CHAPTER 11

# Hyperadrenocorticism in Cats

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CHAPTER CONTENTS



## FELINE HYPERADRENOCORTICISM (FELINE CUSHING'S SYNDROME), HYPERALDOSTERONISM, SEX HORMONE SECRETING ADRENAL TUMORS

In 1932, long before the physiology of the adrenal cortex was understood and before identification of glucocorticoids, Dr. Harvey Cushing authored a report in which he described a group of people with a disorder that appeared to be "the result of pituitary basophilism." Subsequent study of the clinical, biochemical, and histologic features of these individuals are consistent with each having had a syndrome resulting from chronic exposure to excess circulating concentrations of glucocorticoids (cortisol). The eponym "Cushing's syndrome" is an umbrella term referring to all causes of "hyperadrenocorticism" in people and, more recently, in animals.

There are several causes for Cushing's syndrome. In addition to the common iatrogenic condition, one of the naturally occurring disorders is caused by an autonomously functioning, adrenocorticotropic hormone (ACTH)-secreting, pituitary tumor (usually an adenoma) resulting in excess cortisol synthesis/secretion and adrenocortical hyperplasia (pituitary

dependent hyperadrenocorticism [PDH]). ACTH-secreting pituitary tumors have been demonstrated to be derived from a single aberrant cell line. A less common cause of naturally occurring hyperadrenocorticism (NOH) in animals is that caused by an autonomously functioning, cortisol-secreting, adrenocortical tumor (adenoma or carcinoma; adrenal tumor hyperadrenocorticism [ATH]). PDH is about five-to-six times more common in people, dogs, and cats than ATH. Both iatrogenic and NOH is being diagnosed with increasing frequency in cats. This rising number of cats diagnosed with hyperadrenocorticism is likely associated with feline medicine becoming more specialized, cats being better understood, owners requesting more sophisticated care, awareness of this condition increasing, veterinarians becoming more familiar with the many variations on the theme of glucocorticoid excess, and an expanding number of aging feline pets.

NOH is unusually common in dogs, resulting in veterinary clinicians becoming quite familiar with the condition and the inevitable comparisons of "dog hyperadrenocorticism" and hyperadrenocorticism in cats. There are both similarities and differences. The obvious clinical features of hyperadrenocorticism in dogs include polyuria, polydipsia, polyphagia, panting, muscle weakness, thin skin, potbelly, and symmetrical alopecia. These common and obvious signs in dogs are not noted with frequency in cats with hyperadrenocorticism unless they have diabetes mellitus which, in turn, causes polyuria and polydipsia (PU/PD). Confirming a diagnosis is more problematic in cats, in part because the disease is far less common. Most reports in the literature describe "obvious" diagnoses in cats with dramatic abnormalities, suggesting that confirming a diagnosis in subtle cases is difficult or that the subtle cases are not often recognized or reported. Most dogs with NOH respond quite well and live years after commencement of treatment. In cats, however, treatment is more frustrating and difficult.

Since the underlying physiologic causes for hyperadrenocorticism are similar in dogs, and cats, the reader interested in applied physiology and in mechanisms of disease is encouraged to review the appropriate sections in Chapter 10. The focus of this chapter is to review the current state of knowledge regarding the diagnosis and treatment of feline Cushing's syndrome (FCS) in cats. As will be discussed later in this chapter, some adrenocortical tumors in cats primarily secrete sex hormones and/or mineralocorticoids.

To aid in this discussion, information from the records of 56 cats diagnosed as having FCS at our hospital, including some reported in the literature (Duesberg et al, 1995) were added to the information from 31 cats described in the literature (Immink et al, 1992; Daley et al, 1993; Goossens et al, 1995; Schwedes, 1997; Watson and Herrtage, 1998; Moore et al, 2000a; Meij et al, 2001; Skelly et al, 2003; Neiger et al, 2004), for a total of 87 cats with naturally occurring FCS. This literature includes only those reports published since 1992, to have greater confidence that valid and currently available assays were used in the assessment of each cat and that current concepts in diagnosis and treatment were used. Before 1990, only a few cats with this disease were mentioned in the literature (Swift and Brown, 1976; Meijer et al, 1978; Peterson and Steele, 1986; Zerbe et al, 1987a; Nelson et al, 1988). Furthermore, in the reports that we arbitrarily chose to use, we set the following selection criteria: Each cat must have had clinical signs associated with FCS and each diagnosis must have been confirmed using an accepted screening test. Most cats had advanced imaging (computed tomography [CT] or magnetic resonance imaging [MRI] scans) confirmation or histologic confirmation of the diagnosis.

## ETIOLOGY

### Iatrogenic Cushing's Syndrome

Clinical signs of iatrogenic cortisol excess are relatively common in dogs. Clinical signs due to iatrogenic cortisol excess are much less dramatic or common in people and seem even less obvious in cats. This can be explained, in part, by what appears to be a relative insensitivity to the negative or deleterious side effects of chronic glucocorticoid administration in cats. In other words, owners of dogs being treated with glucocorticoids are far more likely to observe unwanted or worrisome side effects than are owners of similarly-treated cats, simply because cats do not often demonstrate such side effects.

In studies on cats experimentally treated with glucocorticoids, those treated for a 4-week period had few abnormalities on physical examination and no consistent hematologic or biochemical changes (Scott et al, 1979; 1982). When treated for 9 weeks or longer, most cats continued to have no or few clinical signs (Lowe et al, 2008). However, a minority of cats exhibited some of the following: polydipsia, polyuria, polyphagia, abdominal enlargement, lethargy, weakness, thin skin, and medial curling of their ear tips. Some cats with iatrogenic cortisol excess developed hepatomegaly, muscle wasting, ecchymoses, and skin fragility (Scott et al, 1979; 1982; Lowe et al, 2008). Many cortisol-treated cats tended to develop mild hyperglycemia, and a minority became overtly hyperglycemic due to diabetes mellitus. Less common abnormalities included increased white blood cell numbers, a "stress leukogram," increased liver enzyme activities, hypercholesterolemia, hypertriglyceridemia, glycogen accumulation in hepatocytes, and a vacuolar hepatopathy. Cataracts developed in some laboratory cats treated with topical glucocorticoids (Brightman, 1982; Zhan et al, 1992).

A small number of privately owned cats treated with exogenous glucocorticoids had "clinical iatrogenic FCS" and were reported (Green et al, 1995; Schaer and Ginn, 1999; Ferasin, 2001; Lien et al, 2006). Among the features likely due to chronic glucocorticoid exposure were abdominal enlargement, muscle wasting, poor hair coats, and skin fragility. The skin fragility in one report included thin skin, easy bruisability, and skin tears. Several cats had increased liver enzyme activities and hepatic vacuolar hepatopathy. In one report, four of twelve cats developed transient diabetes mellitus, and four of twelve had transient hypothyroidism (Lien et al, 2006). Diabetes mellitus in cats identified after initiation of glucocorticoid treatment may be transient. Some cats had PU/PD in one study, but urine specific gravities were more than 1.035 in all cats (Lien et al, 2006). Despite these observations, iatrogenic FCS usually does not cause owner-discernable concerns. Interestingly, some features of iatrogenic cortisol excess (e.g., ear curling) in cats are not commonly seen in cats with the naturally occurring condition.

### Naturally Occurring Feline Hyperadrenocorticism

The causes of naturally occurring FCS are similar to those recognized in people and dogs. It has been suggested that resistance to glucocorticoid-induced side effects, likely in cats as compared with dogs, may help explain the relative low diagnosis rate of FCS in cats as compared with dogs. In other words, if excess glucocorticoids cause few clinical signs in cats, how would the diagnosis ever be suspected in the first place? Fewer than 100 cats have been reported in the veterinary literature that had been diagnosed with naturally

occurring FCS. The incidence of the FCS in cats (assessed non-scientifically) does appear similar to the incidence of the syndrome in human beings. However, people seem more sensitive than cats (but less sensitive than dogs) to clinical side effects associated with glucocorticoid administration. Therefore, FCS may simply be less common in cats as compared with dogs and people.

The majority of cats with naturally occurring FCS (approximately 80%) have PDH. Cats with PDH have a pituitary tumor, adenomas far more common than carcinomas, that autonomously synthesize and secrete ACTH. The persistent excesses of ACTH, in turn, cause excess synthesis and secretion of glucocorticoid (cortisol) from the adrenal cortices. The excess circulating cortisol has effects on cells within organs throughout the body, including suppressive effects on healthy pituitary cells responsible for synthesis and secretion of ACTH, luteinizing hormone (LH), follicle-stimulating hormone (FSH), thyroid-stimulating hormone (also known as thyrotropin; TSH), and growth hormone (GH). Chronic exposure to excessive concentrations of circulating cortisol is also likely to have suppressive effects on the synthesis and secretion of antidiuretic hormone (ADH) from the posterior pituitary in dogs, but there is little evidence of this happening in cats. Over time, excesses in circulating ACTH cause adrenocortical hyperplasia and somewhat symmetrical adrenal gland enlargement.

At the time of PDH diagnosis in dogs, about 50% of their pituitary tumors are microscopic in size and about 50% are large enough to be visualized with CT or MRI scans (usually greater than 3 to 4 mm in greatest diameter). A similar number (approximately 50%) are grossly visible at surgery or necropsy. Approximately 20% to 30% of dogs with PDH, usually after successful management of the condition for a prolonged time period, develop pituitary tumors large enough to cause clinical signs secondary to the compressive or invasive effects of the mass. Although many of these clinical scenarios have been described in cats with FCS, their incidence is not as well established.

Approximately 20% of cats with FCS have an autonomously functioning adrenocortical tumor (adrenal tumor hyperadrenocortisolism, ATH). About 50% or more of adrenocortical tumors are adenomas and somewhat less than 50% are carcinomas. Regardless of their histologic classification, adrenocortical tumors that cause FCS do so via the autonomous and excessive synthesis and secretion of glucocorticoids (cortisol). Chronic and persistent exposure to excess cortisol, in turn, is responsible for the various problems (clinical, biochemical, and so on) that are conveniently placed under the umbrella "Cushing's syndrome." As mentioned, cortisol affects cells in every organ. As with PDH, the chronic and excessive amounts of circulating cortisol also cause chronic negative feedback to healthy cells within the hypothalamus and pituitary gland. In this condition, however, with both hypothalamus and pituitary suppressed, the chronic inhibition of synthesis and secretion of ACTH causes "normal" cortisol-secreting cells to atrophy within the zona fasciculata and zona reticularis of the adrenal cortices. Therefore, over time, the cortex of one adrenal gland contains a functioning tumor and atrophied non-tumorous cells, whereas the opposite adrenal cortex contains primarily atrophied cells and may appear small or thin on imaging studies or gross evaluation. Atrophy of the opposite (non-tumor containing) adrenal becomes clinically relevant not only on imaging studies, but when the adrenal containing the tumor is surgically removed as a treatment for FCS. In this scenario, the clinician must remember that the cells responsible for cortisol synthesis and secretion in the remaining adrenal cortex will likely be unable to immediately provide adequate hormone to sustain health. Therefore, such individuals are treated with tapering doses of exogenous glucocorticoids, allowing function to be regained over time.

TABLE 11-1 **AGE AT TIME OF FELINE CUSHING'S SYNDROME DIAGNOSIS IN 61 CATS*†**

| AGE (YEARS) | PITUITARY DEPENDENT NUMBER OF CATS | ADRENOCORTICAL TUMOR NUMBER OF CATS |
|---|---|---|
| 5 | 1 | — |
| 6 | 5 | — |
| 7 | 2 | — |
| 8 | 3 | 1 |
| 9 | 4 | 2 |
| 10 | 4 | 1 |
| 11 | 5 | 2 |
| 12 | 6 | 3 |
| 13 | 4 | 2 |
| 14 | 6 | 2 |
| 15 | 2 | 2 |
| 16 | 3 | — |
| 17 | 1 | — |
| Mean | 11.0 | 11.9 |

*46 pituitary dependent hyperadrenocorticism; 15 adrenal tumor hyperadrenocorticism.
†Mean age of all 61 cats was 11.3 years

Later in this chapter, syndromes in cats with adrenocortical tumors synthesizing and secreting non-cortisol steroids will be reviewed.

## SIGNALMENT (AGE, SEX, BREED)

FCS is a disease of middle-aged and older cats. As can be seen in Table 11-1, both mean and median ages of 46 cats diagnosed as having PDH was 11 years (range, 5 to 17 years). The mean age of 15 cats, each with a functioning adrenocortical tumor, was 11.9 years (median 12 years), with a range of 8 to 15 years. The mean age for all 61 cats was just over 11 years. Among these 61 cats were 31 males and 29 females. All cats diagnosed as having naturally occurring FCS at our hospital had been neutered at an early age. The most commonly afflicted breed is the Domestic Short-Haired (DSH) cat (Table 11-2)—38 of 61 cats (62%), and if DSH and domestic long-haired cats are combined, the totals are 46 of 61 cats (75%). Cats representing various other breeds have been diagnosed with FCS.

## DURATION OF CLINICAL SIGNS, CHIEF COMPLAINT, AND GENERAL HISTORY

### Duration of Clinical Signs

The duration of clinical signs or the duration of specific owner concerns were available for 53 cats diagnosed as having FCS (Table 11-3). The range in duration of signs was from as little as 1 month to greater than 12. Fifty-one of the 53 cats with either PDH or ATH had clinical signs for less than 1 year at the time of diagnosis.

### Owner Chief Concern/Explanation for Being Referred

The "chief concern" is the primary reason or reasons that an owner seeks veterinary assistance, or in these cats, the primary reason(s) for seeing a specialist. The chief concern in 32 of 58 cats with FCS (55%) was "difficult to regulate diabetes mellitus." Most

TABLE 11-2 **BREEDS OF CATS WITH NATURALLY OCCURRING FELINE CUSHING'S SYNDROME (TOTAL OF 61 CATS)**

| | Pituitary Dependent | | Adrenocortical Tumor | |
|---|---|---|---|---|
| **BREED** | **NUMBER** | **PERCENTAGE** | **NUMBER** | **PERCENTAGE** |
| Domestic Short-Hair | 28 | 65 | 10 | 66 |
| Domestic Long-Hair | 7 | 13 | 1 | 7 |
| Siamese | 3 | 4 | 1 | 7 |
| Persian | 2 | 4 | 1 | 7 |
| Abyssinian | 2 | 4 | — | — |
| European Short-Hair | 2 | 4 | — | — |
| Devon Rex | 1 | 2 | — | — |
| Japanese Bobtail | — | — | 1 | 7 |
| Russian Blue | 1 | 2 | 1 | — |
| Maine Coon | — | — | — | 7 |
| Total | 46 | | 15 | |

TABLE 11-3 **DURATION OF CLINICAL SIGNS PRECEDING DIAGNOSIS OF FELINE CUSHING'S SYNDROME IN CATS (53 CATS)**

| DURATION (MONTHS) | NUMBER OF CATS WITH PITUITARY DEPENDENT DISEASE | NUMBER OF CATS WITH ADRENOCORTICAL TUMOR |
|---|---|---|
| 1 | 2 | — |
| 2 | 6 | 1 |
| 3 | 5 | 1 |
| 4 | 3 | 3 |
| 5 | 4 | 2 |
| 6 | 4 | 1 |
| 7 | 1 | 3 |
| 8 | 2 | — |
| 9 | 2 | 1 |
| 10 | 3 | — |
| 11 | — | — |
| 12 | 4 | 3 |
| > 12 | 2 | — |
| Total | 38 | 15 |

TABLE 11-4 **CHIEF COMPLAINTS BY OWNERS OF CATS ULTIMATELY DIAGNOSED AS HAVING CUSHING'S SYNDROME**

| COMPLAINT | PITUITARY DEPENDENT (43 CATS) | ADRENOCORTICAL TUMOR (15 CATS) |
|---|---|---|
| Resistant diabetes mellitus (PD/PU/PP)† | 28 | 4 |
| Polyuria/polydipsia (of the eight non-diabetic) | 6 | 2 |
| Fragile (torn) skin | 6 | 3 |
| Weight loss | 3 | 1 |
| Lethargy | 2 | 2 |
| Alopecia/failure to regrow hair | 2 | 2 |
| Diarrhea | 2 | — |
| Weakness | 1 | — |
| Vomiting | 1 | — |
| Abdominal enlargement | 1 | 1 |
| Not grooming | 1 | — |
| Polyphagia | 1 | — |
| Referral for ultrasound | 1 | 3 |
| Referral for Cushing's syndrome | 2 | — |

*Total of 58 cats; 50 of these 58 cats had diabetes mellitus, four had periodic diabetes mellitus, and four did not have diabetes mellitus.
†*PD,* Polydipsia; *PP,* polyphagia; *PU,* polyuria.

commonly, their diabetes mellitus was classified as difficult to regulate when owners felt that their pet had persistence of polyuria despite administration of insulin (Table 11-4). Other, less frequent observations that caused owners to believe their cats' diabetes mellitus was poorly controlled include continued weight loss, failure to gain weight, persistent lethargy, poor grooming habits, not consistently utilizing the litter box, and failing to be interactive with the family. Occasionally, "difficult to regulate diabetic" was designated by the referring veterinarian, rather than by the owner. Often, insulin dose and type had been altered numerous times by the primary care veterinarian in an effort to gain control of the diabetes mellitus prior to referral.

Owner chief concern was recorded in 58 cats. Forty-six of those 58 FCS cats had been previously diagnosed as having diabetes mellitus, four had been documented to have "episodic" diabetes mellitus prior to referral, and eight were not believed to be diabetic. Of the eight cats that did not have diabetes mellitus at the time of referral, six were believed to have PU/PD, and four of these six cats had diabetes when evaluated at our hospital. Thus, 50 of 58 FCS cats had

TABLE 11-5 **OWNER OBSERVATIONS IN CATS WITH NATURALLY OCCURRING CUSHING'S SYNDROME (TOTAL OF 72 CATS)**

| | Pituitary Dependent (57 Cats) | | Adrenocortical Tumor (15 Cats) | |
|---|---|---|---|---|
| **OBSERVATION** | **NUMBER** | **PERCENTAGE** | **NUMBER** | **PERCENTAGE** |
| Polyuria/polydipsia | 46 | 80 | 11 | 73 |
| Polyphagia | 39 | 68 | 8 | 53 |
| Weight loss | 27 | 47 | 6 | 40 |
| Lethargic/sleeps more | 25 | 44 | 7 | 47 |
| Weakness | 20 | 35 | 4 | 27 |
| Alopecia/failure to regrow hair | 18 | 32 | 12 | 80 |
| Stopped grooming | 10 | 18 | 4 | 27 |
| Coarse hair coat | 9 | 16 | 2 | 13 |
| Decreased appetite | 4 | 7 | 2 | 13 |
| Fragile (torn) skin | 9 | 16 | 5 | 33 |
| Weight gain/potbelly | 5 | 9 | 4 | 27 |
| Over grooming | 2 | 4 | 1 | 6 |
| Diarrhea | 2 | 4 | — | — |
| Periodic diabetes mellitus | 4 | 7 | — | — |
| Vomiting | 1 | 2 | — | — |

diabetes mellitus when first seen at our hospital and four had had "episodes" of diabetes. Fourteen of the 46 diabetic cats were believed to be well controlled with insulin. Among the less common primary owner concerns were fragile (torn) skin in nine cats (16%), lethargy in four, weight loss in four, and alopecia or failure to regrow hair that had been previously shaved in four. Four cats were suspected as having FCS and were specifically referred for abdominal ultrasonography. Two cats were referred for "evaluation of Cushing's."

### Owner Observations

Owner observations, other than their "chief concern," were available from 72 cats diagnosed as having FCS (57 cats with PDH; 15 cats with ATH; Table 11-5). The most common owner observation was PU/PD in 57 cats (79%), polyphagia in 47 (65%), weight loss or failure to gain weight in 33 (46%), and lethargy or reports of "sleeps more" in 32 cats (44%). Weakness, usually worse in the rear legs, was noted in 24 (33%) cats, 15 of whom had a plantigrade stance.

Concerns about skin problems were noted in a majority of the 62 cats; including the extremely worrisome fragile or torn skin noted in 14 cats (20%). Additionally, failure to grow hair after it had been shaved (usually for venipuncture or abdominal ultrasonography examination) was noted in 30 cats (42%), having "stopped grooming" was a concern in 14 cats (20%), and 11 owners thought their cat had abnormally coarse hair. Multiple skin problems were noted in some cats, whereas others had none. The owners of 21 cats with PDH (from the total of 57, or 37%) and the owners of three cats with ATH (from the total of 15, or 20%) did not mention any problem relative to the skin or hair coat. In general, owners of either PDH or ATH cats had similar observations, underscoring the final common denominator of chronic exposure to excess circulating cortisol. One exception was that 32% of PDH-cat owners noted alopecia or failure to regrow hair, whereas 80% of ATH cat owners mentioned this concern.

