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# Feline Acromegaly

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Feline acromegaly is a disease characterized by excessive growth hormone (GH) secretion, leading to a wide array of clinical signs caused by the hormone's effects on multiple organ systems. These effects can be divided into two major classes: catabolic and anabolic. The catabolic actions of growth hormone include insulin antagonism and lipolysis, with the net effect of promoting hyperglycemia. The slow anabolic (or hypertrophic) effects of growth hormone are mediated by insulin-like growth factors. The regulation of GH secretion is illustrated in Figure 1.

Growth hormone stimulates the production of insulin-like growth factors in several tissues throughout the body. Insulin-like growth factor-1 (IGF-1), which is produced in the liver, is thought to be the key factor that facilitates the anabolic effects of growth hormone that are responsible for the characteristic appearance of people, dogs, and cats with acromegaly. Similar to its etiology in people, acromegaly in cats is the result of a functional adenoma of the pituitary gland that releases excessive growth hormone despite negative feedback.

## Signalment

Feline acromegaly is an uncommon disease, although it is thought to be underdiagnosed. It most commonly affects middle-aged and older, male castrated cats. In one study, 13 of 14 cats with acromegaly were males, with an average age of 10.2 years. This association may be biased, however, as most cats in which acromegaly is diagnosed are presented for complications associated with diabetes mellitus, which is also common in older male castrated cats. Based on available data, no known breed association for feline acromegaly exists.

## Clinical signs

Cats with acromegaly are commonly presented for insulin-resistant diabetes mellitus (insulin doses dependent on insulin type) with concurrent weight gain rather than weight loss. Other clinical signs vary because of the wide range of effects the disease has on the body. Physical changes associated with feline acromegaly include increased body weight, a broadened face (Figure 2), enlarged feet, protrusion of the mandible (prognathia inferior), increased interdental spacing (Figure 3), organomegaly, and a poor coat.

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Respiratory disease may result from excessive growth of the soft palate and laryngeal tissues, leading to stertorous breathing and even upper airway obstruction. Cardiovascular signs include the presence of a heart murmur, hypertension, arrhythmia, and congestive heart failure associated with hypertrophic cardiomyopathy.

Neurologic disease associated with feline acromegaly is uncommon but can occur with large pituitary adenomas. Neurologic signs that have been observed with acromegaly include dullness, lethargy, abnormal behavior, circling, and blindness. Glomerulopathy and secondary renal failure have also been associated with feline acromegaly. Because of an associated degenerative arthropathy (Figures 4 and 5) and peripheral (diabetic) neuropathy, lameness has also been noted in cats with acromegaly.

## Diagnosis

No single test for the diagnosis of feline acromegaly exists. Diagnosing feline acromegaly starts with a clinical suspicion based on a thorough history, signalment, and clinical signs. Many of the abnormalities noted in the complete blood counts, serum chemistry profiles, and urinalyses of affected cats reflect concurrent diabetes mellitus, which stresses the need to carefully evaluate a patient's clinical history.

Common abnormalities associated with diabetes mellitus include hyperglycemia, increased liver enzyme activities (alanine transaminase, alkaline phosphatase), hypercholesterolemia, glucosuria, and isosthenuria. Additionally, since many cats with acromegaly are presented for evaluation of uncontrolled diabetes mellitus, azotemia and ketonuria are also common. Other common findings include erythrocytosis due to anabolic effects of growth hormone and IGF-1 and proteinuria secondary to glomerulonephropathy. Unexplained hyperphosphatemia and hyperglobulinemia have also been noted.

### Growth hormone assay

Serum growth hormone is often measured to help diagnose acromegaly in people; however, assays specific for feline growth hormone are not widely available. An assay using ovine growth hormone as the antigen has been validated for use in cats, but it is only available in Europe.

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Even if an assay were available, growth hormone concentrations alone may not be a reliable diagnostic test for acromegaly since growth hormone production is cyclic and concentrations may vary throughout the day. Relying on a single growth hormone measurement can be misleading.

