

# Endocrinology

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A COMPENDIUM OF LEADING ARTICLES IN THE FIELD OF VETERINARY ENDOCRINOLOGY SELECTED FOR THE VETERINARY PRACTITIONER

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## Ghrelin-Stimulation Test for Pituitary Dwarfism

*Bhatti SFM, De Vliegher SP, Mol JA, et al. Ghrelin-stimulation test in the diagnosis of canine pituitary dwarfism. Res Vet Sci 2006;81:24-30.*

### \* INTRODUCTION:

**Background:** The secretion of growth hormone (GH) is stimulated by sleep, high protein diet, exercise, and hypoglycemia, among some other causes. A potent stimulus for GH release is a peptide from the stomach wall, ghrelin. In young dogs, ghrelin is more potent in stimulating GH release than is GH releasing hormone. In humans, ghrelin also stimulates the secretion of prolactin, adrenocorticotrophic hormone (ACTH), and cortisol.

The most common cause of pituitary dwarfism in dogs is from a recessive autosomal trait in German shepherd dogs and Karelian bear dogs. The utility of ghrelin stimulation of GH secretion as a diagnostic test for canine pituitary dwarfism is unknown.

**Objectives:** The purpose of this study was to investigate the value of ghrelin in diagnosing canine pituitary dwarfism.

### ▲ SUMMARY:

**Methods:** Six German shepherd dogs from different litters with pituitary dwarfism and eight normal beagle dogs of similar age to the dwarfs were administered human ghrelin intravenously at 2 µg/kg. Blood samples for GH, ACTH, cortisol, thyroid-stimulating hormone (TSH), luteinizing hormone (LH), and prolactin determinations were collected at 15 minutes prior to — and 0, 5, 10, 20, 30, and 45 minutes after — ghrelin administration. Plasma for insulin-like growth factor-1

(IGF-1) was also collected at 15 minutes before and at the time of ghrelin administration.

**Results:** The mean basal plasma concentrations of GH, IGF-1, ACTH, and cortisol were not significantly different between dogs with pituitary dwarfism and the normal dogs. Mean basal plasma concentrations of TSH and prolactin were significantly lower in dogs with pituitary dwarfism compared to normal dogs. Mean plasma concentration of LH in pituitary dwarfs was significantly higher than in normal dogs.

Ghrelin-stimulated plasma GH concentrations were significantly lower in pituitary dwarfs than in normal dogs. No pituitary dwarf had post-ghrelin plasma GH concentration of more than 5 µg/l, and neither did three normal dogs. Ghrelin administration did not affect plasma ACTH, cortisol, TSH, LH, and prolactin concentrations. The intravenous administration of ghrelin did not cause adverse effects.

**Conclusions:** Ghrelin is an effective stimulus for GH secretion in most normal dogs, but pituitary dwarf dogs have a significantly lower GH response to ghrelin (5 µg/l, or less).

### ◆ CLINICAL IMPACT:

The response to ghrelin in dogs is similar to that from α-adrenergic drugs, clonidine and xylazine, without the adrenergic drug risks of

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A response in post-ghrelin GH concentration in excess of 5 µg/l rules out pituitary dwarfism.

