) The hypothalamic-pituitary axis without negative feedback. Corticotropin-releasing hormone (CRH) is released by neurons in the hypothalamus and transported to the anterior pituitary by portal circulation. CRH then stimulates the release of ACTH from the pituitary gland into systemic circulation. ACTH then stimulates the synthesis and secretion of cortisol. (b) Negative feedback is the mechanism by which the endocrine system regulates secretion of its hormones. In the HPA-axis, ACTH feeds back to the hypothalamus to inhibit continued release of CRH, which then leads to decreased release of ACTH. Cortisol feeds back to both the hypothalamus to decrease CRH secretion, and to the pituitary gland to decrease ACTH release. By this mechanism, the HPA-axis is able to maintain the physiologically necessary concentration of cortisol in the bloodstream—not too much, nor too little.

a. Adrenocortical necrosis caused by mitotane is usually selective to the zonae fasciculata and reticularis, resulting in decreased cortisol production. However, inadequate monitoring or use in a particularly sensitive patient may lead to destruction of the cells of the zona glomerulosa, resulting in aldosterone deficiency as well.

b. The other commonly used medication to treat hyperadrenocorticism is trilostane. As an inhibitor of at least one enzyme involved in steroid synthesis ( $3\beta$ -hydroxysteroid dehydrogenase), trilostane overdose may lead to cortisol deficiency and, less frequently, aldosterone deficiency. Additionally, idiosyncratic adrenocortical necrosis has been reported to occur in some dogs taking trilostane, resulting in hypoadrenocorticism.

**3. Hypoadrenocorticism secondary to decreased ACTH production is characterized by isolated glucocorticoid deficiency since ACTH has little regulatory control of aldosterone production:**

a. The most common form of secondary hypoadrenocorticism is iatrogenic, resulting from exogenous glucocorticoid administration (Figure 1.3). Exogenous glucocorticoids inhibit the release of adrenocorticotrophic hormone (ACTH) from the pituitary gland. Adrenal gland atrophy then occurs, resulting in decreased secretion of cortisol. Following acute withdrawal of the exogenous glucocorticoid, a stressful event will cause increased release of ACTH, but the atrophied adrenal glands will be unable to respond by secreting an appropriate amount of cortisol, which may result in signs of cortisol deficiency. Chronic administration of glucocorticoids is more likely to result in hypoadrenocorticism than short-term use, and longer-acting repositol steroids (such as methylprednisolone acetate) are more potent suppressors of ACTH than shorter-acting glucocorticoids (such as oral prednisolone). Topical, otic, and ophthalmic preparations containing glucocorticoids may also lead to iatrogenic hypoadrenocorticism, particularly in smaller patients.



**Figure 1.3** Diagrammatic representation of the relationship between iatrogenic hyperadrenocorticism and iatrogenic hypoadrenocorticism. Chronic glucocorticoid administration leads to clinical signs of glucocorticoid excess (“iatrogenic hyperadrenocorticism”). At the same time, the exogenous glucocorticoid provides feedback inhibition to the pituitary gland, decreasing the production of ACTH. Without ACTH, the dog’s own adrenal glands atrophy. While the dog is still taking the exogenous glucocorticoids, the dog will appear to have hyperadrenocorticism. Upon abrupt withdrawal of the steroid, the dog’s own atrophied adrenal gland will be unable secrete cortisol, potentially resulting in clinical signs of hypoadrenocorticism. Clinical signs may be seen more often following a stressful event in these patients.

**b.** Naturally occurring causes of secondary hypoadrenocorticism include pituitary masses, trauma, or other lesions that inhibit ACTH release.

**4.** At this time, the etiology of atypical hypoadrenocorticism (isolated glucocorticoid deficiency) is unknown. ACTH deficiency has been ruled out in many cases. It may be the result of partial immune-mediated destruction of the adrenal cortex, sparing the zona glomerulosa. Although some have hypothesized that atypical hypoadrenocorticism is simply an early manifestation of “typical” hypoadrenocorticism, many patients never lose their ability to secrete aldosterone.

**C.** Risk factors for hypoadrenocorticism:

- 1.** Dogs with other immune-mediated endocrinopathies, such as diabetes mellitus and hypothyroidism, may be at increased risk for hypoadrenocorticism.
- 2.** Dogs with the disease are more likely to have clinical signs during or following a stressful event.