Additionally, it has been shown that growth hormone concentrations may be elevated in diabetic cats that do not have acromegaly. This elevation may be due to the fact that the liver requires high levels of portal insulin to produce IGF-1 and in uncontrolled diabetics portal insulin concentrations may remain low, resulting in decreased IGF-1 production and, theoretically, decreased inhibition of growth hormone release.

Finally, growth hormone concentrations may not be elevated early in the course of the disease but may increase significantly later.

**Serum IGF-1**

Serum IGF-1 measurement is the most commonly used diagnostic test for feline acromegaly and is readily available in the United States. Unlike growth hormone, IGF-1 concentrations are less likely to fluctuate over the course of the day since most IGF-1 is protein-bound, giving it a longer half-life in the body. In addition, IGF-1 concentrations increase in response to chronically elevated growth hormone concentrations and are thought to be a reflection of growth hormone concentrations over the last 24 hours.

A recent study evaluating IGF-1 concentrations in confirmed acromegalic diabetic cats, diabetic cats, and healthy cats found that acromegalic diabetic cats had significantly higher IGF-1 concentrations than diabetic and nondiabetic cats. This study concluded that serum IGF -1 concentration measurement is 84% sensitive and 92% specific for diagnosing feline acromegaly.

Just as with growth hormone, elevations in IGF-1 concentration alone may not definitively diagnose acromegaly in a cat. One study found that IGF-1 concentrations in nonacromegalic diabetic cats receiving long-term insulin treatment (> 14 months) had higher concentrations of IGF-1 than nondiabetic cats. It was proposed that insulin treatment allowed for beta cell regeneration and increased portal insulin, leading to elevations in IGF-1 concentrations.

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In addition, another study revealed that untreated diabetic cats with acromegaly can have low to normal IGF-1 concentrations that increase after starting insulin therapy. The results of this study indicate that retesting IGF-1 concentrations a few weeks after starting insulin therapy or even after increasing insulin dosages in patients with suspected acromegaly that had low or normal IGF-1 concentrations may be warranted.

### Diagnostic imaging

Advanced imaging is needed to document the presence of a pituitary adenoma. Computed tomography and magnetic resonance imaging (MRI) are both useful for identifying pituitary masses. However, MRI is thought to be the more sensitive imaging modality. (See Figures 6 and 7).

The presence of a pituitary tumor alone is not diagnostic for feline acromegaly since other functional tumors of the pituitary gland, such as ACTH-producing tumors in patients with Cushing's disease, may also result in insulin-resistant diabetes. Conversely, the absence of a pituitary mass does not rule out acromegaly since a case has been reported in which a patient had negative MRI results but a pituitary mass was identified at necropsy and histopathology results confirmed feline acromegaly.

### Adrenocortical testing

As stated earlier, a common presenting complaint for patients with acromegaly is insulin resistance with weight gain. Although rare, hyperadrenocorticism can be mistaken for feline acromegaly since both of these diseases can be associated with insulin-resistant diabetes mellitus (and associated clinical signs), a pituitary mass, and bilateral adrenomegaly. As such, hyperadrenocorticism is an important differential diagnosis to keep in mind should diagnostic testing for feline acromegaly produce vague or unequivocal results.

## Treatment

### Medical treatment

Medical options for the treatment of acromegaly range from increasing a patient's insulin dosage to manage the diabetogenic effects of acromegaly to instituting somatostatin analogue, dopamine agonist, or growth hormone receptor antagonist therapy. Several of these treatments are common in human medicine but have not been studied widely in veterinary medicine.

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**Somatostatin analogues**

Somatostatin is a hypothalamic hormone that acts on the pituitary gland to inhibit growth hormone release. Somatostatin analogues are commonly administered in people with acromegaly and have efficacy rates of 50% to 60%. In addition to acting centrally by suppressing growth hormone release and peripherally by interfering with growth hormone receptor binding on hepatocytes, somatostatin analogues are also thought to result in tumor shrinkage of pituitary adenomas by promoting apoptosis.