- ▶ Ghrelin-stimulation tests do not fully differentiate between normal dogs and those with pituitary dwarfism. *Res Vet Sci* 2006;81:24-30.
- ▶ Acromegaly from a somatotroph adenoma has been reported in a dog. *Dom An Endocrinol* 2007;32:43-54.
- ▶ Pituitary tumor irradiation in cats can be effective primary therapy for associated neurologic signs, hyperadrenocorticism, or acromegaly. *J Vet Intern Med* 2006;20:1151-1154.
- ▶ High doses of aspirin, but not deracoxib, can suppress serum thyroid hormone concentrations. *Am J Vet Res* 2006;67:599-603.
- ▶ Lymphocytic-plasmacytic thyroiditis associated with glomerulonephritis has been reported in a dog. *J Sm Anim Pract* 2006;47:396-399.
- ▶ Oral administration of calcitriol (2.5 ng/kg/day or 8.75 ng/kg/3.5 days) for two weeks does not significantly alter serum parathyroid hormone concentration in cats with chronic renal failure. *J Vet Intern Med* 2006;20:1307-1313.
- ▶ Measurement of fractions of serum fructosamine has no diagnostic advantage over the measurement of total serum fructosamine concentration. *Vet Clin Pathol* 2006;35:307-310.
- ▶ Transient pregnancy-related diabetes mellitus in dogs can result in ketosis. *N Zealand Vet J* 2006;54:360-364.
- ▶ Gastrinomas can be the cause for chronic gastrointestinal ulceration in cats. *J Vet Intern Med* 2006;20:1245-1247.
- ▶ Omeprazole may be helpful in the medical management of canine gastrinoma. *N Zealand Vet J* 2006;54:242-247.
- ▶ Dogs that demonstrate signs of pain or anxiety prior to diagnostic imaging positioning should be induced to a deep level of anesthesia. *Vet Rec* 2006;159:749.
- ▶ ACTH-stimulated serum cortisol and progesterone concentrations are not affected by ovariectomy in cats. *Theriogenol* 2006;66:1482-1487.
- ▶ Persistent hypokalemia is a cardinal sign of primary hyperaldosteronism. *J Vet Med A* 2006;53:467-470.
- ▶ Trilostane inhibits adrenocortical  $3\beta$ -hydroxysteroid dehydrogenase,  $11\beta$ -hydroxylase, and  $11\beta$ -hydroxysteroid dehydrogenase. *Dom Anim Endocrinol* 2006;31:63-75.
- ▶ Mitotane administration has been proposed as a cause of acute hepatopathy. *J Am Anim Hosp Assoc* 2006;42:298-301.
- ▶ Physical exercise from jogging is not detrimental to dogs with primary hypoadrenocorticism that are on standard hormone replacement therapy. *Wien Tierarztl Mschr* 2006;93:29-31.
- ▶ One intramuscular injection of triamcinolone acetonide suppresses adrenocortical responsiveness to ACTH for at least four weeks. *J Endocrinol* 2006;191:491-496.
- ▶ Inhaled corticosteroids may be as effective as systemically administered corticosteroids for the management of chronic bronchitis and eosinophilic bronchopneumonitis and have fewer adverse effects. *J Sm Anim Pract* 2006;47:377-382.
- ▶ Methylprednisolone acetate administration causes a shift of intracellular water to the extracellular space and could precipitate or exacerbate congestive heart failure in predisposed cats. *Am J Vet Res* 2006;67:583-587.
- ▶ Androgen receptors are expressed in perianal gland hyperplasia and adenomas which may initiate or maintain tumor growth. *Res Vet Sci* 2006;81:231-236.

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sedation, bradycardia, hypotension, and collapse. Decreased secretion of TSH and prolactin in pituitary dwarfs is logical since the loss of tropic cells from pressure (enlarging pituitary cysts) usually first affects somatotropes and lactotropes followed by thyrotropes.

The finding of increased basal plasma LH in dwarfs was not expected, nor explained. Gonadotropes are typically depleted early by expanding pituitary cysts and prevent puberty from occurring in pituitary dwarfs. The losses of TSH and ACTH are later developments.

Ghrelin can be used for the diagnosis of GH deficiency in pituitary dwarf suspects. A response in post-ghrelin GH concentration in excess of 5  $\mu\text{g/l}$  rules out pituitary dwarfism. A ghrelin response of 5  $\mu\text{g/l}$ , or less, of GH is compatible with pituitary dwarfism, but it is not diagnostic in itself as some normal dogs will not produce more than 5  $\mu\text{g/l}$  on occasion. However, ghrelin cannot effectively treat pituitary dwarfism. Effective treatment will have to wait until canine GH for injection is available in the future. Most canine pituitary dwarfs must also be treated for secondary hypothyroidism and some must be treated for secondary hypoadrenocorticism.



## Canine Acromegaly from Somatotroph Adenoma

*Fracassi F, Gandini G, Diana A, et al. Acromegaly due to somatotroph adenoma in a dog. Dom An Endocrinol 2007;32:43-54.*

### \* INTRODUCTION:

**Background:** Excessive growth hormone (GH) secretion in dogs with acromegaly primarily results from GH secretion from mammary glands under the influence of high levels of endogenous progesterone or administration of exogenous progestins. Pituitary adenoma secreting GH is the underlying cause of acromegaly in cats and humans, but has not been well documented in the dog.