It has been suggested that clinical signs of FCS are not commonly detected by owners or veterinarians until these cats develop diabetes mellitus. Results of this review are in agreement with this concept for most afflicted cats. However, a few cats with FCS did not have diabetes mellitus and a few had signs that preceded development of diabetes mellitus. Thus, a suspicion of FCS may result from a history and physical examination in non-diabetic cats if thin skin, skin fragility, potbelly appearance, muscle atrophy, weakness (especially in the rear legs), or various hair coat disorders are noted. Any combination of these issues might lead to the suspicion of FCS in non-diabetic cats.

## PHYSICAL EXAMINATION ABNORMALITIES

The physical examination abnormalities from 72 cats with naturally occurring FCS are listed in Table 11-6. Many of the previously described owner concerns were obvious to the veterinarian performing the physical examination. The most common abnormalities observed included abdominal enlargement in 46 cats (66%; Fig. 11-1), muscle atrophy (44 cats; 61%), thin skin (43 cats; 60%), and an "unkempt" hair coat (35 cats; 49%). Less common abnormalities included hair loss, rear leg plantigrade stance, hepatomegaly, skin tears, bruising, and seborrhea. Two cats were noted to have abdominal masses, which were confirmed to be adrenal gland tumors (Immink et al, 1992). The finding of a palpable adrenal tumor is considered quite unusual.

## EXPLANATIONS FOR HISTORY AND PHYSICAL EXAMINATION ABNORMALITIES

### Polyuria and Polydipsia

PU/PD are usually suspected after learning an owner's concerns of their pets' "inappropriate urination" and finding a urine specific gravity less than 1.020. These signs are, perhaps, the most common

TABLE 11-6 **PHYSICAL EXAMINATION ABNORMALITIES IN 72 CATS WITH NATURALLY OCCURRING CUSHING'S SYNDROME**

| | Pituitary Dependent (57 Cats) | | Adrenocortical Tumor (15 Cats) | |
|---|---|---|---|---|
| **OBSERVATION** | **NUMBER** | **PERCENTAGE** | **NUMBER** | **PERCENTAGE** |
| Abdominal enlargement (potbelly) | 35 | 61 | 11 | 73 |
| Muscle atrophy | 35 | 61 | 9 | 60 |
| Thin skin | 32 | 56 | 11 | 73 |
| Unkempt hair coat | 30 | 53 | 5 | 33 |
| Hair loss | 16 | 28 | 5 | 33 |
| Hepatomegaly | 11 | 19 | 3 | 20 |
| Skin tears | 11 | 19 | 2 | 13 |
| Plantigrade stance | 11 | 19 | 4 | 27 |
| Bruising | 7 | 12 | 3 | 20 |
| Seborrhea | 3 | 5 | 5 | 33 |
| Palpable adrenal mass | — | — | 2 | 13 |

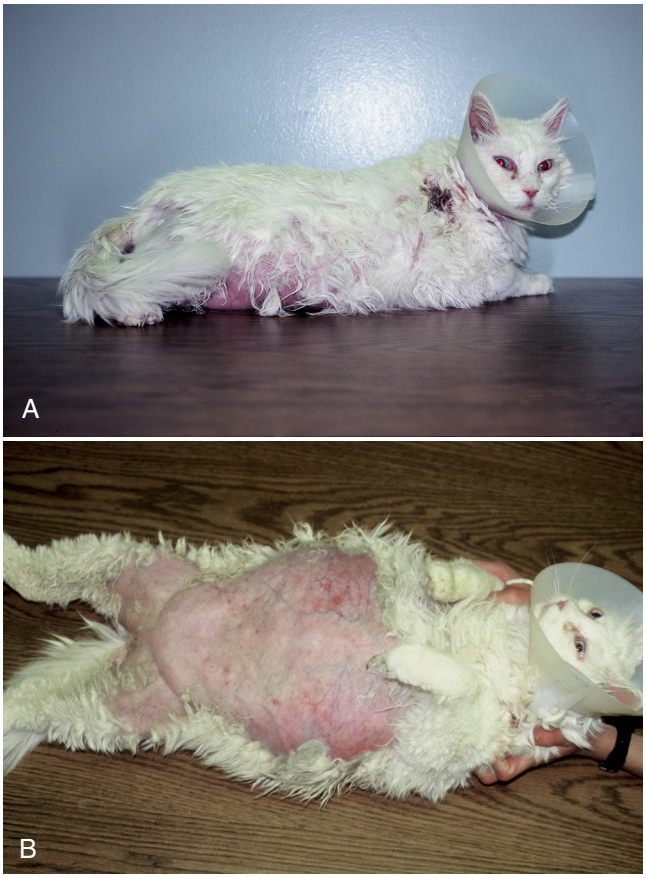


**FIGURE 11-1** **A,** 12-year-old male cat with feline Cushing's syndrome (FCS). Note the unkempt appearance of the hair coat. **B,** Note the pot-bellied appearance and the thin skin. (The hair on the abdomen had been shaved for ultrasound evaluation.)

observations among owners of dogs with hyperadrenocorticism, yet only about 5% of those dogs have diabetes mellitus and glucosuria. This is a much lower percentage of diabetics than is seen in cats with FCS. It is thought that a majority of hypercortisolemic dogs have PU/PD due to central or nephrogenic diabetes insipidus which, in turn, is secondary to their excess circulating cortisol concentrations. It is extremely unusual for such a dog to have concurrent chronic kidney disease (CKD). Cats with FCS, on the other hand, appear to develop PU/PD secondary to diabetes mellitus, CKD, or both. PU/PD occurs uncommonly in non-diabetic people or cats with naturally occurring or iatrogenic hyperadrenocorticism.

Polyuria, polydipsia, polyphagia, and weight loss are the classic signs of diabetes mellitus. For cats with FCS that also have diabetes mellitus (usually secondary to chronic excesses in systemic cortisol concentrations causing insulin resistance), the explanation for their PU/PD is the osmotic diuresis associated with glucosuria, especially if the diabetes is not well controlled. A small number of non-diabetic cats with FCS have been described with PU/PD, and most of them have had "episodes" of diabetes mellitus, CKD, or hyperthyroidism, which are all conditions associated with PU/PD. Although a huge majority of dogs with hyperadrenocorticism have low-to-low-normal blood urea nitrogen (BUN) and serum creatinine concentrations and randomly collected urine with specific gravities less than 1.020, only five urine samples from 52 cats with FCS (Table 11-7; 38 with PDH and 14 with ATH) had a specific gravity less than 1.020 (9%) and none was less than 1.008. Each of those five cats had an increase in their serum urea nitrogen, creatinine, or both (one was also hyperthyroid). Thus the observation of PU/PD in cats diagnosed as having FCS is noted almost exclusively in cats with glycosuria, CKD, or some additional cause of PU/PD (e.g., hyperthyroidism). Some "non-diabetic" FCS cats appear to have episodic insulin resistance with episodes of glycosuria and secondary PU/PD. This hyperglycemia and glycosuria may not be demonstrable at the time that in-hospital testing is carried out.

### Polyphagia

Polyphagia is common in non-diabetic dogs with hyperadrenocorticism. This side effect is not a well-understood. Polyphagia is less common in cats with FCS, unless they are diabetic.

### Weight Loss

A relative or absolute deficiency of insulin, definitive of diabetes mellitus, causes an inability to utilize glucose and a physiologic

TABLE 11-7 URINALYSIS RESULTS FROM 52 CATS WITH NATURALLY OCCURING CUSHING'S SYNDROME

| | Pituitary Dependent (38 Cats) | Adrenocortical Tumor (14 Cats) |
|---|---|---|
| **URINALYSIS** | **NUMBER OF CATS** | **NUMBER OF CATS** |
| **Specific Gravity** | | |
| < 1.020 | 3 | 2 |
| 1.020 to 1.040 | 29 | 6 |
| > 1.040 | 6 | 6 |
| **Protein** | | |
| Negative | 19 | 6 |
| Trace | 11 | 3 |
| > Trace | 8 | 5 |
| **Bacterial Culture** | | |
| Negative | 36 | 12 |
| Positive | 2 | 2 |
| **Ketones** | | |
| Negative | 38 | 14 |
| Positive | 0 | 0 |

condition analogous to starvation. The physiologic response to starvation is hepatic synthesis of glucose and other sources of energy utilizing products derived from the breakdown of muscle and fat. This catabolism of muscle and fat is the explanation for weight loss. Since a majority of cats with FCS have diabetes mellitus, it is difficult for them to gain weight. This is certainly true of those cats whose diabetes is untreated. It is also true of those cats being treated with exogenous insulin but have resistance. Some cats are described as remaining thin (usually with a potbelly) and others have progressive weight loss despite insulin therapy. Nearly every cat with FCS that has an owner concern of weight loss (or failing to gain weight) has concurrent diabetes mellitus. Non-diabetic cats with FCS with CKD are also likely to lose weight. The third most common cause of weight loss among cats with FCS is concurrent hyperthyroidism. Weight loss or "remaining thin" is an important feature of FCS because acromegaly, a differential diagnosis for insulin resistance in cats, is a condition often associated with weight gain.

### Weakness, Lethargy, Potbelly, and Bruising

Explanation for these clinical signs can be directly related to the physiologic effects of glucocorticoids. Cortisol causes protein catabolism and, thus, breakdown of muscle. Muscle breakdown leads to wasting and weakness, which is often obvious to owners (Robinson and Clamann, 1988). Alternatively, weakness may be interpreted by an owner to be "lethargy" or as an "increased amount of time spent sleeping." Furthermore, some cats with FCS have a plantigrade posture, which is most often related to the diabetic neuropathy seen in cats with diabetes mellitus and, in FCS, probably enhanced by steroid-induced muscle wasting.

Chronic cortisol excess is recognized to cause a redistribution of fat from areas throughout the body to the abdominal mesentery, increasing the weight of abdominal content. Abdominal distention is the clinical consequence of this increased amount of abdominal content pressing down upon weakened abdominal musculature (see Fig. 11-1) and is a classic observation in people, dogs, and cats afflicted with hyperadrenocorticism. This type of abdominal distention is the "potbelly" appearance that is classic of Cushing's syndrome. Excess systemic glucocorticoids are associated with a relative decrease in the ability to heal due to blood vessel friability and a decrease in fibrous response to injury. Further, loss of subcutaneous fat (mobilized to the abdomen), blood vessels that are more superficial after losing their fat insulation, and decreases in normal healing properties increase the predisposition to bruising. In cats with FCS, bruising after venipuncture or clipping of hair can be dramatic.

### Curled Ear Tips

As a component of the catabolic state associated with chronic glucocorticoid excesses, decreased strength of ligaments, tendons, and cartilaginous structures in general can be expected. Initial reports on iatrogenic FCS in cats included observations of "ear tip curling." However, this clinical sign has either not been mentioned or not observed in our experience nor in the cats comprising our review.

### Dermatologic Abnormalities

Bilaterally symmetrical nonpruritic alopecia is common in hypercortisolemic dogs but not in cats. The alopecia that most FCS cat owners observe is due to a failure to regrow hair that has been clipped or hair that is lost as a result of normal or excessive grooming (Fig. 11-2). It is difficult to know whether "excessive" grooming truly exists. Are these cats grooming normally but causing hair loss, thereby also causing owner concern or are they grooming more than usual? In addition to hair loss, thin skin (Fig. 11-3), poor wound healing, skin fragility, and increased susceptibility to skin infections are typical sequelae to chronic excesses in circulating concentrations of cortisol. Chronic cortisol excess can result in atrophy of the epidermis, dermis, and hair follicles. This atrophy can be traced to glucocorticoid-induced suppression of dermal fibroblast and keratinocyte proliferation, as well as down-regulation of collagen, hyaluronic acid, sulfated glycosaminoglycans, elastin, and tenascin-C expression (Schacke et al, 2002). Chronic skin infections are likely related to a combination of easily traumatized skin in individuals that lack the ability to heal normally and have glucocorticoid-induced suppression of their immune systems. Glucocorticoids have many immunosuppressive effects, including decreased macrophage expression of inflammatory cytokines, increased expression of some antiinflammatory cytokines, decreased function and maturation of dendritic cells, decreased T cell activation and proliferation in response to mitogens, decreased cell-mediated lysis of target cells, decreased mitogen-induced B cell proliferation, and decreased antibody production (Tuckermann et al, 2005; Lowe et al, 2008).

Skin fragility, not typical of dogs with NOH, and thin skin are well recognized concerns in cats with FCS (Fig. 11-4; see Tables 11-5 and 11-6). Some cats have wrinkling and folding of their skin due to the previously described dermal atrophy and decreased collagen expression. In some cats, their skin is so fragile as to be easily torn. These cats can create full-thickness, self-induced, dermal abrasions from simple grooming. It seems that the most common causes of skin tears are self-induced, associated with routine restraint, or they may be caused by owners pinching the skin to administer insulin. The combination of poor wound healing and increased susceptibility to infection can be serious and result in life-threatening sepsis.

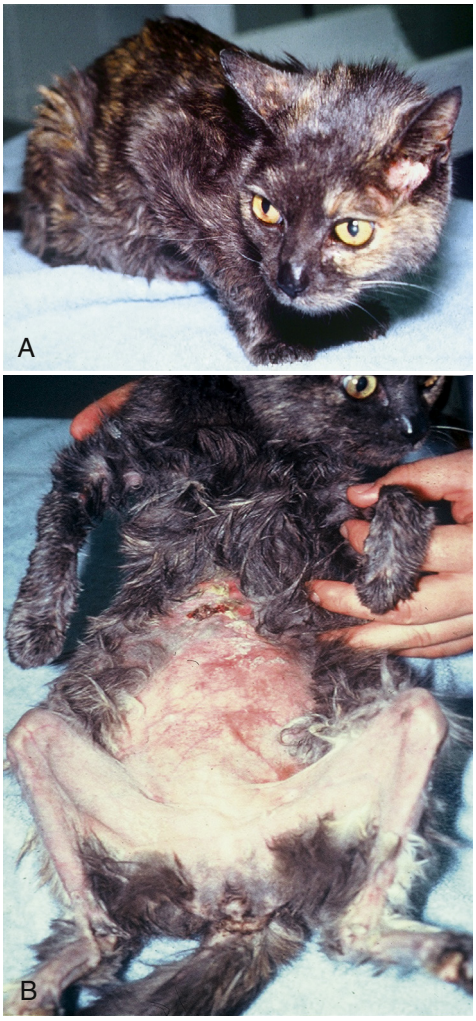


**FIGURE 11-2 A,** 10-year-old female cat with feline Cushing's syndrome (FCS). **B,** Note the hair loss sometimes associated with chronic exposure to excess cortisol.

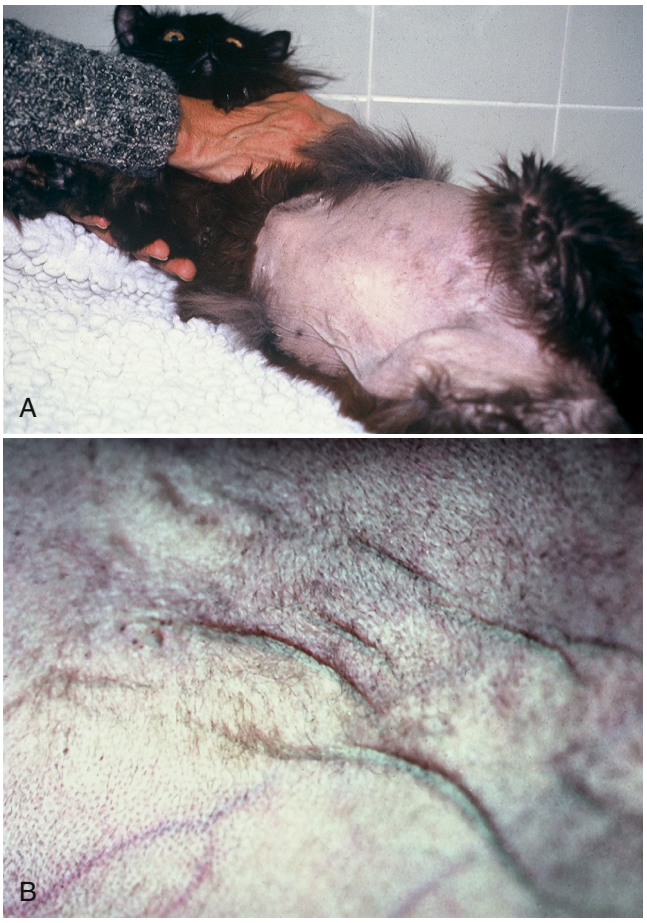


**FIGURE 11-3 A,** 11-year-old male cat with feline Cushing's syndrome (FCS). This cat had a progesterone-secreting tumor (see Excessive Sex-Hormone Secreting Adrenal Tumors in Cats). **B,** Note the thin skin sometimes associated with chronic exposure to excess cortisol.

## ROUTINE CLINICAL PATHOLOGY (COMPLETE BLOOD COUNT, BIOCHEMISTRY, URINALYSIS)

Veterinarians working with dogs are familiar with the side effects associated with chronic excesses in circulating cortisone concentration (hyperadrenocorticism; "Cushing's syndrome") because glucocorticoids ("cortisols") are utilized in the management of many canine conditions, side effects are both common and obvious, and the naturally occurring condition is also frequently encountered. Veterinarians, hearing about side effects from almost every steroid-treated dog owner, are repeatedly reminded of "expected" steroid-induced clinical observations. Laboratory abnormalities are indistinguishable in both iatrogenic and naturally occurring conditions. Veterinary clinicians expect dogs with iatrogenic or naturally occurring Cushing's syndrome to have PU/PD, isosthenuria/hyposthenuria, low-normal or low BUN concentrations, increases in serum cholesterol concentration, and increases in alkaline phosphatase and alanine aminotransferase (ALT) activities. Keeping these alterations in mind, we can state once again with confidence, that "cats are not small dogs."

### Complete Blood Count

Complete blood count (CBC) results from 53 cats with FCS can be reviewed in Table 11-8. The most important feature is the lack of consistency, in agreement with other investigators (Gunn-Moore, 2005; Graves, 2010; Peterson, 2012). About half of 53 cats had a "stress leukogram" (neutrophilia and a relative reduction in both lymphocytes and eosinophils). Of their total white blood cell counts, 26 cats (49%) had a neutrophil percentage of more than 86%, 28 (53%) had a lymphocyte percentage of less than 5%, and 29 (55%) had an eosinophil percentage of less than 2%. Of the 53 cats, one was thrombocytopenic, one was leukopenic, and six were anemic. Of the anemic cats, only one had a hematocrit below 24% (that result was 16%), and five of the six had evidence of CKD, likely a contributing issue to their anemia.

### Blood Glucose Concentrations and Diabetes Mellitus

#### *Overview*

Hyperglycemia represents the most common biochemistry abnormality in cats with FCS (Gunn-Moore, 2005; Lowe et al, 2007; Graves, 2010; Peterson, 2012). Fifty of 58 cats with FCS had diabetes mellitus when first seen at our hospital (four were diagnosed as diabetic at our hospital) and four had had "episodes" of diabetes. Fourteen of the 46 previously diagnosed diabetic cats were believed to be well controlled with insulin. Because a majority of cats with FCS were already being treated with insulin, it is not surprising that hypoglycemia would be identified on a few random blood glucose tests. On random blood glucose measurements in 52 FCS cats, 44 were hyperglycemic, six were hypoglycemic, and two were euglycemic. Both euglycemic and all six hypoglycemic cats were diabetic and

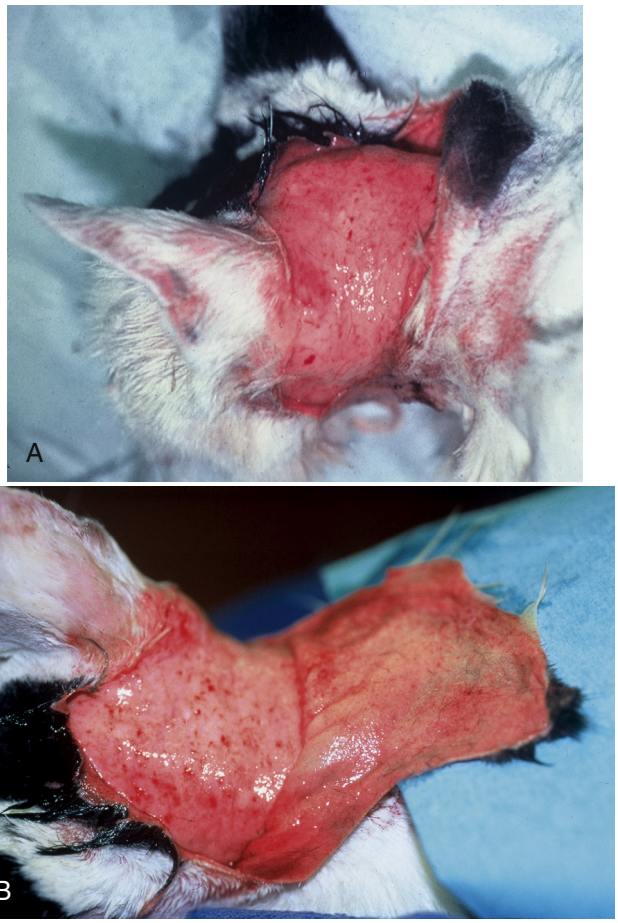


**FIGURE 11-4** **A,** Skin tear in a 15-year-old male cat with feline Cushing's syndrome (FCS). **B,** Skin tear in a 10-year-old cat typical of the skin fragility sometimes associated with chronic exposure to excess cortisol.

had received insulin on the day of testing. The implication from these data is that virtually all the cats included in this review were hyperglycemic or had insulin-induced reduction in blood glucose. One fair question difficult to answer is: "Was stress-induced hyperglycemia a factor in these results?"