The somatostatin analogue octreotide has been evaluated in a few cats with acromegaly with limited success. In a study of four cats with acromegaly, no change in serum growth hormone concentration was noted after treatment with octreotide. Another study, which measured the short-term effects of octreotide in five cats with acromegaly, found a decrease in growth hormone concentrations for up to 90 minutes after octreotide administration. However, a recent study evaluating a long-acting somatostatin analogue (Sandostatin LAR Depot—Novartis) showed no benefit in cats treated for three to six months.

The failure of these drugs to inhibit growth hormone release may be related to differences in somatostatin receptor subtypes found on pituitary adenomas. Future studies to identify the somatostatin receptor subtypes in feline growth hormone-secreting pituitary tumors are required to determine if these subtypes are similar to the ones found in people and if human somatostatin analogue therapy, at least in theory, may be beneficial in cats with acromegaly.

**Dopamine agonists and growth hormone receptor antagonists**

Dopamine agonists and, more recently, growth hormone receptor antagonists are also given to people to treat acromegaly. Growth hormone receptor antagonist therapy has not been reported in cats, but in people, response rates have been reported to be as high as 90%. However, it has been noted that these medications have no effect on tumor size (do not result in tumor shrinkage) and, thus, would not benefit patients with neurologic signs.

A single case study on the treatment of feline acromegaly with a dopamine agonist (L-deprenyl) showed that the medication had no effect on reducing insulin requirements or clinical signs of disease. In people, dopamine agonists are typically only 10% to 20% effective but are often combined with other medications.[1]

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### Increasing insulin dose

Increasing the dosage of insulin to improve glycemic control and clinical signs of diabetes is the most conservative—and most common—method for treating insulin-resistant diabetic acromegalic cats. While helping to control the clinical signs of the diabetes, raising the insulin dose has no effect on GH secretion, progression of the clinical signs of acromegaly and continued growth of the pituitary tumor.

Some patients treated with high doses of insulin unpredictably and inexplicably become sensitized to the effect of the insulin, resulting in hypoglycemic crises. The timing of the insulin sensitization and occurrence of hypoglycemic episodes was extremely variable. In one study, several acromegalic cats were euthanized after experiencing hypoglycemic comas.

### Surgical treatment

Surgically removing the pituitary tumor (adenectomy) is the treatment of choice in people with acromegaly. The procedure can be performed in cats and dogs but typically results in the complete removal the pituitary gland (hypophysectomy). Complications associated with the surgery include hemorrhage and incision dehiscence. After surgery, patients require treatment with cortisone, L-thyroxine, +/- desmopressin to compensate of the loss of pituitary function. Because of this only patients that are easily medicated should be considered for this procedure.

Few case reports exist for the treatment of feline acromegaly with transsphenoidal hypophysectomy. In one case, a patient was receiving 25 U of insulin detemir (Levemir—Novo Nordisk) four times a day before surgery, and three weeks after surgery, the patient no longer required insulin therapy. Up to one year later, the patient's insulin-like-growth factor-1 (IGF-1) and growth hormone concentrations remained normal.

In a case we treated at VCA West Los Angeles Animal Hospital, a 13-year-old castrated male domestic shorthaired cat with acromegaly underwent transsphenoidal hypophysectomy. The patient had a history of insulin-resistant diabetes mellitus and was receiving 15 U of glargine insulin every 12 hours. The patient's diabetes mellitus resolved two weeks after the surgery and remained in remission for eight months, at which time the cat was euthanized for an unrelated issue. Availability of this procedure is limited in the United States.

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## Radiation

Radiation therapy is another option for the treatment of feline acromegaly, especially if the tumor is inoperable, or surgical treatment is not available in the area. In human medicine, radiation therapy is regarded as a second-line treatment since beneficial effects may take years to develop and patients typically experience undesired late-term central nervous system radiation effects.

Most studies that have been performed in veterinary medicine focus on radiation treatment of pituitary masses regardless of functional status. There is no standard treatment protocol for pituitary masses, and varying methods have been used including both single- and multiple-dose fractions, administering total doses from 1,500 to 4,500 cGY. Most of the cats included in these studies had insulin-resistant diabetes (suspected acromegaly or Cushing's disease) or neurologic signs.