**Objectives:** The purpose of this report was to describe the clinical, endocrine, and pathological findings in a dog with acromegaly secondary to a pituitary adenoma.

### ▲ SUMMARY:

**Case Report:** A 10-year-old, neutered male, Dalmatian was evaluated for progressive stiffness, difficulty standing, and a rigid neck without apparent pain. Polyuria, polydipsia, excessive panting, and weight gain were noted, as well as a three year history of progressive thickening of the skin and tongue enlargement. Inspiratory stridor, thick, redundant skin, macroglossia, enlarged head, widened interdental spaces, and a stiff gait were present on physical examination. Hypercholesterolemia and mild elevations of serum fructosamine concentration and creatine kinase activity were the only significant findings on routine laboratory tests. Thyroid function tests, including serum  $T_4$  and TSH concentrations were normal. Impaired glucose tolerance was demonstrated by finding elevated insulin during an intravenous glucose tolerance test. Severe spondylosis deformans was present from the cervical to lumbar vertebrae. An

**An acidophil adenoma of the pituitary gland was identified on histopathology, and immunocytochemistry confirmed that it contained GH.**

enlarged pituitary gland was found on computerized tomography (CT) images. Basal serum GH concentration was increased and failed to suppress as would normally occur after administration of glucose or somatostatin. A marked elevation of serum insulin-like growth factor-1 (IGF-1) was also noted. Treatment was not instituted, and the dog was euthanized three months later because of progressive worsening of clinical signs. An acidophil adenoma of the pituitary gland was identified on histopathology, and immunocytochemistry confirmed that it contained GH.

**Conclusions:** This is the first case of acromegaly due to a pituitary adenoma in the dog where excessive GH secretion has been documented.

### ◆ CLINICAL IMPACT:

The historical and physical examination findings in this dog were highly suggestive of acromegaly. The diagnosis can be confirmed by the presence of elevated GH and IGF-1, but the source of GH must be determined in each case. A history of progestin administration or an intact female dog in diestrus should lead to a diagnosis of progestin-induced acromegaly. Imaging using CT or magnetic resonance to identify a pituitary tumor should be considered in male or spayed female dogs without a history of progestin administration. Treatment of acromegaly due to a pituitary tumor should involve external beam radiation therapy. Use of somatostatin analogs can be useful in humans with acromegaly, but their efficacy in dogs has not been established.



## Outcomes of Pituitary Tumor Irradiation in Cats

Mayer MN, Greco DS, LaRue SM. Outcomes of pituitary tumor irradiation in cats. *J Vet Intern Med* 2006;20:1151-1154.

### \* INTRODUCTION:

**Background:** Acromegaly and most cases of hyperadrenocorticism in cats are caused by pituitary neoplasms. Some of the tumors will be of sufficient size to cause neurologic signs. In patients with neurologic abnormalities or acromegaly, irradiation of the pituitary tumor is the only effective treatment. Few cases of radiation treatment of pituitary tumors in cats have been described.

**Objectives:** This study describes the results of radiation therapy in eight cats with pituitary tumors.

### ▲ SUMMARY:

**Methods:** Retrospective analysis of case records of eight cats with pituitary tumors that underwent treatment with 4,500-5,400 cGy in 370-300 cGy fractions of photons from a linear accelerator was undertaken.

**Results:** One cat had an apparently non-functional tumor, three had acromegaly, and four had hyperadrenocorticism. Neurologic abnormalities were present in all cats with hyperadrenocorticism and in the cat with a nonfunctional tumor. All cats with acromegaly and three with hyperadrenocorticism had diabetes mellitus that was poorly controlled. One cat had a carcinoma confirmed on a pituitary biopsy. Carcinoma was suspected in another based on cytology and characteristics of malignancy on computerized tomography (CT). The median survival time was 523 days, although only three cats died of complications related to their tumor. All cats with diabetes mellitus had an improved response to insulin after pituitary radiation treatment, but still required insulin to control hyperglycemia. One cat had epilation in the treated area and another had mild bilateral otitis

externa. Transient neurologic signs including dullness, ataxia, and hypermetria appeared in one cat eight weeks after treatment, but resolved within two weeks of appearance. One cat developed bilateral cataracts but was still visual 13 months after radiotherapy.