### *Hypoglycemia Versus Insulin Dose*

Six of 52 cats with FCS evaluated with a randomly obtained biochemical profile in this review were found to be hypoglycemic, despite expected cortisol-induced insulin resistance. This incidence of hypoglycemia likely underestimates its frequency. Each was diabetic and each had received insulin the day of testing. Four of those six cats were described by their owners and referring veterinarians as "insulin-resistant." Insulin dose (per cat or per kg) among cats with FCS being treated for diabetes varies tremendously, but was often excessive (> 2.2 U/kg). Veterinarians are reminded that insulin can and frequently does induce hypoglycemia. It is also understood that veterinary clinicians occasionally need to manage cats with diabetes mellitus that appear to be "insulin resistant." One obvious response is to repeatedly increase insulin dose "as needed." However, increasing insulin dosage in an attempt to control "resistant" hyperglycemia in diabetic cats can become dangerous. An insulin dose in excess of 2.2 U/kg of body weight should be considered unsafe. Although we do not doubt that some cats appear responsive only to extremely high insulin doses after appearing resistant to lower doses, "resistance" is not a continuum. In other words, insulin resistance in cats with FCS seems to fluctuate or "wax and wane." If true, the dose given when a cat appears resistant may be an overdose in the same cat at another time. Because some cats with FCS have had severe life-threatening hypoglycemic reactions to insulin, especially when insulin doses are in excess of 2.2 U/kg, it is recommended to maintain insulin doses below this admittedly arbitrary level.

### *Diabetes Mellitus and the Diagnosis of Feline Hyperadrenocorticism*

Diabetes mellitus is among the more common conditions diagnosed in small animal practice and, along with hyperthyroidism, one of the two most frequently diagnosed endocrine disorders in cats. In contrast, FCS is considered uncommon-to-rare (Graves, 2010)—having been diagnosed in a few non-diabetic cats, a few cats with easily controlled diabetes mellitus, and many cats with apparent insulin resistance (Gunn-Moore, 2005). A large majority of cats with FCS are afflicted with concurrent diabetes mellitus (approximately 92% in our review) because it may be easier to suspect FCS in an insulin-resistant diabetic than in an older lethargic cat with a large abdomen. Thin skin, skin fragility, alopecia, failure to regrow hair after it has been clipped, muscle weakness, and PU/PD are potential owner concerns that may trigger testing and, ultimately, a diagnosis of FCS.

### *The Differential Diagnosis for "Difficult-to-Control" or "Insulin-Resistant" Diabetics*

Progression of feline diabetes mellitus is notoriously difficult to predict, and the condition can be difficult to manage. Among the concerns to be addressed by the veterinary practitioner: Which "poorly controlled" diabetic cat is truly "insulin-resistant," and which of those truly insulin-resistant cats are candidates for FCS? We encourage veterinarians having difficulty controlling any diabetic cat to prioritize the potential explanations for "difficult control" with the least expensive and most likely explanations considered first. Topping this priority list should be the concept that in-hospital testing may not reflect what is happening in the home environment.

Owner opinion is the single most important monitoring tool in the long-term management of diabetes. If an owner is satisfied with their cat's response to therapy, decisions based on in-hospital test results should not supersede their opinion unless hypoglycemia is documented. In-hospital stress-induced hyperglycemia is common, and home glucose monitoring minimizes this concern. Veterinarians should also consider the possibility of an "error" in management when a diabetic cat fails to respond to insulin therapy as expected. Errors include, but are not restricted to, using the incorrect insulin, mixing the insulin improperly, drawing insulin into the syringe incorrectly, using incorrect syringes, using outdated insulin, and improper administration technique. Every time a diabetic cat is evaluated, owners should be assessed as they handle and administer insulin. Once these potential concerns have been dismissed, the veterinarian should consider the possibility that the insulin being used is being given at too low a dose, too high a dose, the insulin could be too weak, too potent, too short acting, or too long acting. Additionally, one should consider the possibility that a concurrent disorder exists that interferes with insulin sensitivity. This could include any infection (dental, urinary tract or skin, among others) or any source of non-septic inflammation (pancreatitis, among others). Additional conditions that could cause insulin resistance include CKD, neoplasia, heart disease, and trauma. Among the various endocrine causes for insulin resistance are acromegaly, sex hormone excess, and FCS.

## Liver Enzyme Activities

A dramatic increase in serum alkaline phosphatase (SAP) activity (average > 1,000 IU/L) due to glucocorticoid-induction of an

TABLE 11-8 COMPLETE BLOOD COUNT RESULTS FROM 53 CATS WITH NATURALLY OCCURRING CUSHING'S SYNDROME

| | Pituitary Dependent (43 Cats) | | Adrenocortical Tumor (10 Cats) | |
|---|---|---|---|---|
| | NUMBER | PERCENTAGE | NUMBER | PERCENTAGE |
| **White Blood Cell Count** | | | | |
| < 6000 | 1 | 2 | — | — |
| 6000 to 17,000 | 26 | 60 | 6 | 60 |
| 17,000 to 25,000 | 10 | 23 | 3 | 30 |
| > 25,000 | 6 | 14 | 1 | 10 |
| **% Neutrophils** | | | | |
| ≤ 75 | 6 | 14 | 1 | 10 |
| 76 to 85 | 15 | 35 | 5 | 50 |
| ≥ 86 | 22 | 51 | 4 | 40 |
| **% Lymphocytes** | | | | |
| ≤ 5 | 22 | 51 | 6 | 60 |
| 6 to 15 | 19 | 44 | 4 | 40 |
| ≥ 15 | 2 | 5 | — | — |
| **% Eosinophils** | | | | |
| ≤ 2 | 24 | 56 | 5 | 50 |
| 3 to 6 | 13 | 30 | 4 | 40 |
| ≥ 7 | 6 | 14 | 1 | 10 |
| **Platelet Counts** | | | | |
| < 180,000 | — | — | 1 | 10 |
| 180,000 to 400,000 | 33 | 77 | 6 | 60 |
| > 400,000 | 10 | 23 | 3 | 30 |
| **Hematocrit** | | | | |
| ≤ 27 | 4 | 9 | 2 | 20 |
| 28 to 35 | 24 | 56 | 3 | 30 |
| 36 to 46 | 15 | 35 | 5 | 50 |
| ≥ 47 | — | — | — | — |

SAP isoenzyme is the most common serum biochemical abnormality (> 85%) recognized in dogs with NOH. By contrast, only five of 52 cats with FCS (9%) had an increased SAP. An important differential diagnosis for the increase in SAP in cats with diabetes mellitus is pancreatitis causing cholestasis. Further, the short half-life of SAP in cats as compared with dogs should increase concern regarding an increase. Although "steroid hepatopathy" has been observed in a few cats with iatrogenic hyperadrenocorticism, the changes are usually mild (Lowe et al, 2008; Graves, 2010). The cat has no corollary to the classic "steroid-induced-isoenzyme-of-SAP" known in dogs. In cats with FCS and diabetes mellitus, SAP activity may decrease into reference limits with insulin therapy alone, despite progression of the "Cushing's" (Peterson, 2012).

Another common biochemical abnormality in dogs with NOH (> 50%) is a mild to moderate increase in serum ALT activity. Increases in ALT were identified in 14 of 52 cats with FCS (27%). It is probable that increases in either or both liver enzyme activities in cats with FCS are secondary to hepatic changes associated with diabetes mellitus. Another cause for elderly cats to have increases in liver enzyme activities is hyperthyroidism. However, of the 52 cats with FCS that had thyroid testing, hyperthyroidism was only diagnosed in two.

### Serum Cholesterol and Thyroxine

Increase in serum cholesterol concentration is identified in more than 90% of dogs with diabetes mellitus and in more than 60% of dogs with NOH (less than 5% of dogs with hyperadrenocorticism have concurrent diabetes mellitus). Glucocorticoids inhibit lipoprotein lipase activity and increase activity of hormone-sensitive lipase, increasing both serum cholesterol and triglyceride concentrations. Increases in serum cholesterol concentration, however, are not common in cats with FCS, despite a majority having diabetes mellitus and, therefore, two physiologic stimuli for hypercholesterolemia. Serum cholesterol concentrations were increased in 13 of 52 (25%) cats with FCS in our review, each of whom had concurrent diabetes mellitus.

Chronic excesses in serum cortisol concentration feedback on the pituitary, decreasing TSH secretion and causing "secondary hypothyroidism." Hypothyroidism, primary or secondary, is a

TABLE 11-9 **SERUM BIOCHEMICAL RESULTS FROM 52 CATS WITH NATURALLY OCCURRING CUSHING'S SYNDROME**

| Test and Reference Range | | Pituitary Dependent (38 Cats) | | | Adrenocortical Tumor (14 Cats) | | |
|---|---|---|---|---|---|---|---|
| SERUM | | NUMBER WITHIN REFERENCE RANGE | NUMBER BELOW | NUMBER ABOVE | NUMBER WITHIN REFERENCE RANGE | NUMBER BELOW | NUMBER ABOVE |
| Alkaline phosphatase | (14 to 71 IU/L) | 35 | — | 3 | 12 | — | 2 |
| ALT | (28 to 106 IU/L) | 24 | — | 14 | 12 | 2 | — |
| Albumin | (2.7 to 3.9 g/dL) | 33 | 5 | — | 9 | 3 | 2 |
| Globulin | (2.9 to 4.3 g/dL) | 17 | — | 21 | 9 | — | 5 |
| Total protein | (5.6 to 8.4 g/dL) | 31 | — | 7 | 12 | — | 2 |
| BUN | (18 to 33 mg/dL) | 17 | — | 21 | 8 | — | 6 |
| Creatinine | (0.9 to 1.8 mg/dL) | 26 | 1 | 11 | 10 | — | 4 |
| Cholesterol | (89 to 258 mg/dL) | 24 | 2 | 12 | 13 | — | 1 |
| Glucose | (73 to 134 mg/dL) | 0 | 4 | 34 | 2 | 2 | 10 |
| Calcium | (9.4 to 11.4 mg/dL) | 34 | 4 | — | 11 | 3 | — |
| $PO_4$ | (3.2 to 6.3 mg/dL) | 34 | 2 | 2 | 11 | — | 3 |
| $TCO_2$ | (15 to 25 mm/L) | 31 | 4 | 3 | 14 | — | — |
| K | (3.6 to 5.3 mm/L) | 37 | 1 | — | 12 | 2 | — |
| Na | (145 to 156 mm/L) | 36 | 2 | — | 12 | — | 2 |
| $T_4$ | (1.0 to 2.5 µg/dL) | 33 | 5 | — | 12 | — | 2 |
| Magnesium | | 3 | 0 | 3 | 2 | 0 | 1 |

*ALT,* Alanine aminotransferase; *BUN,* blood urea nitrogen; *$PO_4$,* phosphorus; *$TCO_2$,* total carbon dioxide; *K,* potassium; *Na,* sodium; *$T_4$,* thyroxine.

classic cause of hypercholesterolemia. Secondary hypothyroidism, together with the direct lipolytic actions of glucocorticoids are explanations for the increases in serum cholesterol concentration typically identified in non-diabetic dogs with hyperadrenocorticism. Of the 52 cats with FCS in our review, serum thyroxine ($T_4$) concentrations were lower than the reference range in five (9%), three of which had serum cholesterol concentrations within reference limits. Most cats with FCS are euthyroid. Histologically confirmed thyroid disease was only identified in the two cats with hyperthyroidism.

### Blood (Serum) Urea Nitrogen, Serum Creatinine, Urinalysis

A consistent group of abnormalities seen in dogs that have hyperadrenocorticism are those related to PU/PD. A majority (> 90%) of hypercortisolemic dogs have urine specific gravities less than 1.020 (especially on samples obtained by owners from dogs in their home environment) and about 30% are less than 1.008. Polyuria in dogs represents one of the most frequent explanations for owners to seek veterinary care. In addition to PU/PD and isosthenuria/hyposthenuria in dogs with hyperadrenocorticism are their low-normal-to-low BUN and normal serum creatinine concentrations. These are classic features of canine hyperadrenocorticism. Increases in BUN are extremely uncommon in dogs with hypercortisolemia and represent a serious contraindication to treatment, because poor appetite and severity of CKD may be masked by hyperadrenocorticism. If the hyperadrenocorticism were to be treated, there is risk of "unmasking" and worsening CKD and its clinical signs.

A review of the serum biochemical and urinalysis data presented in Tables 11-7 and 11-9 from cats with naturally occurring FCS demonstrates several differences in results as compared with those from hypercortisolemic dogs. Not one of 52 cats with FCS had a BUN concentration below the reference range. Only five of 52 cats had a randomly obtained urine specific gravity less than 1.020. Each of those cats had isosthenuria secondary to CKD. Furthermore, 27 of 52 cats (52%) had an increased BUN concentration at the time of diagnosis. Fifteen of those 27 cats (29% of all 52) also had an increased serum creatinine concentration. It seems likely that the PU/PD recognized in some cats with FCS is secondary to CKD. Other polyuric conditions (e.g., hyperthyroidism) may need to be considered. There is little evidence to suggest that cats with FCS have a physiologic syndrome similar to the diabetes insipidus–like condition with dilute urine that occurs in hypercortisolemic dogs.

### Serum Sodium, Serum Magnesium, Serum Potassium, and Muscle Weakness

Cats with FCS are often described by their owners as being weak, a condition most commonly related to "feline diabetic neuropathy" causing posterior paresis. Other possible contributors to weakness are the glucocorticoid-induced catabolic effects on muscle and hypokalemia, documented in three of the 52 cats with FCS (6%; see Primary Hyperaldosteronism in Cats). We recommend that serum electrolyte concentrations be evaluated in any weak patient. Assuming that these hypokalemic cats did not specifically have hyperaldosteronism, one may still hypothesize that circulating

cortisol excess could act as weak mineralocorticoids and predispose cats to hypokalemia and muscle weakness. Serum sodium concentrations are usually within reference limits. Four of nine cats with FCS cats were hypermagnesemic, the significance of which is not yet fully appreciated.

### Serum Calcium, Albumin, Globulins, and Total Protein

Perhaps related to the incidence of CKD in cats with FCS, seven of the 52 cats (13%) were mildly hypocalcemic (based on total serum calcium concentrations). However, each hypocalcemic cat also had a decreased serum albumin concentration. Eight of 52 cats had mild hypoalbuminemia. Hyperglobulinemia was observed on 26 of the 52 chemistry profiles (50%); this was perhaps simply a normal response to chronic antigen exposure, which occurs in any older individual. However, the degree of hyperglobulinemia was such that 11 of the 52 cats (21%) had hyperproteinemia.

### Urinary Tract Infection

Urinary tract infection was confirmed in four of the 52 cats with FCS tested (8%; Table 11-9). Because many had been referred after being given antibiotics, perhaps this explains our failure to identify infection in more cats. In contrast, dogs with NOH have a high incidence of urinary tract infection and most are also referred after being treated with antibiotics.

### Blood Pressure

Blood pressure assessments have not been commonly reported from cats with FCS, and there is little data regarding the incidence of hypertension among cats with iatrogenic or NOH. However, hypertension is quite common among human beings and dogs with NOH, presumably due to the weak but significant mineralocorticoid actions of glucocorticoids. Further, hypertension is often a component of CKD (common in cats with FCS) or of aldosteronism (unknown incidence).

## "SCREENING TESTS" TO AID IN DIAGNOSING FELINE CUSHING'S SYNDROME

FCS is an uncommon condition, can be difficult to diagnose, and carries a guarded prognosis. Results from one of several endocrine tests may aid in discriminating cats that have naturally occurring FCS from cats that do not. The tests most commonly employed are the ACTH stimulation test, the low-dose dexamethasone suppression test (LDDST), and the urine cortisol-to-creatinine ratio (UC:CR); protocols for which can be seen in Table 11-10. Each of these tests has advantages, each has disadvantages, and no test is perfect. The diagnosis of FCS should be reserved for cats with clinical signs as well as endocrine test results consistent with the diagnosis.

### Sensitivity and Specificity (A Simple Review)

Discussion on testing invariably includes the concepts of test sensitivity and specificity. Sensitivity, in simple terms, refers to the number of patients with a condition who test positive for that condition. An extremely sensitive test, for example, is glucosuria in dogs with diabetes mellitus. The test is 100% sensitive because diagnosis is restricted to dogs with glucosuria. Specificity refers to the number of patients who do not have a disease and do not test positive for that disease. Using glucosuria again, it is quite specific for diabetes mellitus because "renal glucosuria" is uncommon. Although not perfect, glucosuria is a test that is strong in both sensitivity and specificity.

### Urine Cortisol-to-Creatine Ratio (UC:CR)

#### *Background in People and Dogs*

One of the most sensitive and specific screening tests for a person suspected as having NOH is to measure the total amount of cortisol excreted in their urine over a 24-hour period as compared with healthy controls (repeating the test enhances result validity). Despite advances that have taken place since this 24-hour urine collection was introduced as a screening test for humans suspected as having hyperadrenocorticism more than 60 years ago, the test remains a "cornerstone" assessment (Molitch, 2012; Nieman, 2012). The amount of cortisol excreted in urine over a 24-hour period reliably reflects the total amount of cortisol synthesized and secreted over time. Assessing the 24-hour urine excretion of cortisol negates any concern of minute-to-minute pulsatile fluctuations in adrenocortical secretory patterns or any concern regarding diurnal patterns that could affect serum cortisol concentrations at any moment. The use of a randomly collected single urine sample, assessed for cortisol concentration and then compared via ratio with the urine creatinine (UC:CR) is a "short-cut" to the more cumbersome 24-hour collection of urine. See Chapter 10 for a thorough explanation.

#### *Background in Cats*

The UC:CR is readily available to veterinary clinicians. Its reference range is higher in cats than dogs, despite their relatively low urinary cortisol excretion rate. The higher UC:CR reference range in cats may be due to their higher glomerular filtration rates and/or lower renal free cortisol reabsorption rates (Goossens et al, 1995). As in dogs, UC:CR in cats is not affected by age, gender, or neuter status. Attributes of the UC:CR include its sensitivity, low expense, east of implementation, and straight-forward interpretation. About 70% to 90% of cats with FCS have an abnormal UC:CR. UC:CR reliability is enhanced if owners bring urine samples from home, usually using small quantities of litter or nonabsorbable litter to make urine easier to collect. Owners should be informed that at least two samples from separate days should be assessed and that a third sample may be necessary if the first results are contradictory. Home-collected urine negates concern of spurious results due to the stress associated with travel and in-hospital collection.

Those who do not recommend the UC:CR mention its lack of specificity. In evaluating the UC:CR from 16 ill cats in one study, three had test results consistent with FCS ($\geq 36 \times 10^{-6}$) and seven had results considered "borderline" (i.e., $10 - 36 \times 10^{-6}$). Thus 10 of 16 ill cats that did not have FCS had UC:CR results that could be considered consistent with that diagnosis (Henry et al, 1996). In a subsequent study, hyperthyroid cats were found to have increased UC:CR results (de Lange et al, 2004).

#### *Test Interpretation*

Two independent studies suggested similar reference ranges for feline UC:CR ($< 28 \times 10^{-6}$ and $< 36 \times 10^{-6}$) (Henry et al, 1996; Goossens et al, 1995, respectively). Both are higher than that for dogs ($\leq 16 \times 10^{-6}$). A UC:CR more than $36 \times 10^{-6}$ is consistent with FCS in a cat with appropriate clinical signs and in-hospital test results. UC:CR values between 10 and $36 \times 10^{-6}$ in cats with appropriate clinical signs should be considered "borderline," inconclusive, and worth repeating. It is possible for a cat with test results in this range to have FCS, as was true for

TABLE 11-10 **A SUMMARY OF DIAGNOSTIC TEST PROTOCOLS USED IN CATS SUSPECTED OF HAVING CUSHING'S SYNDROME**

| SCREENING TESTS | TEST PROTOCOL |
|---|---|
| Urine cortisol-to-creatinine ratio (UC:CR) | 1. Owner collects urine from the cat; urine is then taken to veterinary clinic.<br>2. Sensitivity and specificity improve if repeated on separate mornings. |
| Low-dose dexamethasone suppression test (LDDST) | 1. Obtain blood for baseline control.<br>2. Administer 0.1 mg/kg dexamethasone, IV.<br>3. Obtain blood for cortisol 4 and 8 hours after dexamethasone. |
| Hair cortisol | Obtain appropriate samples for submission. |
| ACTH stimulation (ACTHST) | Not recommended. |
| Combination LDDST and ACTHST | Not recommended. |
| **DISCRIMINATION TESTS** | **TEST PROTOCOL** |
| High-dose dexamethasone suppression test (HDDST) | 1. Owner collects two urine samples from the cat (on different days).<br>2. After second collection, give three doses of dexamethasone orally (0.1 mg/kg every 8 hours: 8 AM, 4 PM, and midnight).<br>3. Next morning, collect urine for HDDST portion of test. |
| Abdominal ultrasonography | Excellent ultrasonographer and equipment are quite important. |
| Plasma endogenous [ACTH] (ACTH precursors, as well) | 1. Collect blood in chilled tube containing protease inhibitor.<br>2. Immediately separate plasma, freeze until assayed. |
| Low-dose dexamethasone suppression test (LDDST) | 1. Protocol as described earlier and used as screening test.<br>2. Criteria as discrimination test are distinct (> 50% decrease from basal level); see text. |
| HDDST (in-hospital protocol) | 1. Obtain blood for baseline cortisol.<br>2. Administer 1.0 mg/kg dexamethasone, IV.<br>3. Obtain blood for cortisol 4 and 8 hours after dexamethasone. |
| Abdominal radiographs | These are of limited value. |

*ACTH,* Adrenocorticotropic hormone; *[ACTH],* ACTH concentration; *IV,* intravenous.