## II. Signalment

**A.** Any breed of dog may be afflicted with hypoadrenocorticism, including mixed-breeds. However, an increased prevalence of hypoadrenocorticism has been documented in all sizes of poodles, West Highland white terriers, Great Danes, bearded collies, Portuguese water dogs, Leonbergers, Nova Scotia duck-tolling retrievers, and possibly Saint Bernards.

**B.** A genetic basis has been proved in standard poodles, Bearded collies, and Nova Scotia duck-tolling retrievers.

**C.** Young to middle-aged dogs (2–5 years old) are predisposed. However, dogs of any age can be diagnosed with hypoadrenocorticism. Nova Scotia duck-tolling retrievers may be diagnosed at a younger age, as early as 2 months.

**D.** Females appear to be predisposed in some studies, while other studies reveal a more equal distribution between the sexes.

**E.** Dogs diagnosed with isolated glucocorticoid deficiency have a similar signalment to those with combined mineralocorticoid/glucocorticoid deficiency. As a population, however, dogs with atypical Addison's tend to be 2–3 years older at diagnosis compared to those with typical Addison's.

### III. Clinical Signs

**A.** The clinical manifestation of hypoadrenocorticism is highly variable in presenting complaint, chronicity, and severity. Some dogs present for chronic clinical signs, whereas others present more acutely in “Addisonian crisis.” Rigid rules differentiating acute from chronic hypoadrenocorticism do not exist; the pathophysiology is the same, and these presentations represent a continuum of disease progression. If not diagnosed and treated early in the course of the disease, many dogs with chronic signs will decompensate and present in crisis. However, they will be discussed separately, since initial treatment differs. Likewise, dogs with isolated cortisol deficiency (atypical hypoadrenocorticism) will also be discussed separately in order to highlight the contrasting features.

#### 1. Chronic hypoadrenocorticism:

**a.** Addison's disease often causes vague, nonspecific clinical signs that can be confused with other diseases, thus earning it the moniker “The Great Pretender” (Table 1.1). Most patients experience **lethargy, decreased appetite, and weight loss** with varying severity. The owner may report that the patient just is not acting normally. A **waxing and waning pattern**, with improvement of clinical signs specifically noted following fluid or steroid administration, is common (Schaer and Chen 1983; Herrtage 2000).

**b.** **Vomiting and diarrhea** are frequently reported, with or without concurrent **melena**. Rectal examination may also reveal melena previously unnoticed by owners. Dogs occasionally present with abdominal pain. These gastrointestinal signs are thought to occur due to loss of the “trophic” effects of cortisol on the gastrointestinal mucosa. Exacerbation of or onset of gastrointestinal signs following a stressful event is often noted in dogs later diagnosed with hypoadrenocorticism. Thus, it is critical that hypoadrenocorticism is considered in patients diagnosed with “stress colitis,” particularly if the diarrhea is accompanied by melena, vomiting, and/or generalized lethargy and weakness.

**c.** Patients may also exhibit **polyuria and polydipsia**. This is likely due to a combination of the decreased renal medullary concentration gradient resulting from hyponatremia, and decreased sodium (and, consequently, water) resorption in the collecting ducts of the kidney.

**d.** Some dogs with hypoadrenocorticism present with **generalized or hindlimb weakness**, which may be the primary presenting complaint (Figure 1.4). Reflexes are generally normal in these dogs. The reason for this weakness is unclear. Generalized debility is a plausible explanation, but some of these dogs have hindlimb weakness only. Another hypothesis is that electrolyte abnormalities lead to aberrant neuromuscular function. Whatever the cause, hypoadrenocorticism should be considered in patients that are “down in the hindlimbs.”

**e.** Some dogs with hypoadrenocorticism have concurrent **megaesophagus**. Rarely, regurgitation is the major presenting complaint in dogs with hypoadrenocorticism. The severity of the megaesophagus is variable; **regurgitation** may be noted, but radiographic evidence without clinical signs is also possible. The esophageal dilation seems to be less severe than that seen in other cases of megaesophagus. Proposed explanations for this megaesophagus include disturbed neuromuscular function caused by electrolyte abnormalities and muscle weakness secondary to cortisol deficiency. Hypoadrenocorticism is one of the few underlying causes of megaesophagus in which appropriate treatment results in the resolution of esophageal abnormalities, so it should be ruled out in all cases of megaesophagus.