Radiation therapy has been shown to be successful in improving both insulin resistance and neurologic signs. Neurologic improvement was generally seen within weeks to months. Improved insulin response was seen within the first month; however, most patients still required insulin therapy. In cases in which repeat imaging was available, a decrease in tumor size was also noted.

Disadvantages of radiation therapy are the early and delayed effects of radiation, repeated anesthesia, and expense. Early effects from radiation therapy include hair loss, skin pigmentation, and otitis externa.  Reported late-term side effects include brain necrosis, tumor regrowth, loss of vision, and hearing impairment.

In one study, 12 cats with pituitary tumors were treated with a coarse fractionated radiation protocol, delivering a total dose of 37 Gy in five once-weekly doses. Eight of these cats had insulin-resistant diabetes mellitus secondary to acromegaly. After radiation therapy, 5/8 cats no longer required insulin therapy, two became stable diabetics, and one required less insulin. In addition, three of four cats had improved neurologic signs. The mean survival time of cats in this study was about 18 months.

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In another study, 14 cats with confirmed acromegaly and insulin-resistant diabetes mellitus were treated with a total dose of 3,700 cGy divided into 10 fractions (three a week). Thirteen of the 14 cats had improved insulin responses, with an average insulin dosage reduction of about 75%. Six of the cats went into complete diabetic remission, and three of the six remained in remission at the time of this writing. The median survival time of cats in this study was 28 months.

## Conclusion

Many options exist for treating feline acromegaly. However, clinical studies on their long-term safety and efficacy are limited and often lack controls. Until more work is done evaluating medical treatments such as somatostatin analogues and growth hormone antagonists, most patients are best treated with radiation therapy or surgery to control growth hormone concentrations and neurologic signs, or increased insulin doses to improve glycemic control. When making your recommendation regarding treatment, be sure to consider the patient's clinical status (stable diabetic, no significant co-existing diseases, good candidate for anesthesia), the availability of treatments in your area, and the advantages and disadvantages of each treatment modality.

## Keep acromegaly top of mind

Feline acromegaly is likely an underdiagnosed disease in older male cats, especially in ones with insulin-resistant diabetes. A recent study in the United Kingdom measured IGF-1 concentrations in variably controlled diabetic cats. Of the 184 cases, 59 (32%) had markedly increased IGF-1 concentrations. Eighteen of these 59 cats underwent pituitary imaging, confirming a diagnosis of acromegaly in 17/18 (94%). This study illustrates the importance of ensuring that we remain aware of feline acromegaly so that we may more consistently diagnose and treat these patients.■

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**Figure Legends**

Figure 1: Schematic Representation of the Regulation of GH Release

Figures 2 and 3: A cat affected with acromegaly showing the pronounced enlargement of the skull and widening of the interdental spaces.

Figures 4 and 5: Radiographs showing the marked thickening of the calvarium (Fig 4) and presence of significant degenerative joint disease with osteophyte production (Fig 5).

Figures 6 and 7: Axial (Fig 6) and sagittal (Fig 7) post contract T1 – weighted images revealing a large contrast enhancing sellar mass consistent with a pituitary adenoma, in a cat with insulin resistant diabetes and a markedly elevated IGF-1 concentration.