The cat was euthanized because of blindness at 19 months. Another cat had impaired vision 42 months after treatment, but ophthalmic examination failed to reveal a cause. Of two cats with reported hearing loss, one had mild impairment one year after treatment and the other had gradually progressive loss resulting in deafness 34 months after radiotherapy.

Late adverse effects of radiation on the brain may have occurred in two cats. One cat with a pituitary carcinoma had a focal area of brain necrosis adjacent to the tumor on necropsy 252 days after radiotherapy that may have been the result of pressure from the tumor or radiation injury. Another cat had progressive neurologic signs for several weeks before its death at 523 days after treatment. A necropsy was not performed.

**Conclusions:** Radiotherapy is an effective treatment for reducing neurologic signs in cats with pituitary tumors

### ◆ CLINICAL IMPACT:

Similar to other reports of pituitary irradiation in cats with pituitary tumors, the neurologic signs were effectively treated. All diabetic cats continued to require insulin administration. Additional details on improvement in clinical signs attributable to acromegaly or hyperadrenocorticism were not included in the report. In another recent report of pituitary irradiation of cats with acromegaly, over 50% of the diabetic cats did not require ongoing insulin treatment. Although the

studies used a similar source of radiation, the difference in results may be explained by the fact that the protocols differed considerably. The difference in protocols and planning for delivery of radiation might also explain the relatively high incidence of adverse effects noted in the current study. Because no effective medical treatment exists for acromegaly in cats, pituitary irradiation should be considered. However, it is not clear that survival or quality of life was improved in cats with acromegaly.

**Because no effective medical treatment exists for acromegaly in cats, pituitary irradiation should be considered.**



## Deracoxib and Aspirin Effects on Serum Thyroid Hormone Concentrations

*Pancieria DL, Refsal KR, Sennello KA, et al. Effects of deracoxib and aspirin on serum concentrations of thyroxine, 3,5,3'-triiodothyronine, free thyroxine, and thyroid-stimulating hormone in healthy dogs. Am J Vet Res 2006;67:599-603.*

### \* INTRODUCTION:

**Background:** More than 99% of thyroid hormones in circulation are bound to plasma proteins. Failure to bind with plasma proteins or displacement from binding sites lower total thyroid hormone concentrations.

Some nonsteroidal anti-inflammatory drugs (NSAID) affect thyroid function test results, but all do not. Deracoxib is a NSAID which is believed to have strong binding to plasma proteins which could reduce plasma protein binding of  $T_4$  and  $T_3$ .

**Objectives:** The purpose of this study was to assess deracoxib and aspirin effects on the secretion of thyroid hormones and thyroid-stimulating hormone in dogs.

### ▲ SUMMARY:

**Methods:** Twenty-four healthy dogs were randomly and equally assigned to one of three treatment groups. One group received deracoxib tablet vehicle (placebo), per os, every eight hours. Another group received aspirin (23-25 mg/kg) per os, every eight hours. The third group received deracoxib (1.25-1.8 mg/kg) per os, every 24 hours. Determinations of serum  $T_4$ ,  $T_3$ , free  $T_4$  ( $fT_4$ ), and thyroid-stimulating hormone (TSH) concentrations were performed a week before the treatments began, on days 14 and 28 of treatment, and 14 days after completing the treatments. On days -7 and 28, plasma was analyzed for total protein, albumin, and globulin concentrations.

**Results:** In dogs receiving aspirin, mean serum  $T_4$ ,  $T_3$ , and  $fT_4$  concentrations significantly declined by days 14 and 28 of treatment compared to baseline and placebo-treated dogs. Mean plasma protein, albumin,

and globulin concentrations also significantly decreased by day 28 of aspirin treatment. Differences in serum concentrations associated with aspirin administration were eliminated within 14 days of discontinuing aspirin treatment. Serum TSH and  $fT_4$  concentrations were not changed by treatment. Deracoxib administration did not affect any of the thyroid hormone secretion parameters.

**Conclusions:** Aspirin administration suppresses serum thyroid hormone concentrations; dexacoxib does not. Aspirin should be discontinued at least a week prior to evaluating thyroid function.