12 of the 48 cats in our review (Tables 11-11 and 11-12). The UC:CR has high negative predictive value, meaning that a reference range result makes the diagnosis of FCS much less likely (Graves, 2010).

#### *Results*

As can be seen from the data presented in Tables 11-11 and 11-12, UC:CR data was collated from a total of 48 cats with FCS (34 with PDH and 14 with ATH), including cats from the literature (Goossens et al, 1995 [six cats]; Schwedes, 1997 [one cat]; Skelly et al, 2003 [one cat]; Meij et al, 2001 [seven cats]; and Neiger et al, 2004 [five cats]). Thirty-five of the 48 cats (71%; 27 from the PDH group and 8 from the ATH group) had UC:CR results above the reference range, 12 cats (25%) had "borderline" (13 – 36 $\times 10^{-6}$) results (six from each group). One cat had a UC:CR result that was considered normal (that cat had PDH). Thus the UC:CR appears to be a sensitive test for confirming the diagnosis of FCS in cats; in that only 1/48 cats had a result within the reference range.

#### *Conclusions*

The UC:CR is a sensitive diagnostic aid for distinguishing cats that have FCS from cats that do not. Sensitivity of this test appears to be similar to that for dogs with NOH. Because specificity remains a concern, the negative predictive value of the UC:CR is emphasized (i.e., cats with a negative UC:CR are less likely to have FCS, especially if that result is repeatable). Veterinarians are encouraged to place a great deal of importance on the history, physical examination, and "routine" in-hospital test results when deciding whether to perform the UC:CR. Veterinarians are encouraged to consider having owners collect urine samples on two separate mornings from their cat as an excellent means of screening for FCS (please see the section, Urine Cortisol-to-Creatinine Ratio and High-Dose Dexamethasone Suppression Test).

### ACTH Stimulation Test

#### *Background*

The adrenocorticotropic hormone stimulation test (ACTHST) has been recommended as an aid for confirming a diagnosis of NOH in dogs for about 50 years. More recently, the ACTHST has been recommended as an aid to confirm or refute the diagnosis of FCS, presumably as an extension of its use in dogs. A complete discussion on the physiologic basis for this test and its usefulness is provided in Chapter 10. In general, humans suspected of having hormone deficiency syndromes (e.g., hypoadrenocorticism [Addison's disease]), are typically evaluated with "provocative" or "stimulation" tests to aid in diagnosis, and those suspected of having hormone excess syndromes (e.g., NOH), are typically evaluated with suppression tests.

***Background in Cats.*** Those who recommend using the ACTHST point out several attributes: the test requires little time (1 or 2 hours depending on the ACTH used), only two or three venipunctures are needed, results are easy to interpret, it is the only test useful for distinguishing iatrogenic from naturally occurring disease, and it is the only test used in the long-term monitoring of

**TABLE 11-11 ENDOCRINE SCREENING TEST RESULTS FROM CATS WITH NATURALLY OCCURRING PITUITARY-DEPENDENT CUSHING'S SYNDROME**

| | Urine Cortisol-to-Creatinine Ratio | Serum Cortisol (μg/dL) Low-Dose Dexamethasone | | | Serum Cortisol (μg/dL) ACTH Stimulation | | |
|---|---|---|---|---|---|---|---|
| | | PRE | 4 HOUR | 8 HOUR | PRE | FIRST POST | SECOND OR FINAL POST |
| Reference range | $< 36 \times 10^{-6}$ | 1-5 | < 1.4 | < 1.4 | 0-5 | 5-15 | 5-15 |
| Borderline range | $10 - 36 \times 10^{-6}$ | — | 0.9-1.3 | 0.9-1.3 | — | 15-19 | 15-19 |
| Number of cats included | 34 | 46 | 46 | 43 | 46 | 35 | 55 |
| Number of results within reference range | 1 | — | 4 | 0 | 23 | 24 | 33 |
| Number of results in "borderline" range | 6 | — | 0 | 0 | — | 3 | 5 |
| Number of results consistent with Cushing's syndrome | 27 | — | 42 | 43 | — | 8 | 17 |
| Range of test results | $3 - 810 \times 10^{-6}$ | 1.5-20.2 | 0.3-14.9 | 1.5-14.7 | 1.5-27.3 | 5.4-32.7 | 5-36.0 |
| Mean ± standard deviation | 48.7 ± 31.6 | 6.8 ± 3.7 | 4.2 ± 2.9 | 4.9 ± 2.1 | 6.3 ± 3.8 | 12.2 ± 5.6 | 14.7 ± 10.1 |
| Median | 39 | 5.4 | 4.6 | 5.2 | 5.6 | 11.5 | 13.7 |

**TABLE 11-12 ENDOCRINE SCREENING TEST RESULTS FROM 14 CATS WITH CUSHING'S SYNDROME CAUSED BY A FUNCTIONING ADRENOCORTICAL TUMOR**

| | Urine Cortisol-to-Creatinine Ratio | Plasma Cortisol (μg/dL) Low-Dose Dexamethasone | | | Plasma Cortisol (μg/dL) ACTH Stimulation | | |
|---|---|---|---|---|---|---|---|
| | | PRE | 4 HOUR | 8 HOUR | PRE | FIRST POST | SECOND OR FINAL POST |
| Reference range | $< 36 \times 10^{-6}$ | 0.5 | < 1.4 | < 1.4 | 0-5 | 5-15 | 5-15 |
| "Borderline" range | $10 - 36 \times 10^{-6}$ | — | 0.9-1.3 | 0.9-1.3 | — | 15-19 | 15-19 |
| Number of cats included | 14 | 12 | 10 | 12 | 8 | 6 | 8 |
| Number of results within reference range | 0 | — | 0 | 0 | 5 | 4 | 4 |
| Number of results in "borderline" range | 6 | — | — | — | — | 1 | — |
| Number of results consistent with Cushing's syndrome | 8 | — | 10 | 12 | — | 1 | 4 |
| Range of test results | $11 - 160 \times 10^{-6}$ | 1.5-11.0 | 1.5-11.6 | 1.8-10.2 | 2.6-11.8 | 2.7-50.0 | 3.3-52.8 |
| Mean ± standard deviation | 42 ± 81.4 | 4.9 ± 2.9 | 5.2 ± 3.5 | 4.9 ± 2.7 | 5.2 ± 3.4 | 17.3 ± 16.9 | 22.3 ± 18.2 |
| Median | 3.8 | 4.1 | 4.1 | 5.5 | 3.7 | 13.1 | 21.5 |

medically treated NOH dogs and cats. Detractors suggest that the test lacks sensitivity and specificity and is far more expensive than either the UC:CR or the LDDST.

A number of studies have evaluated the ACTHST in either laboratory or privately-owned cats. One of the earliest studies compared the use of two different doses of synthetic ACTH (cosyntropin) with the use of natural ACTH in stimulation tests conducted on privately-owned healthy cats. Synthetic ACTH was administered at doses of 125 and 250 μg per cat IM with blood samples obtained for cortisol analysis before administration and again at 15, 30, 60, 90, and 120 minutes after (Smith and Feldman, 1987). No significant difference was found between responses to the two doses of synthetic ACTH. Because two cats vomited and remained obtunded for several hours after receiving the higher dose, the lower dose was recommended. Peaks in plasma cortisol concentration were most often documented 30 and 60 minutes after starting the test, and therefore both post-ACTH sampling times were recommended. Using the mean ± standard deviation (SD) to establish the reference range for the post-ACTH plasma cortisol resulted in a range of about 6 to 19 μg/dL at 30 or 60 minutes after the intramuscular (IM) injection.

Response to intravenous (IV) synthetic tetracosactrin (another form of synthetic ACTH) was evaluated in laboratory cats given 125 μg/cat, IV. Cats demonstrated peak responses 180 minutes after injection (Sparkes et al, 1990). The longer duration of action and greater potency of IV versus IM administration was further supported in a subsequent study, again using 125 μg/cat. Peak cortisol response occurred between 60 and 90 minutes after starting the test (Peterson and Kemppainen, 1992a). No significant difference was noted in drug response after IV cosyntropin was compared with IV tetracosactrin in another study, and it was recommended that blood for cortisol be obtained

60, 90, 120, and 180 minutes after administration (Peterson and Kemppainen, 1992b). These two studies were followed by one in which 1.25, 12.5, and 125 µg of cosyntropin were administered to cats, demonstrating comparable peak cortisol responses after each dose but a more prolonged response with the highest dose (Peterson and Kemppainen, 1993). Another group demonstrated increases in hypothalamic-pituitary-adrenal activity as cats age (Goossens et al, 1995), although this phenomenon does not alter reference ranges. This study was then followed by one on overweight, older, privately-owned cats, using 125 or 250 µg of IV tetracosactrin/cat. Results complemented previous reports that had utilized young, relatively lean, laboratory cats. Peak cortisol concentrations after ACTH administration were similar to those reported in the other studies (Schoeman et al, 2000). Slight variations in post-ACTH cortisol concentration reference ranges may result from the use of cosyntropin versus tetracosactrin, various doses, or employing IV versus IM administration. The critical question, however, not addressed in any of these studies is simply whether or not the test should be employed in cats suspected of having FCS.

***Test Interpretation.*** One generally agreed upon ACTHST protocol for cats is to administer 125 µg of synthetic ACTH, IV, with blood samples obtained 60, 90, 120, and 180 minutes after. (Veterinarians should use the protocol recommended by their laboratory.) Most laboratories suggest that post-ACTHST cortisol concentrations of 6 to 15 µg/dL are within their reference interval, 15 to 19 µg/dL are borderline and inconclusive, and results more than 19 µg/dL are consistent with FCS. Some laboratories may utilize slightly lower or higher reference intervals. Lower reference intervals could lose specificity, raising the risk that more cats without FCS are incorrectly diagnosed as having the condition. Higher reference intervals could lose sensitivity, potentially resulting in missing the diagnosis of FCS. As demonstrated in the study on privately owned, overweight cats that did not have FCS, baseline (pre-ACTH) cortisol concentrations were as high as 13 µg/dL and post-ACTH cortisol concentrations as high as 19.7 µgdL (Schoeman et al, 2000). Just the basal values, therefore, might include some cats in the FCS group if lower cortisol concentrations were considered "diagnostic," and others would have been described as "borderline." The ACTHST, regardless of dose, form of ACTH, timing, and so on has been demonstrated in most reports to have unacceptably poor sensitivity and specificity regarding its use as a screening for FCS.

***Results.*** ACTHST results were available from 65 cats with FCS; 55 cats diagnosed with PDH and 10 with ATH. The results were from 51 cats in our series and 14 cats reported in the literature (Immink et al, 1992 [one cat]; Schwedes, 1997 [one cat]; Watson and Herrtage, 1998 [five cats]; Moore et al, 2000a [one cat]; Skelly et al, 2003 [one cat]; Neiger et al, 2004 [five cats]). All 65 cats had at least one post-ACTHST result, 56 had basal cortisol concentrations reported, and 41 had more than one post-ACTHST result. If only a solitary post-ACTH test result was available, it was arbitrarily considered the "final" result (see Tables 11-11 and 11-12). Thirty-eight of the 65 cats (58%) had post-ACTHST cortisol concentrations within the reference interval, five (8%) had "borderline" results, and 22 (34%) had abnormal results. Of the 55 cats with PDH, 33 (60%) had results within the reference interval, five (9%) had borderline results, and 17 (31%) had abnormal results. Of the 10 ATH cats, five had results within the reference interval and five were abnormal. Thus, the sensitivity (the number of cats that had FCS and tested positive) of the ACTHST for all the cats was about 33%. Forty-one cats with FCS (35 with PDH, six with ATH) had two post-ACTH administration samples obtained, allowing assessment of the "middle" result (see Tables 11-11 and 11-12). Twenty-eight cats (68%) had results within the reference interval, four (10%) had borderline results, and nine (22%) had abnormal results. There was little diagnostic value associated with adding the intermediate sample during ACTH stimulation testing.

Lack of ACTHST sensitivity as a screening test for FCS, demonstrated in our review, has also been noted by others (Gunn-Moore, 2005; Graves, 2010, Peterson, 2012). In a more recent study, 56% of cats with FCS had an abnormal ACTHST result (Valentin et al, 2014). Thus, the ACTHST is not sensitive as an aid in identifying cats with FCS, because so many of the results are normal. Evaluation of different blood sampling times and various doses of ACTH does not improve this index of diagnostic usefulness. Even a single basal serum cortisol measurement has a greater sensitivity (67%) for detecting cats with FCS than the ACTHST (Duesberg and Peterson, 1997; Graves, 2010). Specificity of the ACTHST has also been questioned (Graves, 2010; Peterson, 2012) because a variety of chronic illnesses not associated with FCS can influence results (Zerbe et al, 1987b). It has been suggested that "stress" associated with chronic illness could cause adrenocortical hyperplasia, accounting for an exaggerated cortisol response to ACTH (Peterson, 2012).

***Conclusions.*** The attributes of ACTHST as a screening test for cats suspected as having FCS—the test is brief, easy to complete, and easy to interpret–all lose value when collated results indicate that it lacks sensitivity. Further, there are tests (UC:CR and LDDST) that are clearly superior. The ACTHST remains the best test to confirm iatrogenic hyperadrenocorticism, but this condition is rare in cats.

## Low-Dose Dexamethasone Suppression Test (LDDST)

### *Background*

A complete discussion on the physiologic basis for the LDDST and its usefulness is provided in Chapter 10. Use of the analogous "overnight LDDST" is a well-established test for confirming the diagnosis of NOH in people, with a sensitivity and specificity similar to that of the 24-hour urine cortisol excretion test. The basis of LDDST, as is true for the overnight test employed in people, assumes that administered dexamethasone circulates throughout the body, including to the hypothalamus and pituitary, in which it has potent suppressive effects. The "low" dose of dexamethasone is the minimum necessary to directly and completely suppress synthesis and secretion of both hypothalamic corticotrophin-releasing hormone (CRH) and pituitary ACTH in healthy individuals, which in turn decreases synthesis and secretion of adrenocortical glucocorticoids (Peterson and Graves, 1988). Effect of dexamethasone is profound within an hour and persists until the dexamethasone is metabolized, which is usually well beyond 8 to 10 hours (about 30 hours in dogs). Dexamethasone has been the traditional glucocorticoid for suppression testing because early cortisol assays cross-reacted with prednisone or prednisolone. Consistent hypothalamic-pituitary-adrenocortical axis suppression, in healthy individuals as well as those with non-adrenal illness, is the single most important criterion of a reliable LDDST.

Individuals with ATH have an autonomous, cortisol secreting, adrenal adenoma, or carcinoma. Secretion of glucocorticoids

from these tumors is independent of hypothalamic-pituitary control. Glucocorticoids derived from adrenocortical tumors act the same as administered dexamethasone: it persistently and chronically suppresses hypothalamic and pituitary function. Therefore, administration of dexamethasone to a patient with ATH should have no suppressive effects on endogenous serum cortisol concentrations.

Individuals with PDH and secondary adrenocortical hyperplasia have a pituitary tumor less sensitive to glucocorticoid-associated negative feedback, otherwise hyperadrenocorticism would never develop. Administration of dexamethasone to an individual with PDH typically has one of two results: (1) the dexamethasone fails to cause lowering (suppression) of circulating cortisol concentrations because the pituitary tumor is resistant to negative feedback and results of this test are indistinguishable from that seen with ATH, or (2) hypothalamic, pituitary, and then adrenocortical cortisol secretion *is* suppressed and circulating cortisol concentrations do decrease, but this effect is far more transient than "normal" due to rapid metabolism of the administered drug. In this latter condition, dexamethasone causes a decrease in circulating cortisol concentrations, but rather than persisting for more than 8 hours, it lasts far less than 8 hours and circulating concentrations of cortisol "escape" from the suppression earlier in individuals with PDH than in healthy individuals.

#### *Protocol*

The LDDST dose and protocol established in dogs, 0.01 mg/kg of dexamethasone IV with cortisol concentrations determined before and 4 and 8 hours after administration, fails to cause suppression in 15% to 20% of healthy cats. Increasing the dose to 0.1 mg/kg was consistently effective in suppressing healthy cats but not cats with FCS (Smith and Feldman, 1987; Hoenig, 2002; Kley et al, 2007).

#### *Test Interpretation*

The established reference ranges for results 4 and 8 hours after administration of 0.1 mg/kg of dexamethasone in healthy cats is less than or equal to 0.8 µg/dL. A value greater than or equal to 1.4 µg/dL is consistent with a diagnosis of FCS due to PDH or ATH, in the context of a cat also having appropriate signs and supportive evidence. The "nondiagnostic" range of 0.9 to 1.3 µg/dL is meant improve both sensitivity and specificity by forcing additional testing.

#### *Results*

A total of 58 cats with FCS (46 with PDH and 12 with ATH) have their LDDST results included in Tables 11-11 and 11-12. Forty-seven cats were from our series, and data from 11 cats were obtained from the literature (Immink et al, 1992 [two cats]; Goossens et al, 1995 [three cats]; Meij et al, 2001 [three cats]; Neiger et al, 2004 [three cats]). Not all cats had both 4 and 8 hour post-LDDS results available. Forty-three out of 43 cats with PDH and 12 out of 12 cats with ATH cats (100%) had abnormal 8-hour LDDST results consistent with FCS (cortisol concentrations > 1.4 µg/dL), suggesting that this LDDST protocol is "highly sensitive" and more sensitive than either UC:CR or ACTHST. Although these results indicate 100% sensitivity, readers must understand that no test is perfect. In a related study, LDDST results were consistent with a diagnosis of FCS in 93% of afflicted cats (Valentin et al, 2014). Their conclusion was that the screening test of choice in the evaluation of a cat suspected as having FCS is the LDDST; however, there is no "gold standard."

#### *Conclusions*

The 0.1 mg/kg dexamethasone test is an excellent and extremely sensitive screening test in the evaluation of a cat suspected as having FCS. Specificity of the LDDST was not critically assessed here, although previous studies indicate that some cats with non-adrenal illness will have LDDST results consistent with FCS (Zerbe et al, 1987b; Duesberg and Peterson, 1997). The LDDST is the screening "test of choice" in evaluating a cat for FCS.

### Hair Cortisol Concentrations

Hair cortisol concentrations were higher in dogs with NOH as compared with healthy dogs and ill dogs that did not have NOH (Corradini et al, 2013). This non-invasive laboratory aid could revolutionize the diagnosis of NOH in dogs and FCS in cats if results are both sensitive and specific.

### Combined Dexamethasone Suppression Test/ Adrenocorticotropic Hormone Stimulation

This combination test can be completed in 1 day with collection of only three blood samples. An ACTHST is begun 3 to 5 hours after beginning the LDDST. However, the addition of the unacceptably insensitive ACTHST to the quite sensitive LDDST seems unnecessary while having the potential to provide misleading results. This test is *not* recommended (Peterson, 2012).

### Combination "Screening" and "Discrimination" Tests

#### *Urine Cortisol-to-Creatinine Ratio and High-Dose Dexamethasone Suppression Test*

***The Screening Portion of the Test.*** The UC:CR can be combined with a high-dose dexamethasone suppression test (HDDST) in a practical and cost-effective alternative to more "traditional" testing options (Goossens et al, 1995). This test is designed to be completed in the home environment, negating need for cats to be brought into the hospital with its attendant stress, time, and expense. Owners are instructed to collect urine from their cat on two separate mornings. It is not necessary for urine to be collected on consecutive days, but doing so shortens the process. There are a variety of methods for owners to obtain urine. Simply leaving their cat in a room with a box containing insufficient litter to absorb the urine produced overnight is easiest, allowing owners to pour urine into a clean container (alternatively, use nonabsorbable litter). Collected urine is then brought to the veterinarian for measurement of UC:CR. This portion of the test is the screening test to aid in separating cats with FCS (abnormally increased UC:CR) from cats that do not have the disease (UC:CR result within the reference range). The use of two separate samples is used to improve sensitivity and specificity by not relying on one result. If both samples suggest FCS, one may continue to the second phase of the test. If one result is within reference range and one is abnormal, additional samples (one or two) may be collected and evaluated.