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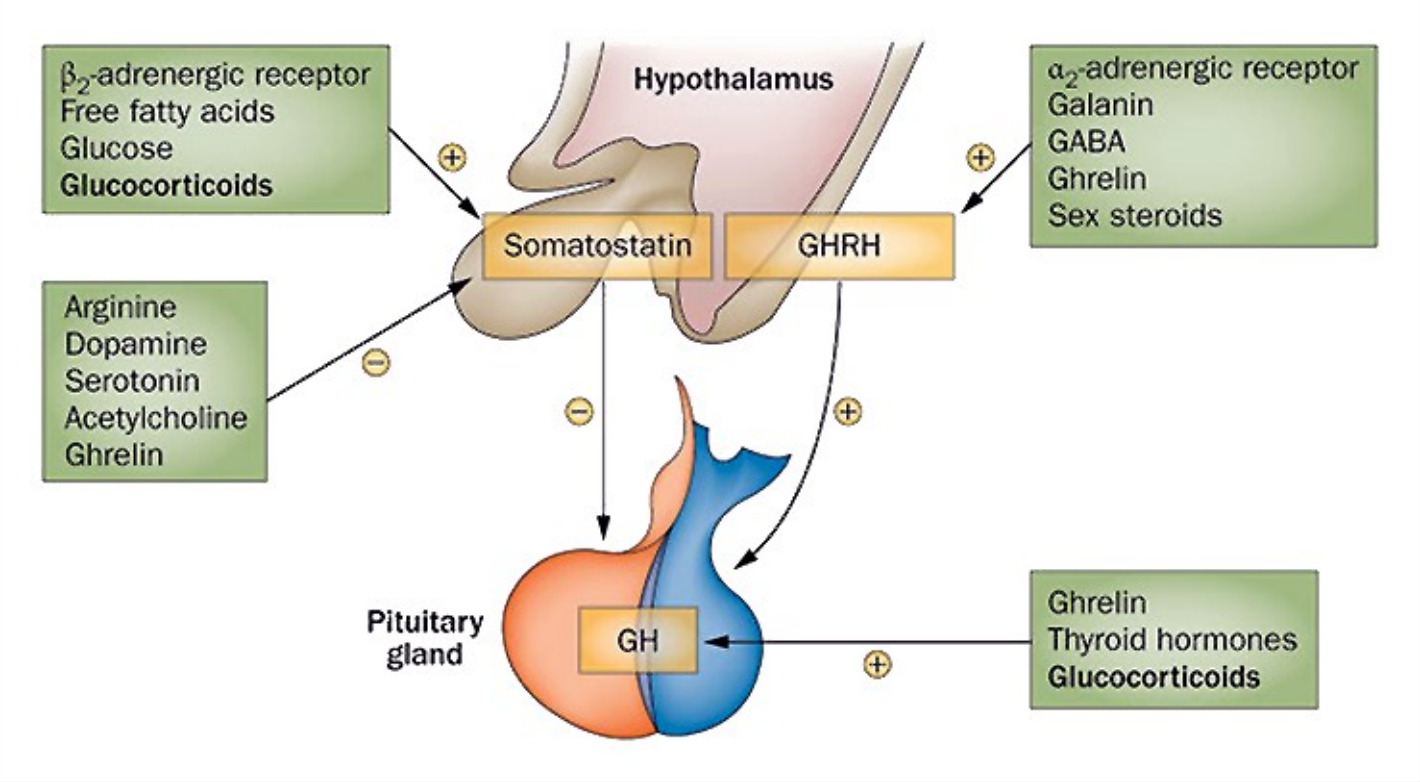


Figure 1.

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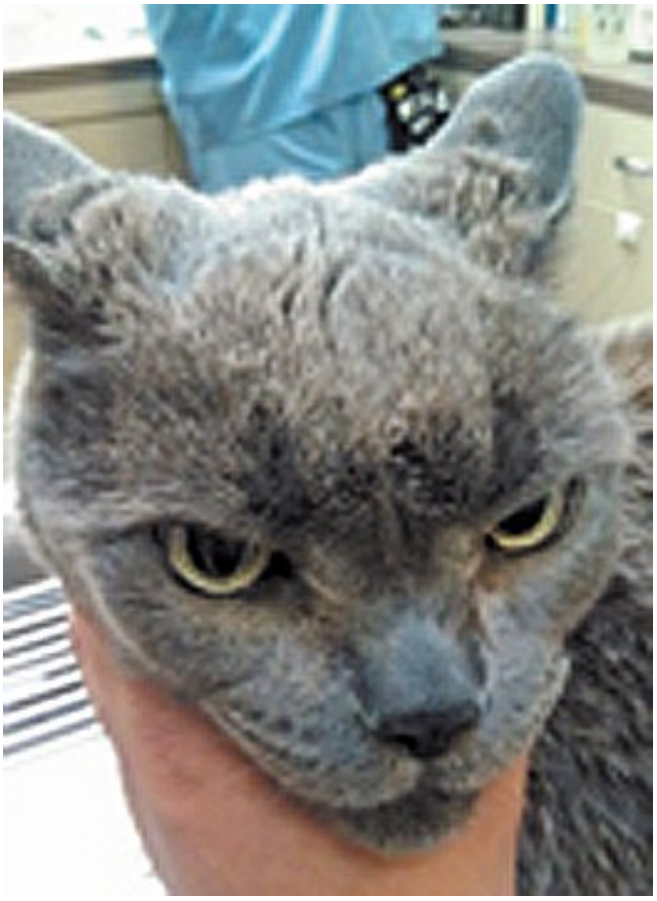