**f.** **Muscle cramping** has been described in two Standard Poodles with hypoadrenocorticism. Again, aberrant electrolyte concentrations are hypothesized to cause an underlying neuron conduction abnormality.

#### 2. Acute hypoadrenocorticism:

**a.** Approximately 30% of dogs with hypoadrenocorticism present in **hypovolemic shock**. Any of the clinical signs described for patients with chronic hypoadrenocorticism may be found in dogs with an

**Table 1.1** Clinical signs and physical exam findings in dogs with hypoadrenocorticism.

Clinical signs and physical exam findings	Incidence (%)
Lethargy/depression	90
Decreased appetite/anorexia	80
Vomiting	80
Weakness	70
Weight loss	45
Diarrhea	40
Waxing/waning illness	40
Dehydration	40
Hypothermia	35
Shaking/shivering	30
Weak pulses	30
Polyuria/polydipsia	25
Melena	15
Painful abdomen	15

Data modified from Willard et al. (1982); Peterson et al. (1996); and Melian and Peterson (1996).



**Figure 1.4** Hypoadrenocorticism is known as “The Great Pretender” because of the variety of presenting complaints and clinical signs seen in patients. This 8-year-old bearded collie presented for hindlimb weakness and collapse. Serum chemistry revealed hyperkalemia and hyponatremia, and ACTH stimulation confirmed hypoadrenocorticism.

acute presentation. History may reveal chronic gastrointestinal signs with acute presentation of vomiting and/or diarrhea. Collapse secondary to hypovolemia and/or generalized weakness is not uncommon.

**b.** Classic signs of hypovolemic shock are usually present, including **weak pulse, pale mucous membranes, and prolonged capillary refill time**; **hypothermia** occurs occasionally. Heart rate, however, is variable. Whereas most dogs in hypovolemic shock are tachycardic (>160 bpm), **patients in hypoadrenocortical crisis often have a normal to decreased heart rate**. This is due to the effects of

hyperkalemia in lowering the heart rate. Thus, the presence of a decreased or normal heart rate (“relative bradycardia”) in a patient in hypovolemic shock should raise suspicion of hyperkalemia and hypoadrenocorticism. Rapid treatment and correction of cardiac changes associated with hyperkalemia is critical for the survival of the patient.

**c. Melena** is frequently present in patients in Addisonian crisis, and may be severe enough to necessitate blood transfusion. Hematochezia is seen less frequently. Melena may be noted on initial exam, or may not be evident until after beginning therapy. Progressively decreasing hematocrit during treatment (more than by hemodilution alone) should increase suspicion of melena, and the possibility of melena should not be excluded due to its initial absence in feces or upon rectal examination. Ileus may decrease gastrointestinal (GI) transit enough to delay its appearance for 1–2 days. It is not uncommon for melena to appear 2–3 days into treatment. For this reason, hospitalization is recommended until the hematocrit stabilizes or increases.

**d.** Generalized muscle weakness results in **shaking** and/or **shivering** in some patients.

**e.** Rarely, severe hypoglycemia leads to **seizures** in dogs with Addison’s disease.

### 3. Atypical hypoadrenocorticism:

**a.** Dogs with isolated cortisol deficiency generally present with the same **nonspecific clinical signs** (lethargy, weight loss, and anorexia) as other dogs with hypoadrenocorticism.

**b. Gastrointestinal signs** (vomiting and diarrhea) are also common, and **megaesophagus** and **seizures** (secondary to hypoglycemia) have been reported with atypical hypoadrenocorticism as well.

**c. Atypical Addisonians infrequently present in acute crisis.** This is probably because **hyperkalemia** and **hyponatremia** do not occur in these dogs. **Hypotension** is possible, however, as a result of decreased vascular tone in the absence of cortisol. Acute collapse secondary to hypoglycemia and hemorrhagic shock secondary to GI hemorrhage has also been reported in this group of Addisonian patients.

**d.** Patients with atypical Addison’s disease have a slightly longer duration of clinical signs prior to diagnosis. This may be due to the fact that diagnosis is delayed because there are no electrolyte disturbances to stimulate the clinician’s suspicion of hypoadrenocorticism.