### ◆ CLINICAL IMPACT:

The dosage of aspirin in this study was above that required for analgesia, antipyrexia, or anti-platelet function. It was in the high range of anti-inflammation. After two weeks on this dosage of aspirin, serum thyroid hormone concentrations were decreased and after four weeks plasma protein concentrations were decreased. Aspirin at this dosage should be discontinued at least a week prior to assessing thyroid function. However, any inflammatory condition requiring this dose of aspirin for at least two weeks will have nonthyroidal sick syndrome effects on thyroid function test results. So, in addition to discontinuing aspirin, the accompanying nonthyroidal inflammatory disorder may have to be corrected too before thyroid function assessment can be done with proper interpretation of the results. Deracoxib may be an NSAID that would permit continued suppression of inflammation while thyroid function is evaluated.

**Deracoxib may be an NSAID that would permit continued suppression of inflammation while thyroid function is evaluated**



## Lymphocytic-Plasmacytic Thyroiditis and Glomerulonephritis

*Mansfield CS, Mooney CT. Lymphocytic-plasmacytic thyroiditis and glomerulonephritis in a boxer. J Sm Anim Pract 2006;47:396-399.*

### \* INTRODUCTION:

**Background:** At least 50% of cases of hypothyroidism in the dog are the result of autoimmune destruction of the thyroid gland. Autoimmune thyroid disease has been reported rarely in humans to be associated with glomerulonephritis including a few cases where thyroglobulin was identified as the antigen in antigen:antibody complexes present in glomeruli. However, most cases are more likely the results of concurrent but independent immune-mediated disorders.

**Objectives:** The aim of this report was to describe a case of autoimmune hypothyroidism in a dog with concurrent glomerulonephritis.

### ▲ SUMMARY:

**Case Report:** An 18-month-old, male, boxer was evaluated for a two-month history of lethargy, weight loss and decreased appetite. The dog was dull, reluctant to stand, in poor body condition, hypothermic, had alopecia over the pinnae, thickened facial skin folds, decreased proprioception on the hind limbs with normal patellar reflexes, and was unilaterally cryptorchid. Mild non-regenerative anemia, hypercholesterolemia, mild azotemia, hypoalbuminemia, proteinuria, and minimal urine concentration were found on routine laboratory testing. Hypothyroidism was confirmed by finding serum T<sub>4</sub> and thyroid-stimulating hormone concentrations below and above, respectively, their reference intervals. Thyroglobulin autoantibodies were also detected in the serum, indicating the presence of autoimmune thyroiditis. The kidneys were hyperechoic and had a poorly defined corticomedullary junction on abdominal ultrasound. Azotemia and proteinuria persisted

after fluid therapy and antibiotic treatment of bacterial cystitis. Treatment with levothyroxine and a diet formulated for dogs with renal disease for two months resulted in normalization of the dog's attitude, improvement in body condition, and hematocrit. The azotemia was improved but not resolved. Proteinuria, hypoalbuminemia, and hypercholesterolemia persisted. An increase in the levothyroxine dosage to 0.03 mg, twice per day, was made based on insufficient post-pill serum T<sub>4</sub> concentration. One year after initial presentation, the dog presented with weakness progressing to collapse, oral ulceration, edema of the limbs, bradycardia, and hypothermia. Azotemia was severe, and proteinuria, anemia, and hypercholesterolemia were also present. The post-pill serum T<sub>4</sub> concentration was slightly lower than optimal. The dog was euthanized and found to have lymphoplasmacytic thyroiditis and chronic membranoproliferative glomerulonephritis.

**Conclusions:** The combination of glomerulonephritis and autoimmune hypothyroidism makes the diagnosis of the diseases more complex. Glomerulonephritis may be a complicating factor of autoimmune thyroid disease.

### ◆ CLINICAL IMPACT:

The relationship between the thyroiditis and glomerulonephritis described in this report is purely speculative, and it seems most likely that they are unrelated diseases. While protein-losing nephropathy has been reported in a few cases in retrospective studies of canine hypothyroidism, the paucity of reports makes a similar pathogenesis unlikely. Perhaps more important in this case report is the high dosage

of levothyroxine administered that ultimately was insufficient to adequately control the hypothyroidism. It is likely that the renal disease resulted in increased loss of free and protein bound thyroxine. The proteins that act as plasma transport proteins for thyroxine, namely thyroxine binding globulin, transthyretin, and albumin, are all small proteins that could be excreted excessively in a dog with protein-losing nephropathy. Consistent monitoring and dosage adjustment should be considered in any hypothyroid dog with concurrent protein-losing enteropathy.