Figure 2.

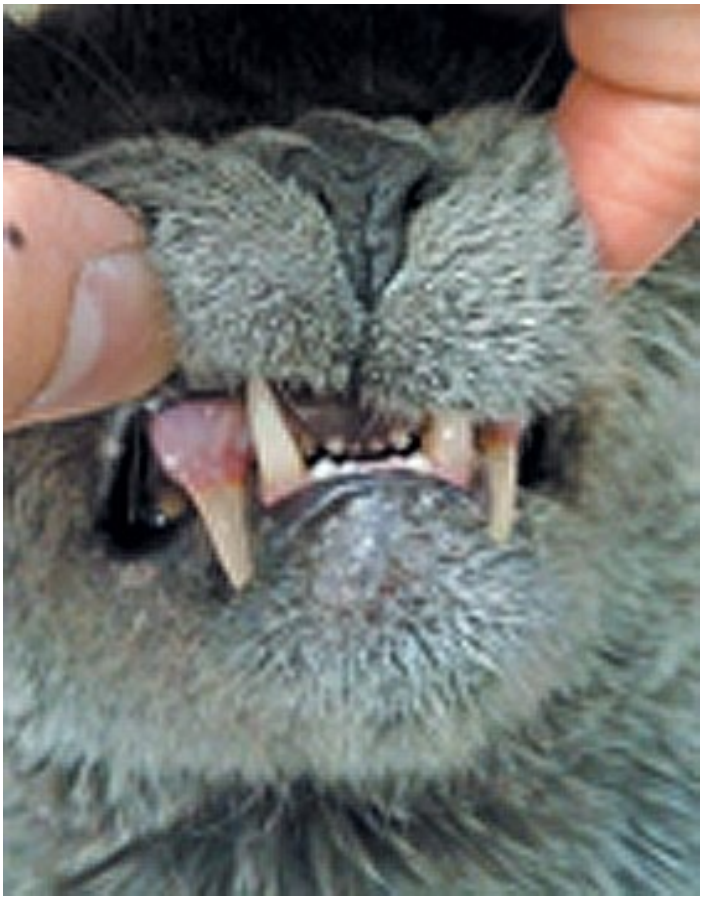

Figure 3.