## IV. Diagnosis

### A. Chronic hypoadrenocorticism:

**1.** Most of the diagnostics performed in dogs with hypoadrenocorticism are done early in the workup, often prior to significant suspicion of hypoadrenocorticism. **A complete blood count, serum biochemistry analysis, and urinalysis should be performed in each patient with clinical signs consistent with hypoadrenocorticism** (Table 1.2). It is critical that electrolyte analysis is included in the biochemistry panel, as sodium and potassium abnormalities are often the first specific indicators of hypoadrenocorticism. Additionally, electrolyte disturbances are common in patients with gastrointestinal signs of any etiology, and need to be addressed during treatment:

#### a. Serum biochemistry and urinalysis:

**1)** Most dogs with “typical” hypoadrenocorticism are **hyperkalemic** (90%) and **hyponatremic** (85%) at diagnosis. Potassium concentration usually remains below 8 mEq/L, but may be as high as 11 mEq/L. Sodium concentrations are usually in the range of 120–140 mEq/L, but may be as low as 100 mEq/L. Some present with one abnormality without the other (e.g., hyperkalemia without hyponatremia). **Hypochloremia** often parallels hyponatremia and is seen in approximately half of the patients. Electrolyte disturbances are not always present early in the course of disease; they may appear when the patient’s disease progresses, or not at all, as with atypical hypoadrenocorticism. Emphasis is sometimes placed on calculation of the **Na<sup>+</sup>/K<sup>+</sup> ratio**. The lower the sodium and the higher the potassium concentration, the lower the ratio. The lower the ratio, the higher the likelihood that the patient has Addison’s disease (Adler et al. 2007). However, a high ratio does not rule out hypoadrenocorticism, nor does a low ratio definitively diagnose it; thus, the utility of the ratio is debatable. Any dog with hyponatremia or hyperkalemia should be considered a suspect for hypoadrenocorticism, regardless of the ratio.

**Table 1.2** Clinicopathologic abnormalities common with hypoadrenocorticism.**Clinicopathologic abnormalities associated with hypoadrenocorticism**

Hyperkalemia  
 Hyponatremia  
 Hypochloremia  
 Azotemia  
 Isosthenuria  
 Hypoalbuminemia  
 Hypercalcemia  
 Hypcholesterolemia  
 Lymphocytosis  
 Lack of stress-related neutrophilia  
 Eosinophilia

**2) Azotemia** is a frequent finding, and is usually prerenal in nature. Both **creatinine** (increased in 65% of cases) and **blood urea nitrogen (BUN)** (increased in 90%) concentrations increase as a result of decreased renal perfusion due to hypovolemia; BUN may be further increased by GI blood loss. Phosphorus is also usually increased in azotemic patients (70% of all Addisonians):

**a)** Despite the **prerenal** nature of the azotemia, most dogs with hypoadrenocorticism also have a urine-specific gravity <1.030 (frequently <1.020). This is more dilute than would be expected in most patients with prerenal azotemia alone. For this reason, many of these patients are incorrectly thought to be in renal failure. It is imperative that clinicians **consider hypoadrenocorticism as a differential diagnosis in any azotemic dog**, particularly if the dog has a history of gastrointestinal signs.

**3)** Impaired excretion of acid (H<sup>+</sup> ions) in the distal tubule results in mild **metabolic acidosis** in half the canine Addisonians.

**4)** Approximately 15% of Addisonian dogs have **hypoalbuminemia**. Although the mechanism remains to be elucidated, it is likely due to loss through gastrointestinal hemorrhage, impaired gastrointestinal absorption, or decreased hepatic synthesis.

**5)** Although hypocortisolemia should result in decreased hepatic gluconeogenesis, **hypoglycemia occurs infrequently** (15%) in dogs with hypoadrenocorticism, and is usually subclinical. However, dogs with hypoadrenocorticism have been reported to present for hypoglycemic seizures. **Hypoadrenocorticism should always be a differential diagnosis for an adult dog with severe hypoglycemia.**

**6)** Total and ionized hypercalcemia occurs frequently, in approximately 30% of hypoadrenocortical dogs (Adamantos et al. 2008). Mild increases in calcium are most common, but severe hypercalcemia is possible. The reason for this hypercalcemia is unclear, but is likely related to decreased renal clearance. Hypoadrenocorticism accounts for anywhere from 5% to 25% of dogs with hypercalcemia; thus, **it should be considered a differential diagnosis in the workup of hypercalcemic dogs.**

**7)** Decreased hepatic production and gastrointestinal malabsorption are suspected to cause **hypcholesterolemia** in approximately 10% of Addisonian dogs.