***The Discrimination Portion of the Test.*** Before interpreting this test, it is assumed that the previously obtained UC:CR results were abnormal and consistent with the strong clinical suspicion of FCS. In this second phase of the test, the owner should administer 0.1 mg/kg of dexamethasone orally every 8 hours beginning in the morning (i.e., dexamethasone is administered at about 8 AM, 4 PM, and midnight). That night, the cat should again be restricted to a

location that allows urine to be collected on this third morning. The urine is delivered to the veterinarian and again assessed for UC:CR. Using the calculated mean from the first two samples, a result less than 50% of that mean (on average) would be consistent with PDH. A result more than 50% of that mean does not allow discrimination of PDH from ATH.

***Conclusions.*** This test was suggested in the literature about two decades ago. It has not been critically evaluated, in part because FCS is an uncommon condition. The test may have a sensitivity and specificity as good as or better than other recommended protocols. It is not strongly recommended here only because we have little experience with this combination test. In people suspected as having NOH, a single overnight dexamethasone suppression test is a trusted and reliable screening test. Thus, the precedent for such a test in cats is solid (Molitch, 2012; Nieman, 2012).

## TESTS TO "DISCRIMINATE" PITUITARY FROM ADRENAL TUMOR CUSHING'S SYNDROME

After diagnosis of FCS has been confirmed, several tests can be used to help "discriminate" individuals with PDH from those with ATH. Four tests are commonly used to help "discriminate" ATH from PDH. These include the LDDST, the HDDST, plasma endogenous ACTH concentrations, and abdominal ultrasonography. Because of expense, need for specialized facilities and anesthesia, CT and MRI scans (although somewhat sensitive and quite specific) are not as widely used. The reason for discriminating ATH from PDH is their different therapeutic options. Ideally, adrenocortical tumors should be surgically removed. The most effective medical option for treating cats with ATH is trilostane. Pituitary tumors could also be surgically removed or treated with external radiation, but neither of these therapies is widely available. Trilostane is the medical alternative. If an owner is to refuse surgery in any scenario, it could be argued that discrimination testing is unnecessary.

### Low-Dose Dexamethasone Suppression Test (LDDST)

#### *Background*

The LDDST, as discussed earlier, is extremely sensitive in helping to separate cats with FCS from cats that do not have the condition. Individuals with ATH typically demonstrate no response to administration of dexamethasone, whereas some with PDH do demonstrate suppression but for a shorter period of time than noted in healthy individuals. Three criteria define "suppression" on the LDDST in attempting to identify *dogs* likely to have PDH: a 4-hour cortisol less than a laboratory-determined absolute value (often < 1.4 μg/dL), a 4-hour cortisol less than 50% of the baseline value, and an 8-hour cortisol less than 50% of the baseline value. Approximately 65% of dogs with PDH demonstrate "suppression," because they meet one or more of these criteria.

#### *Results*

Forty-six cats with PDH in our review had their 4-hour cortisol concentrations assessed during LDDST, 42 had values more than 1.4 μg/dL (no suppression) and four had values less than or equal to 0.9 μg/dL. Ten cats with ATH had a 4-hour post-LDDST blood sample assessed for cortisol, and all had both 4- and 8-hour results more than 1.4 μg/dL. Thus, use of the absolute value of less than 1.4 helped to identify only four of 56 cats (7%) with FCS as having PDH. All four results were correct, but sensitivity is poor. Use of more than 50% suppression from the baseline cortisol concentration proved to be far more sensitive. Of 12 cats with FCS due to ATH, none demonstrated more than 50% suppression at either 4 or 8 hours. Of 46 cats with PDH, however, 24 cats (41% of all 58 cats; 52% of cats with PDH) demonstrated more than 50% suppression of serum cortisol concentrations at either 4 or 8 hours (seven cats at 4 hours, two cats at 8 hours, and 15 cats at both 4 and 8 hours). The LDDST does have sensitivity and specificity in discriminating ATH from PDH. In other words, a cat with FCS that meets any of the three established criteria for PDH on an LDDST, likely has PDH.

### High-Dose Dexamethasone Suppression Test (HDDST)

#### *Background*

The HDDST is an aid for discriminating patients with PDH from those with ATH. Physiologic basis for this test, in part, is the same as for the LDDST: administration of dexamethasone decreases adrenocortical (endogenous) cortisol secretion via the suppression of hypothalamic synthesis and secretion of CRH, thereby decreasing pituitary ACTH synthesis and secretion. Dexamethasone also directly suppresses pituitary synthesis and secretion of ACTH. Without ACTH, adrenocortical cells cease synthesizing and secreting cortisol. As circulating cortisol is metabolized, plasma and urine cortisol concentrations decrease quickly after administration (within an hour) and remain suppressed throughout the period of dexamethasone activity (30 hours in healthy dogs).

Adrenocortical tumors function autonomously and are independent of hypothalamic and pituitary control. Negative feedback associated with chronic excesses in circulating glucocorticoids cause atrophy of pituitary ACTH-secreting cells in ATH patients. Therefore dexamethasone, regardless of dose administered, does not suppress cortisol secretion from an adrenocortical tumor. By contrast, although pituitary tumors in PDH function "somewhat" autonomously, secretion of ACTH by some (not all) pituitary tumors can be suppressed with "low" doses of dexamethasone. In dogs and cats with PDH, about 65% and 52%, respectively, demonstrate enough suppression on LDDST to indicate that ATH is not an explanation for their hyperadrenocorticism. Using a higher dose of dexamethasone is based on the concept that if some individuals with PDH demonstrate at least some suppression on LDDST, a higher dose will increase the number.

#### *In-Hospital Protocol*

Administer 10 times the dose of dexamethasone used for the LDDST. In cats, it is generally accepted to use a dexamethasone dose of 1.0 mg/kg, IV, with blood samples obtained for cortisol concentration before and 4 and 8 hours after administration. Remember, before employing this test, one should first confirm that the cat has FCS.

#### *At-Home Protocol*

An alternative method employs the UC:CR, and the entire test is carried out by the owner at home (described in previous section).

#### *Interpretation of the In-Hospital HDDST*

Four "criteria for suppression" can be utilized to aid in the interpretation of results: more than 50% decrease in cortisol concentration, from the basal value, at 4 or 8 hours; or cortisol concentrations less than 1.4 μg/dL at 4 hours or 8 hours. If any one of these four criteria for suppression is met, the result is most consistent with PDH. Failure to meet any of the criteria adds support for the diagnosis of FCS but is inconclusive regarding PDH versus ATH.

***Interpretation of the At-Home Protocol.*** The interpretation of the at-home protocol is described in previous section.

### Results

***In-Hospital High-Dose Dexamethasone Suppression Test.*** As seen in Table 11-13, HDDST results were available from 40 cats with confirmed FCS. Basal and 4- and 8-hour post-HDDST results were available from 24 cats with PDH and four with ATH. Only baseline and 8-hour samples were obtained from an additional 11 cats with PDH and one with ATH. There can only be two interpretations of HDDST results: (1) "consistent with PDH" can be applied to results demonstrating suppression, and (2) "inconclusive regarding PDH versus ATH discrimination" because none of the four criteria were met. Thirteen of 24 cats (54%) had "4-hour" HDDST results that demonstrated suppression; the results were consistent with PDH. All 13 cats had PDH. Thus suppression on the 4-hour test result was modestly sensitive but quite specific for PDH. The four cats with ATH and a 4-hour HDDST result failed to demonstrate suppression, as was expected. Also as expected, some cats (11 of 24; 46%) with PDH failed to respond to the HDDST at 4 hours. Thus failure to suppress plasma cortisol concentration at 4 hours was a nonspecific finding that included cats with ATH and PDH.

Fifteen of 40 cats (38%) had 8-hour HDDST results that demonstrated suppression; the results were consistent with PDH. All 15 of those cats did have PDH, correctly identifying 15 of 35 cats (43%) with PDH. Thus suppression on the 8-hour test result correctly identified cats with PDH. The five cats with ATH and an 8-hour HDDST result failed to demonstrate suppression, as was expected. Also as expected, some cats (20 of 35; 57%) with PDH failed to respond to the HDDST at 8 hours. Failure to suppress plasma cortisol concentration at 8 hours was a nonspecific finding that included cats with ATH and PDH. It is also of interest to note that the 8-hour test was available from all 24 PDH cats tested at 4 hours plus an additional 11 cats with PDH. However, only two additional cats with PDH demonstrated suppression at 8 hours. All 13 cats that met at least one of the two criteria for suppression at 4 hours met at least one of the two criteria for suppression at 8 hours. It seems reasonable to suggest only a 4-hour post-HDDST sample be obtained, because the 8-hour result has not offered significant new information.

### Results

***At-Home Urine High-Dose Dexamethasone Suppression Test.*** As can be reviewed in Table 11-14, 13 cats were tested using the at-home protocol. All 13 cats had PDH (Goossens et al, 1995 [six cats]; Meij et al, 2001 [seven cats]). Ten of the 13 (77%) cats did demonstrate suppression on the UC:CR from the sample obtained post-dexamethasone, using the mean of two basal urine samples for the comparison. The entire test could be carried out by an owner, decreasing cost and stress.

**TABLE 11-13 HIGH-DOSE DEXAMETHASONE SUPPRESSION TEST AND PLASMA ENDOGENOUS ACTH RESULTS FROM CATS WITH CUSHING'S SYNDROME**

| | Plasma Cortisol (μg/dL) High-Dose Dexamethasone Test | | | Plasma Endogenous ACTH |
|---|---|---|---|---|
| | PRE | 4 HOUR | 8 HOUR | (pg/mL) |
| **Pituitary Dependent Hyperadrenocorticism (PDH)** | | | | |
| Reference range | 0-5 | < 1.4 | < 1.4 | 10-60 |
| Borderline range for PDH | — | — | — | 10-45 |
| Results consistent with PDH (definition) | — | < 1.4 or < 50% baseline | — | > 45 |
| Number of cats | 35 | 24 | 35 | 45 |
| Number of results inconclusive (consistent with PDH or ATH) | — | 11 | 20 | 3 |
| Number of results consistent with PDH | — | 13 | 15 | 42 |
| Range of test results | 2.4-39.0 | 0.2-15 | 0.1-25.8 | 38-3653 |
| Mean (± standard deviation) | 8.8 ± 8.8 | 3.0 ± 3.6 | 4.9 ± 6.2 | 457 ± 619 |
| Median | 5.3 | 0.9 | 2.4 | 221 |
| **Adrenocortical Tumor Hyperadrenocorticism (ATH)** | | | | |
| Reference range | 0-5 | < 1.4 | < 1.4 | 10-60 |
| Borderline range for ATH | — | — | — | 10-45 |
| Results consistent with ATH | — | > 1.4 or > 50% of baseline cortisol | — | Undetectable |
| Number of cats | 5 | 4 | 5 | 6 |
| Number of results inconclusive | — | 0 | 0 | 0 |
| Number of results consistent with ATH | — | 4 | 5 | 6 |
| Range of test results | 3.0-7.1 | 3.7-6.1 | 4.4-6.1 | All undetectable |
| Mean (± standard deviation) | 5.1 ± 1.6 | 5.0 ± 0.8 | 5.0 ± 0.7 | — |
| Median | 4.9 | 4.7 | 4.7 | — |

*ATH,* Adrenal tumor hyperadrenocorticism; *PDH,* pituitary dependent hyperadrenocorticism.

TABLE 11-14 **HIGH-DOSE DEXAMETHASONE SUPPRESSION TEST RESULTS FROM 13 CATS WITH PDH UTILIZING THE "AT-HOME" UC:CR PROTOCOL***

| CAT NUMBER | FIRST BASAL UC:CR | SECOND BASAL UC:CR | MEAN UC:CR | POST-DEXAMETHASONE UC:CR | POSITIVE FOR PDH? |
|---|---|---|---|---|---|
| 1 | 139 | 145 | 142 | 13 | Yes |
| 2 | 37 | 64 | 51 | 5 | Yes |
| 3 | 75 | 82 | 78 | 92 | No |
| 4 | 125 | 155 | 140 | 41 | Yes |
| 5 | 104 | 103 | 104 | 26 | Yes |
| 6 | 228 | 316 | 272 | 18 | Yes |
| 7 | — | — | 272 | 18 | Yes |
| 8 | — | — | 80 | 117 | No |
| 9 | — | — | 119 | 5 | Yes |
| 10 | — | — | 73 | 17 | Yes |
| 11 | — | — | 72 | 27 | Yes |
| 12 | — | — | 105 | 119 | No |
| 13 | — | — | 77 | 7 | Yes |

All results compiled from Goossens MMC et al.: Urinary excretion of glucocorticoids in the diagnosis of hyperadrenocorticism in cats, *Domestic Anim Endocrinol* 12:355, 1995; and Meij BP, et al: Transsphenoidal hypophysectomy for treatment of pituitary-dependent hyperadrenocorticism in 7 cats, *Vet Surg* 30:72, 2001.
*PDH,* Pituitary dependent hyperadrenocorticism; *UC:CR*, urine cortisol-to-creatinine ratio.
*Suppression is defined as a post-dexamethasone UC:CR < 50% of the mean of two basal UC:CR. (All UC:CR results multiplied by $10^{-6}$.)

#### *Conclusions*

The in-hospital HDDST is relatively easy to perform and interpret, not expensive, and not harmful. Suppression, after administering 1.0 mg/kg of dexamethasone IV, is consistent with PDH. Cats with ATH usually do not demonstrate suppression, whereas 52% of cats with PDH meet at least one criterion of suppression. The 0.1 mg/kg dexamethasone dose resulted in identification of only 22% of PDH cats. It is noted that the 1.0 mg/kg dexamethasone dose was most effective in identifying PDH at 4 hours. No cat with ATH demonstrated suppression at either 4 or 8 hours of the HDDST, but some cats with PDH also fail to suppress. Therefore, failure to demonstrate suppression should be considered an inconclusive result and is similar to results in human beings and dogs.

The at-home HDDST is easier to perform and interpret than the in-hospital protocol. In addition, at-home test results were superior to those utilizing the in-hospital tests in correctly discriminating PDH from ATH. Assuming an owner can administer dexamethasone, it seems reasonable to recommend the at-home protocol for both screening and discrimination testing, because this protocol is generally easier to perform, less expensive, easier to interpret, safer (less bruising and no chance of skin trauma), and as-good-as or more specific and sensitive.

### Endogenous ACTH and ACTH Precursor Concentrations

#### *Background*

Circulating endogenous ACTH concentrations have been used to help discriminate people with PDH from those with ATH since the 1970s, and they have been used for the same purpose in dogs and cats since the 1980s. Individuals with ATH have autonomously functioning adrenocortical tumors that chronically suppress circulating concentrations of endogenous ACTH and its precursors. Those with PDH have an ACTH-secreting tumor associated with normal-to-increased concentrations.

The attributes of assessing endogenous ACTH include requiring only one blood sample, being easy to interpret and relatively reliable. However, it is important that blood samples for determination of endogenous ACTH concentration be handled as directed by your laboratory. ACTH is a labile protein that degrades quickly in plasma. Samples usually must be collected directly into a tube containing ethylenediaminetetraacetic acid (EDTA) anticoagulant, tubes must be made of plastic or silicone-coated glass (most glass EDTA collection tubes are siliconized); samples should be placed immediately on ice and centrifuged (ideally in a cold centrifuge). Harvested plasma must be placed in plastic tubing, frozen until assayed, and shipped on ice (Graves, 2010). Mishandled samples may falsely lower values suggesting an adrenal tumor (Peterson, 2012). Test results are not always definitive. Some people and dogs with hyperadrenocorticism due to either ATH or PDH have ACTH concentrations that overlap with the reference range. These drawbacks, together with the availability and diagnostic specificity of imaging studies (e.g., ultrasonography) have limited the use of endogenous ACTH assessment.

Some pituitary pars intermedia (PI) cells stain positively for ACTH as do virtually all pars distalis (PD) cells. In contrast, some PI cells cleave ACTH to α–melanocyte-stimulating hormone (MSH) and corticotropin-like intermediate lobe peptide (CLIP), suggesting that increases in plasma α-MSH concentrations could be expected in cats with PI adenomas. However, cats with the highest α-MSH concentrations were those with PD adenomas (Halmi and Krieger, 1983; Rijnberk, 1996; Meij et al, 2001). One explanation could be that the gene encoding the cleavage enzyme (proconvertase 2) may become "de-repressed" in the course of neoplastic transformation of PD corticotrophs (Low et al, 1993). Alternatively, as in people, some PD adenomas may originate from a sparse population of melanocyte cells (Coates et al, 1986). Cat PI and PD adenoma cells stain positively for both ACTH and α-MSH (Peterson et al, 1982).

TABLE 11-15 **LENGTHS AND WIDTHS OF ADRENAL GLANDS MEASURED ULTRASONOGRAPHICALLY IN 20 HEALTHY AWAKE CATS**

| NUMBER OF CATS | PARAMETER | LENGTH OF RIGHT ADRENAL GLAND | WIDTH OF RIGHT ADRENAL GLAND | LENGTH OF LEFT ADRENAL GLAND | WIDTH OF LEFT ADRENAL GLAND |
|---|---|---|---|---|---|
| 20 | Range (cm) | 0.7-1.4 | 0.3-0.45 | 0.45-1.3 | 0.3-0.5 |
| | Median (cm) | 1.0 | 0.4 | 0.9 | 0.4 |

From Zimmer C, et al.: Ultrasonographic examination of the adrenal gland and evaluation of the hypophyseal-adrenal axis in 20 cats, *J Small Anim Pract* 41:156, 2000.

#### *Interpretation of Test Results*

The reference range for endogenous ACTH concentrations in cats is slightly lower than for dogs (Feldman, 1981; Smith and Feldman, 1987). Most cats with PDH have endogenous ACTH concentrations from mid-reference range to several times higher than the upper limit of the assay. Cats with ATH (as well as cats with iatrogenic hyperadrenocorticism) have results that range from undetectable to the lower portion of most reference ranges. However, some cats with iatrogenic hyperadrenocorticism, ATH, or PDH have inconclusive results (Peterson et al, 1994; Duesberg and Peterson, 1997; Benchekroun et al, 2012).

#### *Results*

Plasma endogenous ACTH concentrations were available from 51 cats with FCS. Thirty-eight of these cats were from our series, and 13 were from the literature (Goossens et al, 1995 [six cats]; Meij et al, 2001 [seven cats]). All 13 cats from the literature had PDH, 32 cats from our series had PDH and six had ATH. As can be seen from Table 11-13, the results of endogenous ACTH testing were excellent. All six cats (100%) with ATH had undetectable concentrations, and 42 of 45 cats (93%) with PDH had concentrations more than 45 pg/mL. Nondiagnostic results from three cats with PDH (38, 40, and 41 pg/mL) were still distinct from the results obtained from cats with ATH. Twenty-five of 45 cats with PDH had results typical of those noted in dogs (45 to 450 pg/mL). However, 17 cats with PDH (38%) had plasma endogenous ACTH concentrations in excess of 450 pg/mL (range, 487 to 3850 pg/mL; mean, 1002 pg/mL ± a SD of 731). Why so many cats with PDH had extremely increased plasma endogenous ACTH concentrations (> 450 pg/mL) is not well understood. Is it that their pituitary tumors produce more ACTH, is the assay less reliable in cats, is the assay more reliable in cats, is the assay also measuring precursors in the cat, or is there some other explanation? The extremely high concentrations of ACTH, as noted in many cats from our series, were also noted by Meij and colleagues (2001). These authors pointed out that in one cat, the ACTH assay results as measured by an immunoradiometric assay (IRMA) was only about 20% of the value obtained with an assay employing a polyclonal antibody. It is possible, therefore, that the polyclonal antibody assay is suspect. Perhaps these pituitary tumors secreted precursor-molecule pro-opiomelanocortin (POMC) or POMC-derived peptides recognized as ACTH by the assay. Precursors of ACTH were above the reference range in eight of nine cats that had PDH (Benchekroun et al, 2012).

#### *Conclusions*

Measuring endogenous ACTH or its precursor concentrations in cats with confirmed FCS has value for discriminating PDH from ATH. However, since the diagnostic value, availability, and cost-effectiveness of imaging studies are excellent, use of endogenous ACTH testing is not common.

### Abdominal Radiology

Changes noted on radiography of cats with FCS are similar to those seen in dogs. These changes include excellent contrast (due to fat deposition into the mesentery), hepatomegaly (which is usually secondary to diabetes mellitus in cats, as opposed to being more frequently secondary to steroid-induced hepatomegaly in dogs), and a pot-bellied appearance (caused by steroid-induced abdominal muscle weakness). Use of radiography has been replaced, for the most part, by abdominal ultrasonography as the key abdominal imaging study for cats known or suspected to have naturally occurring FCS. Ultrasonography is favored simply because adrenal glands are not routinely visualized via radiography unless the gland(s) is calcified or extremely enlarged (both situations are rare). By contrast, canine and feline adrenal glands can be routinely visualized on ultrasonography.