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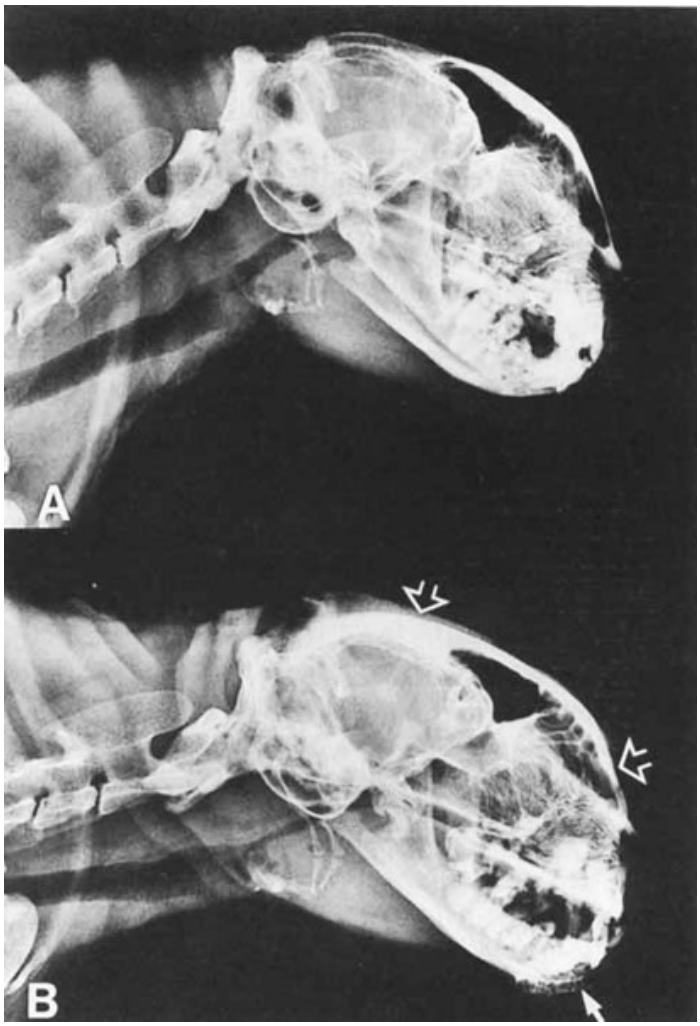


Figure 4.

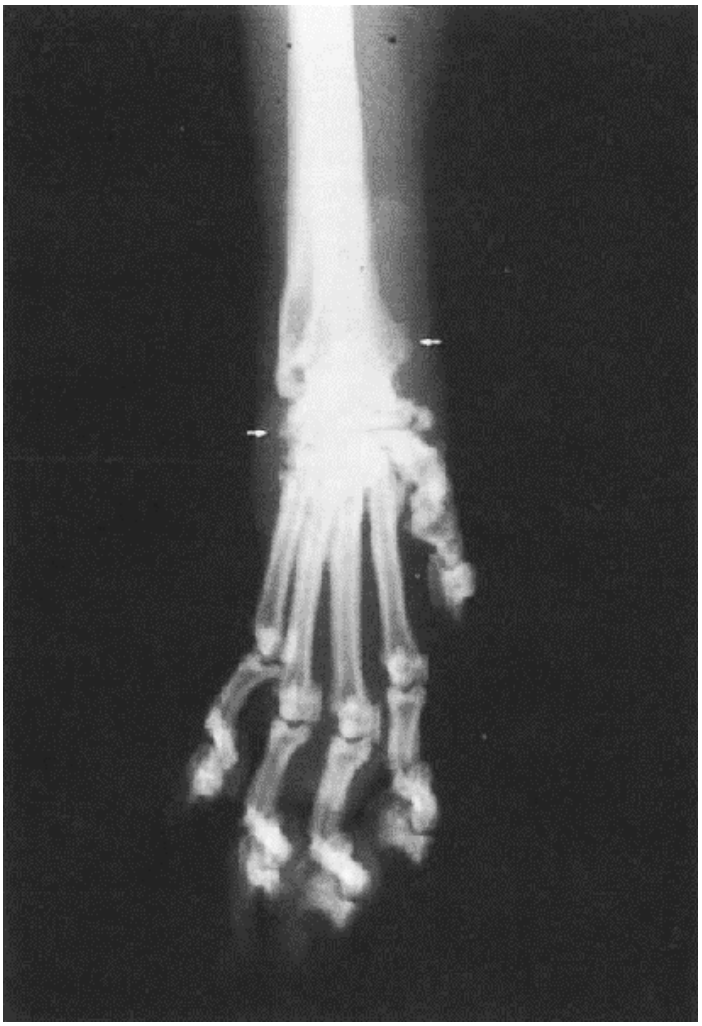

Figure 5.