**8)** Hepatic hypoperfusion and cholestasis may play a role in the mild to moderate increases in **alanine aminotransferase (ALT)**, **alkaline phosphatase (ALP)**, and **aspartate aminotransferase (AST)** seen in 20–30% of hypoadrenocortical dogs.



**Figure 1.5** Microcardia is a nonspecific indicator of hypovolemia, and is frequently seen in dogs with hypoadrenocorticism.

**b. Complete blood count:**

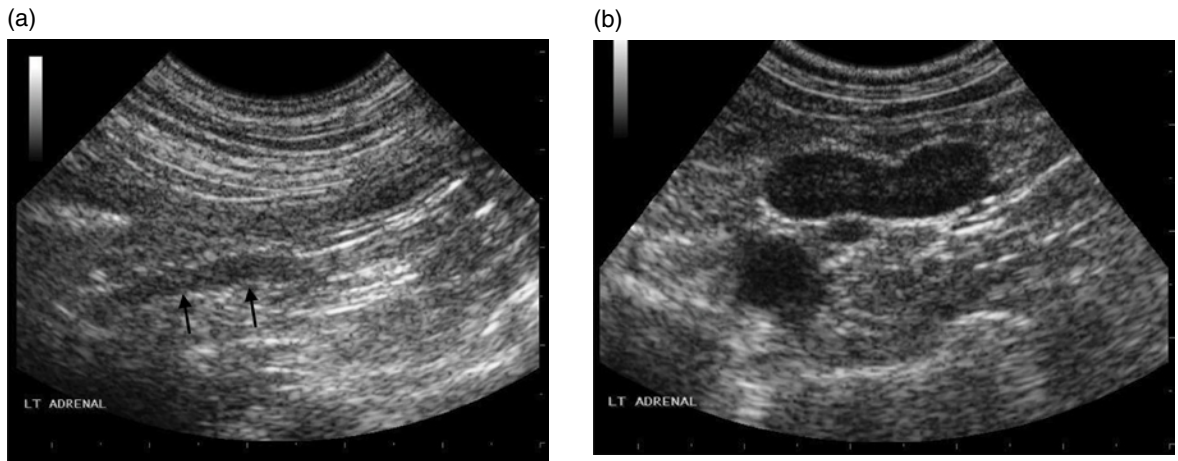
**1)** Cortisol released during illness in dogs with normal adrenocortical function often results in the “stress leukogram” of neutrophilia, lymphopenia, monocytosis, and eosinopenia. These changes, particularly lymphopenia, are often absent in dogs with hypoadrenocorticism. Lymphocytosis and eosinophilia, part of the “reverse stress leukogram,” are only present occasionally (10% of cases), while the final component, neutropenia, is rarely present. Despite the infrequent occurrence of the reverse stress leukogram, the **absence of a stress leukogram in a sick patient should heighten suspicion of hypoadrenocorticism.**

**2)** Approximately 30% of dogs are **anemic** at diagnosis of hypoadrenocorticism, with the proportion increasing to approximately 70% following rehydration. The anemia is typically **normochromic, normocytic, nonregenerative**, and mild. Dogs with more severe anemia almost always have evidence of gastrointestinal blood loss, even if not evident at presentation.

**2.** Radiographs and ultrasound are often performed in patients that present for gastrointestinal signs, including most patients with hypoadrenocorticism. Although results are generally nonspecific, there are some findings commonly present in Addisonian dogs:

**a.** Thoracic radiographs usually reveal nonspecific signs of hypovolemia, including **microcardia and decreased size of the caudal vena cava and pulmonary vessels** (Figure 1.5). Megaesophagus may also be seen, as discussed above.

**b.** Abdominal radiographs and ultrasound may reveal microhepatica, consistent with hypovolemia. Adrenal gland length and thickness, on average, are lower in Addisonians than in normal dogs (Figure 1.6). However, there is significant overlap between values in normal and Addisonian dogs. One study reported that the length and thickness of the left adrenal in a small group of hypoadrenocortical dogs was 10.0–19.7 mm (median, 13.1 mm) and 2.2–3.0 mm (median, 2.4 mm), respectively. The same measurements (length, thickness) of the left adrenal in a group of normal dogs were 13.2–26.3 mm (median, 17.4 mm) and 3.0–5.2 mm (median, 4.1 mm). Despite the trend in smaller adrenal gland measurements in hypoadrenocortical patients, the difference in values is not significant enough to definitively differentiate between normal and Addisonian patients.