**dosage adjustment should be considered in any hypothyroid dog with concurrent protein-losing enteropathy**



## Comparison of the Effects of Daily and Intermittent-Dose Calcitriol

*Hostutler RA, DiBartola SP, Chew DJ, et al. Comparison of the effects of daily and intermittent-dose calcitriol on serum parathyroid hormone and ionized calcium concentrations in normal cats and cats with chronic renal failure. J Vet Intern Med 2006;20:1307-1313.*

### \* INTRODUCTION:

**Background:** Renal secondary hyperparathyroidism contributes to numerous complications including to renal osteodystrophy, anemia, cardiovascular disease, immunosuppression, and possibly progression of renal disease. Chronic renal failure results in hypocalcemia, hyperphosphatemia, and decreased production of calcitriol, resulting in increased parathyroid hormone (PTH) secretion to maintain a normal plasma calcium concentration. Calcitriol administration has been utilized in humans with chronic kidney disease primarily to reduce bone mineral loss and improve survival by reducing the incidence of cardiovascular complications.

**Objectives:** The purpose of this study was to determine if administration of calcitriol would decrease renal secondary hyperparathyroidism in cats.

### ▲ SUMMARY:

**Methods:** Serum PTH, ionized calcium, and calcitriol concentrations were measured in 10 healthy cats and 10 cats with chronic renal failure before and at the end of treatment with calcitriol at two dosages. Calcitriol was administered to all cats orally at 2.5 ng/kg once daily for 14 days, followed by a seven day washout period without treatment, and then were administered calcitriol at 8.75 ng/kg, every 84 hours. Control of serum phosphorus concentrations was accomplished by feeding a restricted phosphorus diet in three cats, administration of aluminum hydroxide alone to two cats, and aluminum hydroxide in combination with restricted phosphorus diet in four cats. One cat did not require treatment for hyperphosphatemia. Ionized calcium was also measured daily for the first

three days of each treatment to ensure hypercalcemia did not occur.

**Results:** There was no progression of renal failure in any cat in the study. The range of serum creatinine concentrations in the renal failure group was 2.2 to 3.9 mg/dl while the mean serum phosphorus concentration was 4.5 mg/dl in cats with renal failure. Serum PTH was significantly higher in cats with renal failure than in healthy cats when all data points were combined, but not at individual time points. There was no difference in serum PTH concentration at either calcitriol dosage when renal failure and control groups were compared or when pretreatment and post-treatment concentrations were compared within the renal failure group. No significant difference was noted in ionized calcium concentrations between or within groups at any time period. Similarly, no differences were noted at any time within or between groups in serum calcitriol concentrations.

**Conclusions:** Calcitriol administration, at the dosages studied, does not alter serum PTH concentrations in normal cats or those with renal failure.

### ◆ CLINICAL IMPACT:

Failure of calcitriol administration to alter serum PTH concentration in this study may have resulted from inadequate dosage or poor bioavailability since serum calcitriol concentrations did not increase significantly after calcitriol administration. Further studies will have to be completed before calcitriol can be recommended for clinical use. Possible adverse effects include hypercalcemia, soft tissue mineralization, and potentially further renal injury, particularly if hyperphosphatemia is present concurrently. Independent

of whether or not calcitriol administration decreases serum PTH concentrations in cats is the question of what are its effects on survival and quality of life in cats with chronic renal failure. Many cats with stable chronic renal failure live for years after diagnosis with treatment consisting of dietary manipulation and control of systemic blood pressure. Therefore, long-term studies utilizing a large number of cats with naturally-occurring kidney disease will be necessary to answer important remaining questions.

**There was no difference in serum PTH concentration at either calcitriol dosage**



## Separated Serum Glycated Proteins in Diabetic and Normal Cats

*Martin GJ, Rand JS, Hickey SA. Separation of serum glycated proteins by agarose gel electrophoresis and nitroblue tetrazolium staining in diabetic and normal cats. Vet Clin Pathol 2006;35:307-310.*

### \* INTRODUCTION:

**Background:** Serum fructosamine concentration is an indirect assessment of the mean blood glucose concentration over the preceding two weeks. Fructosamine is total glycated serum protein composed primarily of albumin and lipoproteins. The diagnostic or other clinical value of individual measurements of glycated albumin,  $\alpha$ -lipoprotein, and  $\beta$ -lipoprotein in diabetic cats is not known.