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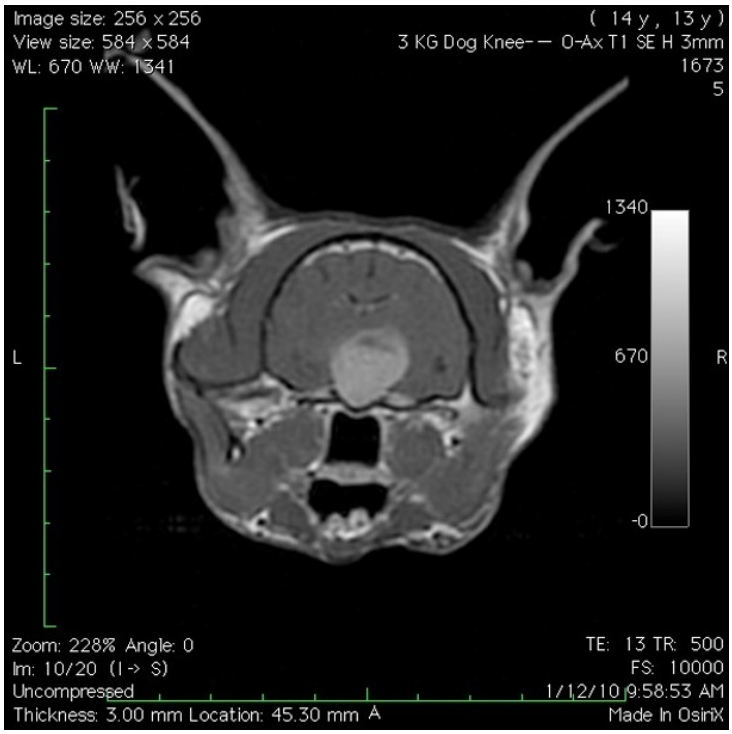


Figure 6.

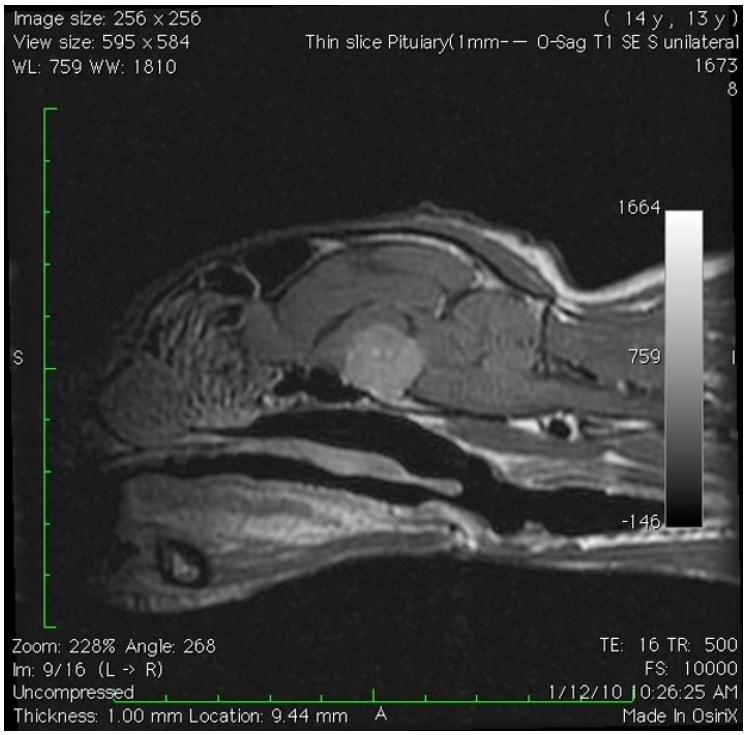


Figure 7.

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Dr. Bruyette received his Doctor of Veterinary Medicine degree from the University of Missouri in 1984. He completed an internship at Purdue University and a residency program in internal medicine at the University of California Davis. He was a staff internist at the West Los Angeles Veterinary Medical Group, as well as a member of the Department of Comparative Medicine at Stanford University, an Assistant Professor and Head of Internal Medicine at Kansas State University, and Director of the Analytical Chemistry Laboratory at Kansas State.

In addition to his duties as Medical Director, Dr. Bruyette practices internal medicine and specializes in the hormonal system and its diseases. His interests also include adrenal disease, diabetes and thyroid disorders. Dr. Bruyette joined VCA West Los Angeles Animal Hospital in 1996.