**Figure 1.6** (a) Abdominal ultrasound often identifies very small adrenal glands in dogs with hypoadrenocorticism. Note how thin this left adrenal gland is (3.3 mm), compared to the one from a normal dog in (b). (b) Note the peanut shape and width (6.7 mm) of this normal left adrenal gland, compared to the gland from an Addisonian dog in (a). (Images provided by Drs. Erin Brinkman and Erica Baravik.)

### 3. Specific endocrine tests:

**a.** The ACTH stimulation test is required for definitive diagnosis of hypoadrenocorticism. A supra-physiologic dose of ACTH is given to maximally stimulate the adrenal glands (Figure 1.7). In dogs with normally functioning adrenal glands, ACTH stimulation will result in a significant increase in cortisol concentration. In hypoadrenocortical dogs, minimal to no increase in cortisol concentration will occur:

#### 1) Protocol:

- a)** A baseline blood sample is obtained.
- b)** Synthetic ACTH (cosyntropin or tetracosactrin), 5 µg/kg (0.005 mg/kg) (up to a maximum of 250 µg/dog) is given, intravenously (Lathan et al. 2008).
- c)** A 1 h post-ACTH blood sample is drawn.
- d)** Pre- and post-ACTH samples are submitted for cortisol analysis.
- e)** Due to inconsistent results, compounded ACTH gel is not recommended for the diagnosis of hypoadrenocorticism.
- f)** In canine Addisonian suspects, intravenous administration of cosyntropin is recommended over intramuscular administration due to potentially altered intramuscular absorption in dehydrated and/or hypovolemic patients.

#### 2) Interpretation of the ACTH stimulation test is based on the value of the post-sample:

- a)** A post-sample of  $<2.0 \mu\text{g/dL}$  ( $55 \text{ nmol/L}$ ) is consistent with a clinical diagnosis of hypoadrenocorticism. Lack of response to ACTH stimulation demonstrates that the adrenal cortex is incapable of secreting cortisol, even when stimulated with a much higher amount of ACTH than the body produces:
  - i.** The ACTH stimulation test does not differentiate between primary adrenocortical failure and secondary hypoadrenocorticism due to decreased ACTH secretion. Without the trophic effects of ACTH, the adrenal cortex atrophies, disabling a response to exogenous ACTH. Thus, dogs with primary and secondary hypoadrenocorticism both fail the ACTH stimulation test.
  - ii.** Patients with iatrogenic hypoadrenocorticism, resulting from acute withdrawal following prolonged administration of exogenous glucocorticoids, will also have a post-stimulation cortisol concentration  $<2.0 \mu\text{g/kg}$  ( $55 \text{ nmol/L}$ ). However, these patients should be easy to differentiate based on historical evidence of glucocorticoid administration.



**Figure 1.7** An ACTH stimulation test is required for definitive diagnosis of hypoadrenocorticism. In order to avoid problems with absorption, synthetic ACTH (cosyntropin) is given intravenously in Addison's disease suspects.

- b)** A post-sample  $>2\mu\text{g/dL}$  ( $55\text{ nmol/L}$ ) rules out the clinical diagnosis of hypoadrenocorticism in most patients.
- c)** Administration of glucocorticoids prior to the ACTH stimulation test can alter the test in two different ways:
  - i.** Several synthetic glucocorticoids, including prednisone and methylprednisolone, cross-react with the cortisol assay. Thus, both the pre- and post-stimulation cortisol concentrations will be falsely elevated following administration of other glucocorticoids. To avoid this, the only glucocorticoids that should be given near the time of the test are dexamethasone and triamcinolone. Short-acting glucocorticoids, such as prednisone or methylprednisolone succinate, should be withheld for 12–24 h before the test. Longer-acting repositol steroids, such as methylprednisolone acetate, may cross-react with the assay for up to 4 weeks following administration. If glucocorticoid supplementation is necessary prior to completion of the ACTH stimulation test, dexamethasone or triamcinolone should be given.
  - ii.** Short-term administration of glucocorticoids within a month of the test may lead to decreased response to ACTH, depending on patient sensitivity, dosage, and duration of treatment. Exogenous glucocorticoid administration (oral or topical) inhibits the release of endogenous ACTH, which causes atrophy of the adrenal cortex. Following removal of the source of exogenous glucocorticoid, the adrenocortical function slowly recovers. However, if an ACTH stimulation test is performed prior to full recovery, the post-stimulation cortisol may be below normal. A post-ACTH cortisol concentration between  $2\mu\text{g/dL}$  ( $55\text{ nmol/L}$ ) and  $5\mu\text{g/dL}$  ( $138\text{ nmol/L}$ ) is often the result of recent steroid administration as compared to spontaneous hypoadrenocorticism:

- i) Chronic administration of glucocorticoids may lead to suppression of the hypothalamic pituitary axis (HPA) and subsequent decreased response to ACTH for more than a month following discontinuation of the medication.
  - 3) For the diagnosis of hypoadrenocorticism, the use of synthetic ACTH (cosyntropin or tetracosactrin) is recommended. Compounded gel formulations are available, but testing results are not as consistent with the gels as they are with synthetic ACTH:
    - a) If compounded ACTH gel must be used, it is recommended to obtain two post-stimulation cortisol samples at 1 and 2 h, due to inconsistent results from the use of the gel.
    - 4) After a 250 µg vial of cosyntropin or tetracosactrin is opened, it can be frozen in plastic syringes and stored for up to 6 months. ACTH binds to glass, so glass syringes should not be used. Freezing in 50 µg aliquots allows dosing for 10 kg dogs with each syringe and minimizes waste. Once thawed, cosyntropin should not be refrozen; a frost-free freezer should NOT be used because of the freeze/thaw cycles.
  - b. A baseline cortisol concentration is a relatively inexpensive way to rule out hypoadrenocorticism.** In almost all patients with hypoadrenocorticism, a baseline cortisol sample will be <2 µg/dL (55 nmol/L) (often <1 µg/mL (28 nmol/L)), so a baseline cortisol sample >2 µg/dL (55 nmol/L) rules out hypoadrenocorticism in a given patient. However, since normal dogs can have baseline cortisol samples <2 µg/dL (55 nmol/L), an ACTH stimulation test MUST be performed to confirm hypoadrenocorticism. **A baseline cortisol concentration can only be used to rule out hypoadrenocorticism—NOT to confirm it:**
    - 1) In rare cases, a patient with clinical hypoadrenocorticism may have pre- and post-stimulation cortisol values between 2 µg/dL (55 nmol/L) and 3 µg/dL (83 nmol/L). Therefore, strong clinical suspicion of hypoadrenocorticism would mandate an ACTH stimulation test in a dog with baseline values between 2 µg/dL (55 nmol/L) and 3 µg/dL (83 nmol/L).
- B. Acute hypoadrenocorticism:**
- 1. Patients presenting in hypoadrenocortical crisis have similar diagnostic findings as patients with chronic clinical signs (see above). However, abnormalities are often more severe and can be immediately life-threatening (Figure 1.8):
    - a. **Hyperkalemia and hyponatremia are often marked in patients in crisis.** Hyponatremia results in weakness, but severe hyperkalemia may be immediately life-threatening. Individual patients vary in susceptibility to the debilitating effects of hyperkalemia, but potassium concentrations less than 7.0 mEq/L generally cause few specific clinical signs. Values between 7.0 and 9 mEq/L result in weakness and moderate to severe cardiac dysfunction, and may be fatal. Values >9.0 mEq/L usually lead to severe cardiac dysfunction and are often fatal:
      - 1) Cardiac function in these patients should be monitored by electrocardiogram (ECG). Although ECG changes do not correlate exactly with specific potassium concentrations, they tend to appear in the following order, with increasing severity of hyperkalemia:
        - a) Increased T-wave amplitude.
        - b) Shortened Q–T interval.
        - c) Decreased P-wave amplitude.
        - d) Prolonged P–R interval.
        - e) Absent P-wave (sinoatrial standstill).
        - f) Severe bradycardia.
        - g) Asystole.
        - h) Bizarre QRS complexes, including paroxysmal ventricular tachycardia and ventricular fibrillation, may also be seen.
    - b. **Most patients in Addisonian crisis will have significant prerenal azotemia** on presentation, which resolves upon correction of hypovolemia. Severe or prolonged hypovolemia, however, can result in ischemic renal damage secondary to hypoperfusion. If tubular epithelial damage results from the ischemia, renal azotemia may occur; however, with appropriate supportive care most patients fully recover renal function. Severe gastrointestinal blood loss is more common in patients in crisis, and may also lead to more severe azotemia (increased BUN).