### Abdominal Ultrasonography

#### *Background*

Knowledge regarding adrenal gland imaging in dogs developed sooner than cats (Barthez et al, 1995; Horauf and Reusch, 1995). A study on ultrasound appearance of adrenals in anesthetized healthy cats (Cartee and Finn-Bodner, 1993) was followed by a study on awake cats. In the latter report, both glands were visualized in each cat. Further, both left and right adrenal glands were virtually identical in size and shape, with both being oblong and oval-to-bean–shaped (Table 11-15; Zimmer et al, 2000). In general, the adrenal glands of cats are less echogenic than the surrounding tissues and the right adrenal may be technically more difficult to image. The central area of the adrenals were identified as more echogenic than the cortex in six of 20 cats. Readers are reminded that ultrasonography is a "subjective" diagnostic tool. In other words, results are dependent on skill and experience of the ultrasonographer, as well as on the equipment used.

#### *Results*

Results of abdominal ultrasonography in cats with FCS are summarized in Table 11-16. Forty-one cats were evaluated: Thirty-five cats from our series and six cats with results taken from the literature (Daley et al, 1993 [one cat]; Watson and Herrtage, 1998 [four cats]; Moore et al, 2000a [one cat]). Thirty-four of the 41 abdominal ultrasound results correctly identified either bilaterally symmetrical adrenals consistent with PDH or an adrenal nodule

TABLE 11-16 ABDOMINAL ULTRASOUND INTERPRETATIONS FROM 41 CATS WITH NATURALLY OCCURRING HYPERADRENOCORTICISM

| POSSIBLE FINDING | NUMBER OF CATS |
|---|---|
| **Cats With Adrenal Tumor Hyperadrenocorticism (ATH) (9 Cats)** | |
| *R* mass, *L* small | 3 |
| *L* mass, *R* small | 0 |
| *R* mass, *L* not seen | 2 |
| *L* mass, *R* not seen | 2 |
| Both adrenals enlarged | 1 |
| No adrenals seen | 1 |
| **Cats with Pituitary Dependent Hyperadrenocorticism (PDH) (32 Cats)** | |
| Both adrenals normal | 5 |
| Both adrenals enlarged | 22 |
| *L* normal or enlarged, *R* not seen | 2 |
| *R* normal or enlarged, *L* not seen | 1 |
| No adrenals seen | 2 |

*L*, Left adrenal gland; *R*, right adrenal gland.

consistent with ATH. Three of the 41 cats (7%) had inconclusive studies, because no adrenal tissue was identified (two of these cats had PDH, and one had ATH). Four of the 41 cats (10%) had potentially misleading results: Three of 32 cats (9%) with PDH had one normal-to-increased-sized adrenal gland, with the other gland not visible, and one cat with ATH was thought to have enlargement of both glands. Twenty-seven of the 32 cats (84%) with PDH had both adrenal glands visualized and correctly described as being relatively equal-sized. A unilateral adrenal mass with the opposite gland being small or not visible was correctly observed in seven of nine cats (78%) with ATH. Thus, ultrasound results were correct in a total of 34 of 41 cats with FCS (83%). In a subsequent study of 32 FCS cats, the accuracy of ultrasound correctly discriminating PDH from ATH was 93% (Valentin et al, 2014).

#### *Conclusions*

Abdominal ultrasonography is not a screening test for separating cats with FCS from cats that do not have the condition. It is an excellent discrimination test for separating cats with ATH from those with PDH. Correct discrimination has been documented consistently in about 80% to 90% of cats with FCS (Duesberg and Peterson, 1997; Kley et al, 2007; Valentin et al, 2014). The reader is reminded that ultrasound examination results are subjective and success will vary.

### Ultrasound-Guided Biopsy

Cats with FCS have undergone successful percutaneous biopsy of suspected adrenal masses. Although percutaneous biopsy can be completed with ultrasound guidance, one must weigh the benefit of obtaining a histologic description of adrenal tissue against risks of complication.

### Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) Scans

#### *Background*

It is recommended that the diagnosis of FCS due to PDH be confirmed before pursuing pituitary imaging using CT or MRI scanning. These imaging modalities provide a noninvasive means of visualizing some pituitary tumors; however, each technique requires specialized facilities and cats must be anesthetized. MRI scanning has been the imaging modality of choice for the pituitary gland area in people (Chakere et al, 1989; Stein et al, 1989). Compared with CT scans, MRI scans have superior anatomic resolution and soft tissue contrast. Also, MRI scans are less likely to create distracting artifacts when the middle and caudal fossae of the brain are imaged (Kaufman, 1984). MRI scanning allows acquisition of images oriented in any plane, which is an important feature when examining the pituitary fossa.

The purpose of considering a sophisticated diagnostic aid such as CT or MRI in a cat suspected of having FCS is to determine whether or not an obvious pituitary mass can be visualized prior to radiation therapy or surgery. In our experience, both CT and MRI scans consistently allow visualization of pituitary masses more than 3 mm in greatest diameter. Therefore, if only one modality is available, we would encourage using that tool. If both imaging modalities are available, we encourage veterinarians to choose whichever tool is less expensive or whichever tool requires the shortest duration of anesthesia.

In a study of healthy cats, the pituitary gland was measured using post-gadolinium (postcontrast) MRI studies in 17 cats. The cats were 1 to 15 years of age and weighed between 2.9 and 6.5 kg. Mean (± SD) pituitary length was 0.54 cm (± 0.06 cm) and the width was 0.5 cm (± 0.08 cm). Pituitary gland height measured on sagittal and transverse images was about 0.33 cm (± 0.05). Mean pituitary volume was about 0.05 $cm^3$. There were no significant correlations between weight, age, and pituitary volume. The pituitary gland appearance on the precontrast scan had "mixed signal intensity," whereas on postcontrast scans the pituitary appeared to have uniform enhancement (Wallack et al, 2003).

Abdominal imaging may be of interest prior to adrenalectomy. Specifically, imaging may identify vascular or local invasion. Assessment of the liver and other structures for evidence of metastatic disease or other concerns may be worthwhile.

#### *Results*

Pituitary imaging scan results were reviewed from 48 cats with confirmed PDH (Table 11-17). A visible mass (5 to 11 mm in greatest diameter) was identified in 34 cats (70%; Fig. 11-5). Thirteen of 22 cats (59%) from three different studies utilizing CT scans had a visible mass (Goossens et al, 1995; Meij et al, 2001; Benchekroun et al, 2012); in the UC Davis series, visible masses were identified in six of nine cats evaluated with CT and four of six evaluated with MRI. As veterinarians develop an ability to identify cats with PDH earlier in the course of disease progression, the "sensitivity" of CT and MRI scans for detecting pituitary tumors should decrease, because earlier diagnosis will be made in cats with smaller less detectable masses. Cats with confirmed PDH without a detectable mass should be assumed to have pituitary tumors simply too small to be seen.

#### *Conclusions*

Pituitary imaging serves several potential roles. Either CT or MRI scans could be used to help confirm a diagnosis of FCS (see Table

TABLE 11-17 **COMPUTED TOMOGRAPHY (CT) AND MAGNETIC RESONANCE IMAGING (MRI) SCAN RESULTS FROM 48 CATS* WITH PDH**

| RESULTS | CT SCAN | MRI SCAN | NOT SPECIFIED† CT/MRI |
|---|---|---|---|
| Normal study (no mass seen) | 12 cats | 2 cats | 0 cats |
| Visible mass (5 to 11 mm in greatest diameter) | 19 cats | 6 cats | 9 cats |
| Total | 31 cats | 8 cats | 9 cats |

*15 cats from UC Davis series; 9 cats from Benchekroun G, et al.: Plasma ACTH precursors in cats with pituitary-dependent hyperadrenocorticism, *J Vet Intern Med* 26:575, 2012; 9 cats from Valentin SY, et al.: Comparison of diagnostic tests and treatment options for feline hyperadrenocorticism: a retrospective review of 32 cases, *J Vet Intern Med* 28:481, 2014.
†7 cats from Meij BP, et al.: Transsphenoidal hypophysectomy for treatment of pituitary-dependent hyperadrenocorticism in 7 cats, *Vet Surg* 30:72, 2001; 6 cats from Goossens MMC, et al.: Urinary excretion of glucocorticoids in the diagnosis of hyperadrenocorticism in cats, *Domestic Anim Endocrinol* 12:355, 1995; 2 cats from Sellon RK, et al.: Linear-accelerator-based modified radiosurgical treatment of pituitary tumors in cats: 11 cases (1997-2008), *J Vet Intern Med* 23:1038, 2009.
*CT*, Computed tomography; *MRI*, magnetic resonance imaging.

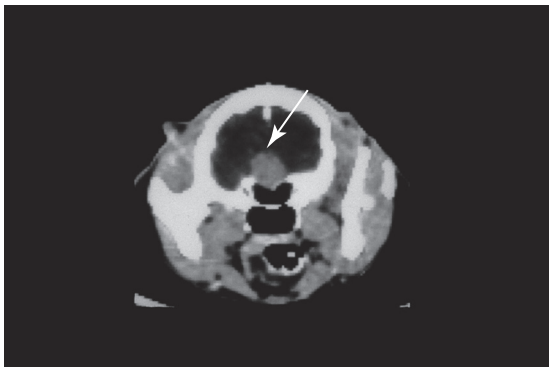

**FIGURE 11-5** Computed tomography (CT) scan of the pituitary brain region from a cat with pituitary-dependent hyperadrenocorticism (PDH) demonstrating a pituitary mass.

11-17). This would be an expensive and insensitive approach, considering that UC:CR or LDDST results are much more sensitive, require no anesthesia, and are less expensive. Either CT or MRI scanning could be used as a discrimination test to help distinguish cats with PDH from those with ATH. This, too, is an expensive and insensitive approach because cats with ATH would have normal (unremarkable) scans along with those confirmed to have PDH but whose pituitary masses are too small for visualization. Thus a normal scan would yield virtually no information other than suggesting that a cat may have ATH or, if a cat has PDH, the tumor is small. The recommendation here is that CT or MRI scans be used to screen cats that might be scheduled to undergo hypophysectomy, pituitary radiation, or radiosurgery. Either CT or MRI scans could be used to evaluate a cat with central nervous system (CNS) signs to determine the likelihood of the macrotumor syndrome.

## MEDICAL TREATMENT

### Introduction and the Options

Trilostane is the most efficacious medical treatment option effective in cats with PDH or ATH. Surgical management of FCS includes bilateral adrenalectomy or hypophysectomy for cats with PDH. Surgical removal of an adrenocortical tumor is the preferred treatment for cats with ATH. External beam radiation therapy can be utilized for cats with PDH, especially if the cat has a large (macro) pituitary tumor. No treatment modality has been employed in a large enough group of cats to allow solid recommendations, but experience with trilostane is promising.

### Trilostane

#### *Background*

Trilostane is an orally active reversibly competitive 3-β hydroxysteroid dehydrogenase inhibitor of adrenocortical and gonadal steroid synthesis. (A full description of trilostane can be found in Chapter 10.) Trilostane inhibits synthesis of both glucocorticoids and mineralocorticoids. Although not efficacious for people with hyperadrenocorticism, trilostane therapy has successfully led to resolution of clinical and biochemical abnormalities associated with hyperadrenocorticism in dogs and cats. As an enzyme blocker, trilostane is effective only when administered consistently, usually once or twice daily. If medication is not given, the effect dissipates in hours. A small number of trilostane treated dogs have developed adrenal necrosis—an effect not described in cats. The number of cats treated with trilostane and reported in the literature (at least 30) is limited, but no other therapeutic modality has been used much more often and no other has had greater success (Skelly et al, 2003 [1 cat]; Neiger et al, 2004 [5 cats]; Mellett Keith et al, 2013 [15 cats]; Valentin et al, 2014 [9 cats]. Twenty-nine of these 30 cats had PDH. We have used trilostane for the treatment of 5 cats with FCS. Although trilostane is not recommended for dogs with pre-existing liver disease, kidney disease, or both, such parameters are often abnormal in cats with FCS, but influence of these conditions on response to therapy is not known.

#### *Indications*

The primary indication for using trilostane is for long-term treatment of PDH or ATH in cats. Among the reasons for using trilostane for a cat with ATH are owner refusal to consider surgery, presence of metastases, tumor size or location that negates surgery as an option, or one of many concurrent conditions making surgery an unacceptable risk (fragile skin, kidney disease, heart disease, and so on). Before surgery is performed on any cat with FCS, treatment with trilostane should be employed in an attempt to gain full control of the disease for a period of time (4 to 8 weeks). In this manner, many of the complications associated with surgery and the perioperative period can be minimized.

#### *High Dose, Low Frequency Trilostane*

The starting dose of trilostane, reported for 21 cats with FCS, varied from about 15 mg per cat once daily to 60 mg b.i.d. (twice a day; 120 mg/cat/day); 4.2 to 13.6 mg/kg, once or twice daily (Skelly et al, 2003; Neiger et al, 2004; Mellett Keith et al, 2013). Recommended starting doses are about 20 to 30 mg/cat orally per day, administered once daily or divided between feeding times (Peterson, 2012). The initial doses used in one

study averaged 4.3 mg/kg, once daily (13 cats) and 3.3 mg/kg b.i.d. (2 cats) (Mellett Keith et al, 2013). Trilostane should always be administered during a meal or within 30 minutes of meal completion to enhance absorption of the drug.

#### Low-Dose, High-Frequency Trilostane

After experience with low-dose trilostane being effective in treating dogs with NOH (Vaughan et al, 2008), a similar approach was used in 4 FCS cats—3 with PDH and 1 with ATH (all managed by the author). Each cat was treated with about 1 mg/kg of body weight (rounded up to the next full kg of weight if needed), t.i.d. (three times a day). Purchased Vetoryl was compounded into appropriate-sized capsules, and good response in lowering cortisol concentrations and in resolving signs of FCS were achieved. In 3 cats, the dose was not changed, and in 1 cat, the dose was increased 20%. Trilostane should always be given during a meal or within 30 minutes of completion to enhance drug absorption.

#### Initial Home Treatment and Monitoring Recommendations

Medical therapy for cats with FCS is best carried out in their familiar home environment. Thus, treatment becomes the owner's responsibility. This is easy to discuss in a textbook but often quite difficult in reality. Remind owners that missing a dose occasionally should not be a problem. Assuming that an owner can consistently administer oral medication, treatment of FCS remains complicated. Therefore, prior to initiating therapy, the veterinarian is obligated to educate the owner as much as possible about FCS, the treatment plan, treatment goals, and potential complications. Treatment goals should never be a certain blood test result. Rather, the primary goal should be to have the owner see improvement in their pet's health and, therefore, therapy should be individualized to the needs of each cat. The patient should be thoroughly assessed before treatment with at least a body weight, history, physical examination, CBC, serum chemistry profile (including blood glucose and electrolytes), and urinalysis. Having this information from samples taken before treatment may be helpful when attempting to determine the explanation for predictable or unpredictable responses.

***Cats with a Poor Appetite.*** No cat should be treated for FCS if inappetent or anorexic. Appetite issues should be understood and resolved prior to starting treatment because control of hyperadrenocorticism is always associated with a reduction in appetite. If appetite decreases with therapy, the veterinarian would want to know whether it is the result of treatment. In such a scenario, blood and urine tests become a valid means of detecting changes that likely took place after treatment began.

***Conditions to Monitor.*** At a minimum, one must monitor the effects of trilostane on FCS, diabetes mellitus (if present), and kidney function. Veterinarians should also be aware of drug-induced side effects as well as changes in other concurrent conditions. Among the reported causes of death or euthanasia in treated FCS cats are kidney failure, worsening diabetes, or diabetes-related complications (ketoacidosis, hypoglycemic reactions, progressive weakness, and so on), overwhelming infection (especially of skin wounds), and perceived poor quality of life. FCS may mask concurrent conditions that become obvious as treatment progresses.

***Feline Hyperadrenocorticism Cats with Diabetes Mellitus.*** Beginning with the first day of trilostane therapy, insulin dose in diabetic cats should be decreased by about 50% or to doses of 0.1 to 0.5 units per kg of body weight per dose, whichever is deemed appropriate. Reducing insulin dose anticipates the physiologic effect that decreases in circulating cortisol concentration will reduce insulin antagonism and enhance insulin action. An attempt to avoid severe hypoglycemia is imperative, because such reactions are traumatic and dangerous for the patient as well as being frustrating, disappointing, and traumatic for owners.

Owners of cats with FCS and diabetes can provide their veterinarian with extremely valuable information. We encourage owners to monitor, as best they can, their cat's appetite, water intake, urine output, litter box usage, activity, muscle strength, interest in family members, grooming behavior, skin wound appearance (healing?), and any other pertinent information. If owners are willing and able, we recommend collection of an overnight urine sample (usually simply by removing most of the litter from the box or using nonabsorbable litter and restricting the cat to that room overnight). Urine should be obtained the morning of any planned in-hospital testing. This allows veterinary personnel to assess, at the least, specific gravity, glucosuria, and UC:CR. If owners are capable, we also recommend checking blood glucose concentrations, using the ear vein technique, every 2 hours over 10 hours every 5 to 7 days in the first month or so of trilostane treatment. Hyperglycemia is common. Euglycemia may be indicative of diabetes resolving or of the cat becoming more sensitive to insulin. Hypoglycemia always indicates insulin overdose. Some overdosed cats are no longer diabetic and others require an insulin dose reduction. Most cats with FCS and diabetes mellitus remain diabetic despite trilostane therapy. We are encouraged that using the low-dose trilostane protocol, two of three cats with PDH had resolution of both FCS and diabetes mellitus. Chapter 7 is dedicated to feline diabetes mellitus and should be consulted.

***Feline Hyperadrenocorticism Cats with Chronic Kidney Disease (CKD).*** Valuable information can be gained from owners of a cat with FCS and CKD. As with owners of diabetic cats, we encourage these owners to monitor, as best they can, their cat's appetite, water intake, urine output, litter box usage, activity, muscle strength, interest in family members, grooming behavior, skin wound appearance (healing?), and any other pertinent information. Concerns regarding worsening kidney function will be raised if the appetite is abnormally poor, if weight loss is suspected, or if the cat has vomiting or worsening PU/PD. Resolution of NOH may be associated with unmasking severe CKD.

#### In-Hospital Monitoring

In-hospital rechecks should be planned 7 to 10 days after starting trilostane, again after a month, and then every 90 to 120 days. Schedules should be individualized. In the ideal situation, we ask owners to collect urine from their cat the morning of any scheduled recheck, as described. While repeatedly obtaining blood from FCS cats is problematic, it is difficult to avoid the ACTHST. While the ACTHST lacks sensitivity and is not recommended as a screening test for FCS, it remains the most informative and objective test used for monitoring response to trilostane administration. ACTHST should be started 2 to 3 hours after feeding and trilostane administration. Whatever the time period from trilostane administration, future ACTHST should begin using the same time interval.

***Assessment of Trilostane Dose and Frequency.*** Together with the UC:CR result from owner collected urine, results of ACTHST will aid in determining if and what kind of adjustments in trilostane therapy are needed. A UC:CR result within the laboratory reference range indicates that a cat is receiving the correct dose or too much trilostane and that the frequency of administration is correct. The correctly dosed cat should be described by the owner as doing well, whereas the overdosed cat may be described as listless, inappetent, having diarrhea, and/or vomiting. The appropriately dosed cat should have a post-ACTHST

cortisol concentration of about 2 to 6 µg/dL, whereas an overdosed cat will have a cortisol concentration less than 2 µg/dL if the ACTHST is carried out at the correct time post-trilostane. If the UC:CR is above the reference limit, an increase in trilostane dose is indicated if the post-ACTHST cortisol concentration is more than 6 µg/dL. If the UC:CR is above the reference limit, an increase in the frequency of trilostane administration is indicated if the post-ACTHST result is in the desired range. This recommendation for repeatedly collecting urine is based on experience.

***Assessment of Cats Not Doing Well.*** Ideally, if the trilostane dose is correct, the ACTHST result should be about 2 to 6 µg/dL. But these are not magic numbers with guaranteed results. Suggestions here are aids to achieving a positive response. Although ACTHST and UC:CR results are objective, owner opinion regarding response to therapy remains most important. If owner opinion and UC:CR or ACTHST results seem discordant, owner opinion should take precedence.

For example, an owner believes the cat is doing great but test results suggest underdose. In this scenario, no change in dose or frequency would be made. What if an owner believes the cat is doing great but test results suggest overdose? Here, we would recommend lowering the dose. Alternatively, an owner believes that the cat is doing poorly but UC:CR and ACTHST results look excellent. First, any cat described as being ill should have the trilostane discontinued because overdose is always a possibility and, even if not overdosed, continued treatment may negatively impact the cat's ability to respond to another condition. Our initial differential diagnoses would include worsening in diabetes control, pancreatitis, or CKD. Other problems may be encountered.

#### *Results*

In a study of five cats treated with trilostane, two died after 16 and 120 days of treatment, respectively. The remaining cats did improve and were alive at 6, 11, and 20 months (Neiger et al, 2004). In the study on 15 cats, survival ranged from 87 to 1280 days. The median survival was about 21 months. In this latter study, only cats treated for 60 days or longer were included, leaving the possibility that some trilostane treated cats failed to remain on the drug or survive 60 days (Mellett Keith et al, 2013). In both studies, cats with diabetes mellitus remained diabetic, although the condition was usually more responsive to treatment.

The four cats treated with low-dose trilostane included one with ATH that improved and had its adrenocortical tumor surgically removed with resolution of FCS. The three cats with PDH all improved clinically, no adverse side effects were noted, and two of the three experienced resolution of their diabetes mellitus. One cat whose diabetes resolved died from pancreatic adenocarcinoma 10 months after treatment started, and the other two are each alive after about 1 year.

### Mitotane

A number of different protocols using mitotane (Lysodren; o,p'-DDD) for the medical management of cats with PDH have been used with varying levels of short-term success. Long-term results have been discouraging (Peterson, 1998). It is interesting to point out that human beings with PDH, like their feline counterparts, are not nearly as sensitive to o,p'-DDD as dogs. (See Chapter 10 for a complete discussion of o,p'-DDD.) When o,p'-DDD was given to clinically normal cats, only 50% demonstrated any adrenocortical suppression (Zerbe et al, 1987a). Adverse effects such as anorexia, vomiting, and lethargy have been described as common, even in cats that did not have discernable cortisol response (Peterson et al, 1994; Duesberg and Peterson, 1997; Peterson, 2012). We have experience in using mitotane in four cats with FCS (Nelson et al, 1988). Mitotane does not effectively suppress adrenocortical function nor alleviate clinical signs of FCS, and its use is not recommended.

### Ketoconazole

Ketoconazole, an imidazole derivative, is an orally active broad-spectrum antimycotic drug that has been used successfully in treating fungal disease in human beings and animals. At adequate doses, it inhibits both 11-β-hydroxylase and cholesterol side-chain cleavage enzymes, inhibiting mammalian steroid biosynthesis. Ketoconazole also has the potential to inhibit pituitary synthesis of ACTH by inhibiting adenyl cyclase activity in pituitary corticotrophs (Stalla et al, 1988). Doses used for mycotic infection can lead to significant reduction in serum androgen concentrations, and at higher doses, decreases in serum cortisol (Engelhardt et al, 1991). Ketoconazole is an efficacious oral medication for the treatment of human beings with PDH.

Ketoconazole does not seem to consistently suppress adrenocortical function in either normal cats or cats with FCS. A study of four healthy male cats given 30 mg/kg/day for 30 days failed to demonstrate significant changes in plasma testosterone or cortisol concentrations. Serum testosterone concentrations tended to decrease after the first 7 days of treatment, but in two of the four cats, values returned to near-pretreatment concentrations by day 30 (Willard et al, 1986). Our experience has been limited to using this drug in five cats with naturally occurring PDH. Three of the five cats responded moderately well but not completely. One cat demonstrated no response, and the fifth cat developed severe thrombocytopenia (which may or may not have been associated with the drug) several weeks after treatment was initiated. Use of ketoconazole for the treatment of cats with FCS is not recommended (Peterson, 2012).

### Etomidate

Etomidate is a short-acting intravenously administered anesthetic agent used for anesthesia induction. Because it has been shown to have minimal deleterious effect on the cardiovascular system, this drug has been used to induce anesthesia in high-risk patients that are critically ill, hypovolemic, in shock, or have pre-existing cardiovascular disease. It has also been shown that administration of this drug suppresses adrenocortical function in people, dogs, and cats. One study on cats demonstrated profound suppression of adrenocortical function during 2 hours of anesthesia (Moon, 1997). Use of a sustained-release form of this drug could be an effective mode of therapy for cats with FCS.

### Metyrapone

Metyrapone (Novartis; East Hanover, NJ) is an orally active drug that inhibits the enzymatic action of 11-β-hydroxylase, which is responsible for converting 11-deoxycortisol to cortisol. Because cortisol precursors have little or no biologic activity, inhibition of cortisol synthesis has the potential to resolve clinical signs and biochemical changes due to hyperadrenocorticism. In people, drugs like metyrapone have been recommended for short-term control prior to surgery, to resolve hyperadrenocorticism while waiting for radiation therapy to take effect, or to provide palliative treatment for metastatic disease (Verheist et al, 1991; Feelders et al, 2010).

Metyrapone has been documented to be effective in people with either PDH or ATH. Although adverse reactions are not common, transient hypocortisolemia has been reported. Chronic use of metyrapone has been demonstrated to result in a compensatory endogenous ACTH concentration increase and "override" of adrenal blockade of cortisol synthesis (Orth, 1978).

There are several reports of using metyrapone in cats with FCS. Clinical response without side effects (other than hypoglycemia) was achieved in two cats using 30 to 70 mg/kg orally, twice daily (Daley et al, 1993; Moore et al, 2000b). The lower end of the dose range should be used for the first 2 to 4 weeks, rechecking the cat and possibly completing an ACTHST. The dose can be increased, as needed, by small increments. Doses greater than 70 mg/kg, twice daily, are not recommended. Higher doses have been mentioned, although these higher doses have been associated with a strong suspicion of drug-induced vomiting and inappetence. Subjective clinical improvement was observed in three cats: One was lost to follow-up after 10 months of treatment, whereas two cats were treated for 21 days and 6 months, respectively, before each had successful bilateral adrenalectomy (Moore et al, 2000a). One of two additional cats was treated and reported to have had slight improvement (Peterson, 1988). Another cat demonstrated transient reduction in ACTHST cortisol concentrations, had resolution of clinical signs, and underwent subsequent successful adrenalectomy (Daley et al, 1993). Metyrapone is often difficult to obtain. There has not been a documented case of rising endogenous ACTH concentrations in cats, overriding adrenocortical blockade with either metyrapone or trilostane.

## SURGERY AND LAPAROSCOPIC TREATMENT

### Hypophysectomy

#### *Background and Results*

The treatment of choice for people with PDH is surgical removal of their pituitary tumor, thus eliminating the cause (Melby, 1988; Thorner et al, 1992). Pituitary tumors are primary and not caused by excessive hypothalamic stimulation. Their removal results in permanent resolution of PDH (Scholten-Sloof et al, 1992; Van Wijk et al, 1992). Hypophysectomy in cats has been used for both physiologic and pharmacologic studies (Reaves et al, 1981; Sallanon et al, 1988). In addition, transsphenoidal hypophysectomy in cats has been described in detail for advanced microsurgical training of physician neurosurgeons (Snyckers, 1975).

Microsurgical trans-sphenoidal hypophysectomy is an effective means of treating cats with PDH (Meij et al, 2001). However, this form of therapy requires CT or MRI imaging facilities to identify the mass, assess its size, establish location for the burr slot needed to perform the procedure, and determine if surgery is appropriate prior to the procedure. In addition to requiring an experienced surgeon, having facilities for perioperative care is imperative. Cats undergoing this procedure had both soft palate and mucoperiosteum incised to expose the sphenoid bone. Access to the pituitary fossa was completed using a burr and punches, the dura mater was incised, and the pituitary carefully extracted (Meij et al, 1997; 2001). The procedure is safest in cats with a small pituitary tumor. Regardless of tumor size, this procedure is associated with risk of surgical and medical problems. After the procedure, some cats develop transient or permanent hypopituitarism. This hypocortisolism, hypothyroidism, and diabetes insipidus requires at least short-term substitution therapy. Two of seven cats were alive 15 and 46 months after surgery, respectively, at the time that the report was written and were in complete remission. Two of the five long-term survivors had resolution of diabetes mellitus (Meij et al, 2001).

#### *Conclusions*

The number of cats treated with hypophysectomy has been limited. However, as more experience is gained, there is no doubt that this could be the treatment of choice for cats with PDH, as it is for similarly afflicted human beings and dogs. Limiting factors include need for expertise and facilities to perform the surgery and the perioperative medical care. As expertise improves, it is anticipated that specific removal of ACTH-secreting tumors will be accomplished while preserving the healthy portion of the pituitary.

### Adrenalectomy

#### *Background*

Pituitary surgery should provide a permanent cure. Bilateral adrenalectomy for PDH is another, rarely used means of permanently resolving FCS. Adrenal nodule or mass removal should be curative for ATH. Perhaps the most important questions to consider prior to surgery are whether the cat is a reasonable surgical and anesthesia risk and, after trilostane treatment for 4 to 12 weeks prior to surgery to control FCS, what would be gained from the surgery that has not been achieved with trilostane? One answer to this latter question is the cat would no longer need to be medicated, although diabetes mellitus and its need for therapy may not resolve. Again, consider risk versus reward, and be certain that the owner is well informed.

#### *Managing Cats Pre- and Post-Adrenalectomy*

Conservative volumes of IV fluids (2.5% dextrose if the cat is diabetic) should be started after withdrawal of food and water prior to surgery. During surgery and in the first days following, fluid therapy should be directed at maintaining hydration, being aggressive in the assumption that some of these cats will develop postsurgical pancreatitis, but not overloading a compromised cardiovascular system. General vague guidelines suggesting individualization of therapy is the only reasonable recommendation that can be made. Use of an antibiotic specific for an identified infection, based on culture and sensitivity results, may represent the best opportunity to avoid resistance. Insulin treated diabetics should be given 50% of the usual morning dose. Insulin dosing from this point until the cat is eating and drinking on its own will be challenging. When the surgeon begins removal of an adrenal tumor or the first of a bilateral adrenalectomy, dexamethasone should be administered (0.2 mg/kg, IV). That dose should be repeated IM when surgery is complete, and 0.1 mg/kg should be given between 10 PM and midnight. Some protocols utilize hydrocortisone. Those cats undergoing adrenocortical tumor removal will be predisposed to low cortisol concentrations because adrenocortical cells in the remaining gland will likely be atrophied. After bilateral adrenalectomy, no adrenal tissue remains.

The morning after surgery, an ACTHST should be completed. There should be an "Addisonian" result—both the basal and post-ACTHST cortisol concentration less than 2 µg/dL. If the result is as anticipated, surgery may have been a success. If results after surgery are similar to those obtained before, adrenal tissue or functioning metastatic sites remain.

After obtaining the ACTHST, begin giving 0.1 mg/kg of dexamethasone subcutaneous (SC), b.i.d. The switch to oral prednisolone replacement (Graham-Mize et al, 2004) should begin about 24 hours after the cat begins to eat without vomiting. Cats that had bilateral

adrenalectomy are permanent Addisonians that will require glucocorticoid and mineralocorticoid replacement the remainder of their lives. They usually have their prednisolone replacement dose determined over a period of weeks to months. Those that had an adrenocortical tumor removed usually have their glucocorticoids tapered over a period of 2 to 4 months before discontinuing treatment.

After bilateral adrenalectomy, desoxycorticosterone pivalate (DOCP; Novartis, East Hanover, NJ) should be administered (2.2 mg/kg, IM). That dose should be repeated 21 to 25 days later, SC. Long-term dose and timing requirements should be individualized (see Chapter 12). It is not common for dogs or cats undergoing solitary adrenocortical tumor removal to need mineralocorticoid medication. If hyponatremia, hyperkalemia, or both are documented after surgery, DOCP should be given. ATH cats given DOCP, usually receive 50% of that dose when due in 25 days and then another 50% reduction is made for the final dose due at 50 days. From this time, it is quite uncommon for DOCP to be needed. During this entire period, monitoring serum electrolyte concentrations is important.

Serum renal parameters and electrolyte and glucose concentrations should continue to be assessed at the end of unilateral or bilateral adrenalectomy that evening, the next morning, and then daily until the cat is returned to the owner or until it is eating on its own without vomiting. The diabetes mellitus should be monitored and treated as if the cat were newly diagnosed, using conservative doses of insulin. The combination of resolved FCS, parenteral and then oral steroids, the stress of surgery and recovery, and a multitude of other factors make diabetes management challenging. Until the dose of oral glucocorticoids is discontinued in ATH cats or until the dose is stable after being tapered to that necessary for long-term health, insulin requirements are unpredictable.

#### *Protocol: Surgery*

If an obvious adrenal tumor is identified, it should be removed, especially if the opposite adrenal gland appears atrophied. If discrimination test results are definitive for PDH, both adrenal glands should be removed regardless of whether they appear normal or enlarged. If discrimination tests are not performed or inconclusive, the surgeon together with those managing the medical aspects should be prepared for intraoperative decisions. If the adrenals appear symmetrical in size and shape, they should be removed, whereas if one is obviously larger, that gland might be removed.

#### *Protocol: Laparoscopy*

Removal of adrenal masses via laparoscopy is becoming more common in veterinary practice (Smith et al, 2012). Mass size, location, presence of tumor thrombi, and invasion of local structures are all factors in deciding which animal is a candidate for this procedure as opposed to celiotomy. Laparoscopic adrenalectomy has the advantage of reducing perioperative complications.

#### *Short-Term Complications*

Complications are frequently encountered in cats undergoing surgery for FCS. Complications that are terminal or that lead a veterinarian to recommend euthanasia can be extremely disheartening to the owner and the entire veterinary team. Potential complications must be thoroughly explained to all decision makers before surgery. Some serious potential complications include sepsis, pancreatitis, thromboembolism, wound infection and/or dehiscence (surgical site or previous skin wounds due to fragility), and adrenocortical insufficiency (Duesberg et al, 1995). Sepsis is common because FCS predisposes to infection via immunosuppression and those with fragile skin can have seriously infected wounds. Preoperative treatment with trilostane for a sufficient length of time to resolve as many FCS-related issues as possible should dramatically reduce complication rates.

#### *Long-Term Complications, Including the Pituitary Macrotumor Syndrome*

The consequences of a growing pituitary tumor are well described in dogs and information on cats is expanding. Questions exist regarding the effect of bilateral adrenalectomy or long-term inhibition of cortisol synthesis with drugs like trilostane on rate of pituitary tumor growth. Some believe that removal of cortisol negative feedback results in an increased rate of growth, a condition called *Nelson's syndrome* in people. Some believe that tumor growth rate is independent of physiologic influence. The possibility of enhanced pituitary tumor growth rate should be discussed with decision makers before surgery.

#### *Experience*

Experience with surgical management of FCS is limited and results have varied. Most cats survive surgery, and postsurgical complications are common. We have reviewed the experience of 21 cats that had PDH and bilateral adrenalectomy. These include 15 cats in our series and 6 cats from the literature (Watson and Herrtage, 1998 [4 cats]; Daley et al, 1993 [1 cat]; Moore et al, 2000a [1 cat]). Eight cats from our series have been reported (Duesberg et al, 1995). Thirteen of 21 cats survived surgery, had complete resolution of FCS, and lived for months or for more than 1 year (Daley et al, 1993; Watson and Herrtage, 1998; Moore et al, 2000). Five cats did not survive an appreciable period of time after surgery. One of the five died about 12 hours after surgery; no explanation was available. The second of five died from acute kidney failure 20 days after surgery (Watson and Herrtage, 1998). Two of the five cats died of sepsis within 1 month of surgery, both due to severely infected fragile skin. One of the five cats died of pulmonary thromboembolism about 3 weeks after surgery. Three additional cats from our series survived the surgery, had complete resolution of their FCS, but died within months of surgery. One died 4 months following surgery due to pancreatic carcinoma, and two died from apparent hypoadrenal crises 3 and 6 months after surgery, respectively.

#### *Conclusions*

Surgical resolution of FCS is difficult. Just the risk of exposing a cat with FCS to celiotomy is significant. Risk can be reduced with a combination of patient selection, preoperative trilostane therapy, minimal time for anesthesia and surgery, and thorough care after surgery. However, these remain older cats that often have serious problems involving other organ systems. Perhaps this is the reason that many cases of FCS are not treated. Bilateral adrenalectomy for PDH or tumor removal for ATH is an alternative to long-term oral trilostane therapy, hypophysectomy, or pituitary radiation.

## PITUITARY RADIATION

### Background

Ionizing radiation can be used in an attempt to destroy a benign or malignant tumor. This is a consultative discipline requiring a veterinary radiation oncologist and appropriate facilities. The objective of radiation therapy is tumor eradication with preservation of normal tissue structure and function (Theon, 2000). Facilities typically needed are a cobalt-60 photon irradiation unit or a linear accelerator photon unit. Treatment usually involves delivery of a predetermined

total dose of radiation. Some protocols call for a large single dose, whereas others recommend smaller doses delivered in fractions over a period of several weeks. We are currently evaluating efficacy of a two-dose protocol, which still limits anesthesia, while possibly improving on disappointing experience with a single-dose approach.

Radiation therapy should always have potential benefit for the pet, even though outcome may not be entirely predictable. Because months may be required for effects of radiation therapy to be fully appreciated, many cats might benefit from prior trilostane control of FCS. Then, one can determine if the cat is a reasonable anesthesia risk. Trilostane should be continued for about 4 to 6 months after completion of radiation therapy. If a protocol calls for multiple treatment/anesthesia sessions, rapid anesthesia recovery is imperative. This provides cats with enough "conscious time" to eat prior to the obligatory cessation of food hours before the next scheduled anesthesia.

### Experience

Radiation therapy has been used with partial success to treat a limited number of FCS cats with PDH (Peterson et al, 1994; Duesberg and Peterson, 1997; Feldman and Nelson, 2004; Mayer et al, 2006; Sellon et al, 2009). The most commonly noted benefit has been tumor shrinkage, prolonging survival in cats with large and/or invasive pituitary masses. Radiation offers a potential for cure, but resolution of FCS has only been reported in a minority of cats.

Our experience in treating PDH cats with pituitary radiation is limited to only seven cats with sufficient follow-up to determine response. Each had obvious clinical signs and five had insulin-resistant diabetes mellitus. Each cat had been evaluated either with a CT scan (3 cats) or an MRI scan (4 cats). Each of the seven cats had a visible pituitary mass (5 to 11 mm in greatest diameter). Four cats were treated with 15 fractions of radiation divided over a period of 3 weeks. One cat demonstrated no response and was euthanized 7 months after radiation because of continuing signs of diabetes mellitus and fragile skin. The two non-diabetic cats appeared to improve by losing weight, becoming more active, and demonstrating healthier skin. However, one of these two cats died of unknown reasons 3 months after completion of treatment, and the other died 14 months after completing radiation as a result of renal failure. The fourth and youngest cat (8 years old at the time of diagnosis) responded quite well to pituitary radiation with improvement in various parameters plus complete resolution of its diabetes mellitus. This cat has lived for 32 months. Each of three cats was treated with a single large dose of radiation. None of these cats had resolution of their FCS, and none had appreciable mass shrinkage. However, experience with seven cats is far too few to draw any conclusions. Pituitary radiation has potential to become a reasonable approach to management of PDH, but many more cats will need to be treated before opinions can be established.

## PROGNOSIS

FCS is a serious condition that carries a guarded to grave prognosis. The deleterious effects of chronic hyperadrenocorticism on skin fragility, pancreatic endocrine function (diabetes mellitus), and the immune system are frequently responsible for morbidity and death of both treated as well as untreated cats. Treatment can be expensive, emotional (to the owner), and stressful (to the cat) without guarantee of success. Medical therapy with trilostane has great promise. Abdominal surgery has not been routinely successful because of the debilitated condition of most cats with FCS. This problem should be less of a concern if cats can be treated with trilostane to resolve FCS before surgery. Pituitary radiation is limited by facilities required, expense, and the multiple anesthetic procedures that are part of some protocols. Hypophysectomy is limited by the few veterinarians who have this expertise. Again, there are the problems of expense and patient debilitation. Experience with "successful" therapies (adrenalectomy [unilateral or bilateral], radiation, hypophysectomy) has resulted in less than 50% of cats surviving well beyond 1 year. Remember, most cats that have FCS are not treated. Most of the treated cats are those considered most stable. Therefore, 50% survival at 1 year (an optimistic number) does not include those cats never treated. Also, as success improves in treating FCS, the incidence and severity of large pituitary tumors (macrotumor syndrome) is likely to increase.

## PRIMARY HYPERALDOSTERONISM IN CATS

### Background

The hormone aldosterone regulates both circulating concentrations of sodium and potassium and intravascular fluid volume homeostasis. It is the principle mineralocorticoid synthesized and secreted by the zona glomerulosa, the outermost zone of adrenal cortices, whose cells lack the capacity to synthesize cortisol. Increases in serum potassium directly stimulate release of aldosterone. Decreases in blood pressure, primarily sensed within the kidneys, stimulates synthesis and release of renin which, in turn, stimulates the angiotensins to stimulate secretion of aldosterone. After synthesis and secretion, aldosterone acts on the distal nephron to promote sodium reabsorption and excretion of potassium and hydrogen ions. In conserving sodium, aldosterone indirectly conserves water, raising blood volume and, in turn, blood pressure. Aldosterone directly increases blood pressure via enhancement of total peripheral resistance. This hormone is also synthesized in tissues within the heart, brain, and vasculature where it is thought to have paracrine or autocrine action (Djajadiningrat-Laanen et al, 2011).

Excess production of aldosterone can be primary or secondary. *Primary hyperaldosteronism (PHA)* is defined as the "autonomous secretion of the hormone by abnormal cells within the adrenal cortex." PHA is characterized by circulating aldosterone excess and renin suppression. For several decades after this condition was described by Conn (1955) it was considered rare. With better understanding, it is now thought to occur in about 6% of all people with arterial hypertension and about 11% of people with therapy-resistant hypertension (Fogari et al, 2007; Douma et al, 2008). Approximately two thirds of people with PHA have bilateral hyperplasia of the zona glomerulosa in whom plasma renin activity may be incompletely suppressed. About one-third of people with PHA have a solitary adenoma in which plasma renin activity is completely suppressed. Unilateral hyperplasia and aldosterone-producing carcinomas are uncommon-to-rare (White, 1994; Young, 2007). Afflicted patients typically have no abnormalities in cortisol production, plasma cortisol concentrations, or in cortisol metabolism. *Secondary hyperaldosteronism* is the result of a condition (e.g., heart failure and CKD) that stimulates renin secretion to begin the cascade of enzyme activity resulting in aldosterone synthesis and secretion. Thus, secondary hyperaldosteronism is associated with enhanced renin concentrations.

Sodium retention, associated with primary or secondary aldosteronism, increases extracellular fluid volume and blood pressure (hypertension). Despite increases in total body sodium content, serum sodium concentrations are usually normal. In cats, because glucocorticoids, estrogens, and progestagens are primarily excreted

via bile into the intestines, it is likely that there are similar excretory pathways for aldosterone.

PHA has been described rather commonly in cats. Underdiagnosis, which seems likely, may be traced to the concept that progression of CKD can lead to hypertension, hypokalemia, or both. However, it appears that CKD may also be the result of PHA. Regardless, PHA may cause hypertension, hypokalemia, or both (Javadi et al, 2005; Djajadiningrat-Laanen et al, 2011). Hypertension and hypokalemia in cats with CKD are often treated symptomatically without further investigation of cause.

## Etiology

### *Adrenocortical Neoplasia*

Classically, PHA in cats is caused by a unilateral solitary adrenocortical adenoma or carcinoma. The incidence of malignant tumors (19 reported cases) exceeds that of solitary benign adenomas (11 reported cases). Feline PHA was first reported in 1983 by Eger and colleagues. In the past 15 years, cats with PHA have been reported more commonly (Flood et al, 1999; MacKay et al, 1999; Maggio et al, 2000; Moore et al, 2000b; Rijnberk et al, 2001; Reimer et al, 2005; Ash et al, 2005; DeClue et al, 2005; Rose et al, 2007; Briscoe et al, 2009; Renschler and Dean, 2009; Djajadiningrat-Laanen et al, 2011; 2013; Lo et al, 2014). Bilateral adrenal adenomas were identified in two cats. One cat with PHA also had an insulin secreting pancreatic tumor and a parathyroid hormone secreting adenoma. Some cats with PHA have had concurrent progestagen excess (DeClue et al, 2005; Briscoe et al, 2009), possibly due to enhanced production of intermediary products (Harvey and Refsal, 2012).

### *Adrenocortical Hyperplasia*

Non–tumor-related PHA has been described in 13 cats (Javadi et al, 2005; Djajadiningrat-Laanen et al, 2013). Afflicted cats, at necropsy, were demonstrated to have bilateral adrenocortical hyperplasia, and most had evidence of CKD. Some cats had zona glomerulosa nodular hyperplasia, renal arteriolar sclerosis, glomerular sclerosis, tubular atrophy, and interstitial fibrosis (Javadi et al, 2005; Harvey and Refsal, 2012).

## Clinical Features and In-Hospital Testing

### *Signalment and Signs*

There does not appear to be a breed predisposition among cats diagnosed with PHA. The mean age at diagnosis is about 12 to 13 years and most are more than 10 years of age. Both genders have been represented, and most have been neutered. The most common clinical sign has been persistent and progressive weakness associated with hypokalemia, called *hypokalemic polymyopathy* (Harvey and Refsal, 2012). Usually seen at serum potassium concentrations less than 3 mg/dL, the most common owner observations have included cervical ventriflexion, hind limb weakness (sometimes plantigrade), difficulty jumping, listlessness, and ataxia. A few cats have had limb rigidity, dysphagia, or collapse. Some cats had episodic signs and a few had signs that were sudden in onset. Weakness was less worrisome in cats with adrenal hyperplasia (Javadi et al, 2005).

The second most common owner-perceived concern in cats with PHA has been associated with hypertension. Some hypertensive cats have had acute blindness and/or sudden change in eye color, usually due to intraocular hemorrhage or retinal detachments. Ocular signs are not as common in cats with adrenal tumors as they are in those with adrenal hyperplasia.

PU/PD have been described in less than 20% of cats with PHA. PU/PD may be due to a concurrent condition (e.g., diabetes mellitus, and/or CKD). Alternatively, hypokalemia can cause acquired and reversible nephrogenic diabetes insipidus (Harvey and Refsal, 2012). Systemic hypertension and hypokalemia have been associated with progressive loss of kidney function (Djajadiningrat-Laanen et al, 2013). About 20% of PHA cats have had decreases in appetite, about 10% have polyphagia, and a few have had worrisome weight loss. Other signs may be related to the insulin antagonistic effects of progestagen excess that also is seen in some cats with PHA.

Physical examination findings are usually related to hypokalemia or to hypertension. Hypertensive ocular signs include retinal detachment, hemorrhage, tortuous retinal vessels, and retinal edema. Weakness due to hypokalemia is consistent with owner observations. Some cats have had muscle atrophy, heart murmur, arrhythmias, palpable adrenal masses (three cats), and fragile skin (Djajadiningrat-Laanen et al, 2011).

### *In-Hospital Routine Testing*

The one abnormality on laboratory testing typical for PHA is hypokalemia, documented in 42 of 50 cats with an adrenal tumor. Several of the remaining eight cats had serum potassium concentrations that were low-normal. Only a few differential diagnoses for low potassium are considered "common": CKD, diabetic ketoacidosis (the condition itself, under supplemented IV fluids, insulin, and bicarbonate all predispose to hypokalemia), acute gastrointestinal disease (vomiting, diarrhea, anorexia), and PHA. By contrast, about half of cats with adrenal hyperplasia have had normal serum potassium concentrations and the others have had mild hypokalemia (Javadi et al, 2005). Volume expansion due to sodium retention is "classic" for PHA, but serum sodium concentrations are usually within the reference range. About 85% of PHA cats are persistently hypertensive.

A number of cats described as having PHA secondary to adrenal hyperplasia have had CKD with abnormal increases in serum urea and creatinine concentrations. The combination of CKD and hypertension would tend to steer clinicians away from a separate investigation of the hypertension. Cats with adrenal tumors usually do not have evidence of CKD. Progressive renal damage associated with aldosterone excess has been implicated in some people due to a combination of increased intraglomerular capillary pressure, inflammation, and fibrosis. This may be associated with excesses in angiotensin II and the chronic hypokalemia of CKD. Hyperglycemia is not common, nor are abnormalities in serum phosphate.

Abdominal ultrasonography is a valuable diagnostic aid when assessing unexplained hypertension. Ultrasonography provides information regarding renal and adrenal anatomy, especially when searching for an adrenal nodule. Cats with an adrenocortical tumor evaluated with ultrasonography typically have had a 1 to 5 cm diameter adrenal mass (Harvey and Refsal, 2012). The contralateral adrenal is usually considered small. Bilateral adrenal tumors are not common (Quante et al, 2009). Adrenal masses that extend into or invade the vena cava or other vessels are called *tumor thrombi*. The liver, retroperitoneum, and other areas should be evaluated for evidence of metastases or unsuspected abnormalities. Abdominal CT or MRI examinations correctly detected a mass or hyperplasia in 32 of 38 cats with confirmed PHA (Flood et al, 1999; MacKay et al, 1999; Rijnberk et al, 2001; Ash et al, 2005; DeClue et al, 2005; Javadi et al, 2005; Rose et al, 2007; Renschler and Dean, 2009; Djajadiningrat-Laanen et al, 2013; Lo et al, 2014). Cats with non-tumor PHA do not have abnormal adrenals other than a few with subtle increases in adrenal echogenicity.

#### *Confirming a Diagnosis: Plasma Aldosterone Concentrations and Abdominal Imaging*

PHA should be strongly considered in any cat with an adrenal nodule identified on ultrasonography and unexplained hypokalemia or hypertension. The condition should also be suspected in hypertensive cats' refractory to therapy. Randomly obtained plasma aldosterone concentrations (PACs) have been above the reference range in 43 of 50 cats with a solitary adrenal mass (Djajadiningrat-Laanen et al, 2011; Lo et al, 2014). In this scenario, PHA is the most likely diagnosis, and a recommendation of surgery is supported. Aldosterone assays are widely available through commercial veterinary laboratories. Sample collection requirements are routine (Harvey and Refsal, 2012). Extremely high PACs have been reported in cats with PHA and in cats with CKD (Yu and Morris, 1998).

Diagnostic imaging with ultrasonography, MRI, and CT has been utilized to identify adrenal abnormalities, to evaluate for vascular invasion, and to attempt visualization of local or distant metastases. Absence of vascular invasion seen on imaging is not a guarantee that it does not exist. Although logic suggests that some adrenal masses may be too small to be detected, most have been easily visualized. Visualizing an adrenal mass does not indicate its function. In a study on people, 38% of CT/MRI scans did not accurately identify the source of aldosterone excess (Kempers et al, 2009). Thus, while extremely helpful, imaging is not a perfect screening test for PHA (Djajadiningrat-Laanen et al, 2011). Use of positron emission tomography (PET) or single photon emission computed tomography (SPECT) may prove valuable but have not yet been assessed.

#### *Confirming a Diagnosis: Ratio of Urine Aldosterone to Creatinine*

The urine aldosterone-to-creatinine ratio (UA:CR) theoretically provides a reflection of aldosterone concentrations over time. This test is not widely available. It has the advantages of urine not needing to be immediately frozen, and urine is easily collected. The UA:CR is often abnormal in cats with PHA, but sensitivity was less than with the random serum aldosterone assessment. The reference interval of the UA:CR is large and did not facilitate differentiation between healthy cats and those with PHA (Djajadiningrat-Laanen et al, 2008). A cat whose PAC is lower than anticipated may be in the early stages of this condition or may have simple minute-to-minute serum fluctuations.

#### *Confirming a Diagnosis: Plasma Aldosterone and Renin Concentrations*

Ideally, circulating aldosterone concentrations should be coassessed with the renin concentration. Individuals with PHA (tumor) should have increases in plasma aldosterone and decreases in plasma renin concentrations, whereas both would be increased in CKD. The aldosterone-to-renin ratio (ARR) has been utilized to improve sensitivity and specificity, but reliable renin assays are not yet widely available, those results reported in PHA cats have been variable and not highly specific (Harvey and Refsal, 2012). In cats with adrenal tumors, the ARR can be quite increased, but in cats with idiopathic bilateral nodular hyperplasia, the ARR may be less impressive. Although the ARR is the gold standard for PHA screening, disadvantages of this test include the necessity for large blood samples, plasma must be instantly frozen, renin values may vary among laboratories, and repeat testing may be required because an unremarkable result does not rule out PHA (Javadi et al, 2004; 2005; Djajadiningrat-Laanen et al, 2011)

#### *Provocative Mineralocorticoid Function Testing*

The combination of owner-observed weakness, hypokalemia documented on routine blood chemistry, an adrenal nodule visualized on ultrasonography, and an increased randomly obtained circulating aldosterone concentration have proven quite sensitive and specific for diagnosing PHA. It is assumed that cats early in the course of their disease and those with a mild condition may not have all these abnormalities. Assessing aldosterone concentrations before and after ACTHST has not improved sensitivity and is not recommended. However, cats with PHA have been reported to have normal-to-low baseline serum cortisol concentrations with subnormal cortisol responses to ACTH (DeClue et al, 2011; Harvey and Refsal, 2012; Eiler et al, 2013). Excesses in aldosterone, its precursors, or other adrenocortical products may suppress endogenous ACTH synthesis and secretion sufficiently to account for the apparent decreases in cortisol. If true, this may help explain the poor appetite observed in some PHA cats.

Fludrocortisone (a synthetic mineralocorticoid described in Chapter 12) promotes sodium retention, water retention, and an increase in blood volume. In cats with a healthy renin-angiotensin-aldosterone system, fludrocortisone administration should suppress renin and aldosterone concentrations. Cats with PHA should be refractory to this effect. In studies of 23 healthy and one PHA cat, fludrocortisone given for 4 days at a dose of 0.05 mg/kg b.i.d. caused significant decreases in the healthy cats' UA:CR but not so for the cat with PHA (Djajadiningrat-Laanen et al, 2008; 2011; Matsuda et al, 2013). In a subsequent study of nine PHA cats and 10 non-PHA cats that were hypertensive and/or hypokalemic, results were not as sensitive as simply measuring the serum aldosterone concentration. PACs were abnormal in all PHA cats, whereas results were within or near the limit of the reference range in the non-PHA cats (Djajadiningrat-Laanen et al, 2013). Guidelines for provocative testing in people include assuring that serum potassium concentrations are normal before testing. Also, before testing, discontinuation of most medications for 2 to 4 weeks is recommended. Use of provocative testing may prove valuable as additional studies are completed. At this time, our recommended approach to a cat that may have PHA is to assess each adrenal via ultrasonography and to measure PAC if a nodule or mass is identified or suspected.

### Treatment

Removal of an adrenal tumor is the treatment of choice for cats with PHA (Rose et al, 2007). Such masses can be removed via celiotomy or laparoscopy. Assessing each cat for tumor thrombi and for metastases is imperative before considering surgery. Preoperatively, hypokalemia should be treated with oral and/or parenteral potassium. After surgery, a high sodium diet has been recommended, although most PHA cats have not been so-treated (Djajadiningrat-Laanen et al, 2011). Temporary administration of oral fludrocortisone acetate or injectable DOCP could be administered post-surgically to manage hypoaldosteronism, but this has not usually been necessary (Lo et al, 2014). Perioperative complications have included hemorrhage, lethargy, anemia, anorexia, vomiting, dysphagia, hyperthermia, upper respiratory infection, and acute kidney failure (Djajadiningrat-Laanen et al, 2011; Lo et al, 2014). Hemorrhage was not predicted by tumor type, location, size, or vascular invasion. The cats that have survived the perioperative period have generally normalized and have an excellent long-term prognosis.

Cats with an unresectable mass, metastases, owners who choose not to have surgery on their cat, and cats with adrenal hyperplasia

are managed medically via potassium supplementation and control of the hypertension. Spironolactone is the aldosterone receptor blocker most often employed at a dose of 2 mg/kg of body weight orally b.i.d. to help control the hypokalemia. Doses in excess of 4 mg/kg have been associated with anorexia, vomiting, and diarrhea. Hypertension may be treated with dihydropyridine calcium channel antagonists (e.g., amlodipine) either alone or in combination with a beta-adrenergic blocker or an angiotension-converting enzyme inhibitor (Brown et al, 2007). Cats with bilateral adrenal hyperplasia have more mild increases in PAC and can be maintained on medical therapy for extended time periods, but their prognosis is far more guarded (Djajadiningrat-Laanen et al, 2011; Harvey and Refsal, 2012; Lo et al, 2014).

## EXCESSIVE SEX HORMONE–SECRETING ADRENAL TUMORS IN CATS

### Background

Adrenocortical tumors have the potential for synthesizing and secreting a variety of steroid products other than cortisol and aldosterone. This physiologic process may be associated with neoplasia-related aberrant biosynthetic pathways and/or enzyme deficiencies. Specific precursors may accumulate due to one of these biosynthetic pathway blockages that would enhance alternative biochemical pathways to be followed, with synthesis of alternate products. Androgen, estrogen, and progestagen-secreting adrenocortical tumors have been diagnosed in people, dogs, and cats. Natural progesterone has a half-life in the blood of only a few minutes and serves as a precursor for androgens, estrogens, mineralocorticoids, and glucocorticoids in many mammals. Progesterone binds to albumin as well as cortisol-binding and sex-hormone-binding proteins. Theoretically, chronic excesses in progesterone results in excess "free" cortisol via their ability to competitively bind to cortisol-binding proteins in the circulation, simulating the actions of glucocorticoids. These physiologic processes, including insulin resistance, have been demonstrated in people, dogs, and cats (Selman et al, 1994; 1996; Syme et al, 2001). It has been suggested that adrenal tumors that synthesize steroids other than cortisol are usually carcinomas (Melian, 2012).

### Clinical Features

#### *Signalment and Signs*

A relatively limited number of cats with increased secretion of progestagens or other sex hormones from adrenal gland tumors has been described (Boord and Griffin, 1999; Rossmeisl et al, 2000; Boag et al, 2004; DeClue et al, 2005; Millard et al, 2009; Blois et al, 2010; Meler et al, 2011). Some cats have had excesses in progestagens with typical signs of FCS. A few cats have had increased androgen concentrations (Rossmeisl et al, 2000; Boag et al, 2004; Millard et al, 2009). A cat with androgen excess may have facial enlargement, typical male territorial urine spraying behavior, produce urine with an unusually strong odor, and act aggressively. A castrated male cat developed penile spines (Millard et al, 2009).

Cats with excess progestagens are most likely to have clinical signs of FCS. To summarize, owners may be concerned about nonpruritic, progressive, symmetric alopecia; greasy and unkempt hair; or thin, easily bruised, fragile skin (see Fig. 11-3). Some owners may be concerned about their cat's diabetes mellitus or be frustrated with the difficulty in controlling the diabetes. Other owners have observed weakness, sudden blindness or changes in eye color (hypertension), polyphagia, unusual behavior, PU/PD, or abdominal distension.

#### *In-Hospital Testing*

The veterinarian, when learning any of these owner concerns or in attempting to treat a cat for diabetes or hypertension, for example, will attempt to find an explanation by conducting a logical, practical, and cost effective approach. This often begins with "routine" blood and urine testing. Other than persistent hyperglycemia and glycosuria in some cats, CBC or serum biochemistry abnormalities are not common in cats with sex-hormone-secreting adrenocortical tumors. Imaging studies are the next tests utilized. Thoracic radiographs as a health screen usually follow abdominal ultrasound. Ultrasound is preferred over radiographs because the concerns established for these cats involve potential pancreatic or adrenal abnormalities. Ultrasound is superior in evaluating these structures. Virtually every cat diagnosed with an adrenocortical tumor has had an adrenal mass visualized on abdominal ultrasonography. Once such a mass is identified, the logical next step is to rule out metastatic disease. The ultrasound examination should have included thorough evaluation of the area around the suspected mass for vascular or tissue invasion and the liver for possible spread. The lungs should be screened as well via radiographs. This allows thorough evaluation of the thorax for suspected or unsuspected issues. Assuming that an owner wishes to proceed and, ideally, if no evidence of metastasis is seen, hormone testing should be considered.

Most cats with a progestagen or androgen producing adrenal tumor have had low-normal or low basal and post-ACTHST plasma cortisol concentrations. Similar results have been noted for LDDST and UC:CR. Thus, if a cat appears to have FCS but does not have the expected abnormalities on screening test results, consideration of a sex hormone disorder is reasonable. Hormone concentrations that may be increased include 17α-hydroxyprogesterone, progesterone, estradiol, testosterone, and/or androstenedione (Melian, 2012). Most cats with a sex-hormone secreting adrenocortical tumor have had excessive basal concentrations of the hormone. Thus, for these adrenal tumors, basal hormone evaluations appear indicative of the underlying physiologic abnormalities. This should negate need for ACTHST. However, the test is recommended to further substantiate one of these unusual diagnoses (Millard et al, 2009; Melian, 2012).

### Treatment and Prognosis

Surgical or laparoscopic removal of an adrenocortical tumor is the treatment of choice. Readers are encouraged to review that section earlier in the chapter regarding perioperative and long-term care. Whenever a cat has clinical evidence of FCS, preoperative treatment with trilostane may reduce morbidity and mortality. Readers are encouraged to review the sections on trilostane earlier in this chapter. Prognosis depends on presence of metastasis, successful removal of the tumor, how stable the cat is prior to treatment, and a myriad of other factors.

One male cat in our series was treated with aminoglutethimide (AGT; a drug we no longer recommend) for about 6 weeks in preparation for surgery. The cat did clinically improve dramatically with resolution of its thin fragile skin and diabetes mellitus. As the cat improved, it also developed dramatic mammary gland enlargement likely due to rapid decrease in plasma progesterone concentrations that stimulated, in turn, synthesis and secretion of prolactin. After AGT was discontinued, our surgeons were able to successfully remove the adrenal tumor. Successful surgery has also been reported in several other cats (Boord and Griffin, 1999).

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