**Objectives:** The purpose of this study was to measure glycated serum albumin,  $\alpha$ -lipoprotein, and  $\beta$ -lipoprotein in healthy and in diabetic cats to determine if any of the fractions of glycated proteins could be more helpful for the diagnosis or monitoring of diabetes mellitus than total glycated serum protein.

### ▲ SUMMARY:

**Methods:** Serum samples from six cats with diabetes mellitus and ten clinically healthy cats were assayed for fructosamine and glycated albumin,  $\alpha$ -lipoprotein, and  $\beta$ -lipoprotein concentrations.

**Results:** Fructosamine and glycated albumin,  $\alpha$ -lipoprotein, and  $\beta$ -lipoprotein concentrations were higher in diabetic cats than in healthy cats. There was a linear association between fructosamine and each of the glycated fractions. The major glycated fraction varied within healthy and diabetic cats. In some, the major glycated fraction was glycated albumin, and in others, it was lipoproteins.

**Conclusions:** There is no diagnostic advantage to measuring fructosamine fractions compared to total fructosamine in diabetic cats.

### ◆ CLINICAL IMPACT:

Measuring glycated serum protein fractions does not appear to be any more helpful in monitoring diabetic cats than is total glycated serum protein (fructosamine). Concurrent hyperthyroidism increases glomerular clearance of albumin and decreases fructosamine concentration in diabetic, hyperthyroid cats. Fructosamine levels are of little value in monitoring diabetic, hyperthyroid cats.

The effects of hyperthyroidism and increased glomerular filtration on lipoproteins in diabetic cats are unknown. Whether measurement of glycated fractions of serum protein might be more useful than fructosamine measurement if hyperthyroidism is present was not addressed. It is not clear why the distribution of glycated serum protein fragments varied erratically in the cats in this study.

**There was a linear association between fructosamine and each of the glycated fractions.**





## Pregnancy-Related Diabetes Mellitus

Norman EJ, Wolsky KG, MacKay GA. Pregnancy-related diabetes mellitus in two dogs. *N Zealand Vet J* 2006;54:360-364.

### \* INTRODUCTION:

**Background:** In bitches, progesterone secretion increases during diestrus and pregnancy. Diabetes mellitus has been reported during diestrus, and it sometimes resolves following ovariectomy. The diabetes mellitus may be the result of the glucocorticoid-like effects of progesterone or could result from excessive growth hormone (GH) secretion from mammary tissue due to prolonged elevation of plasma progesterone. If GH is elevated for a sufficient time period, acromegaly can result in severe insulin resistance and diabetes mellitus in some cases. Diabetes mellitus that develops during pregnancy has not been described in dogs despite studies demonstrating insulin resistance in pregnant bitches.

**Objectives:** This report describes two cases of pregnancy associated diabetes mellitus in dogs.

### ▲ SUMMARY:

**Case Report:** A pregnant, 6-year-old, Labrador retriever was presented 14 days before her predicted whelping date for thickened skin, increased skin folds in the head, neck trunk and tail base, and respiratory stridor. Mild hyperglycemia was present without glucosuria. However, glucosuria occurred four days later and marked hyperglycemia was noted seven days after initial presentation. A tentative diagnosis of acromegaly and secondary diabetes mellitus was made and insulin administration was instituted. A Caesarean section and ovariohysterectomy were performed 61 to 63 days after the predicted date of ovulation. Two live, but underweight, pups were delivered, but they died within 36 hours. The bitch recovered normally from the

surgery, but remained diabetic for the duration of the 18-month follow-up. Clinical signs of acromegaly resolved within two months after surgery.

A 6-year-old, female, Siberian husky was presented for uterine inertia after the birth of one live pup. After medical management failed to result in normal delivery, a caesarean section and ovariohysterectomy were performed. Three live pups were delivered. All pups were normal size and appeared to be healthy, but died within five days despite care by an experienced breeder. Two days after surgery, the dog presented for weakness, vomiting, melena, tachypnea, tachycardia, fever, and severe dehydration secondary to diabetic ketosis. While not confirmed, acute pancreatitis or primary intestinal disease was suspected. Supportive care, consisting of intravenous fluid therapy, antimicrobials, antiemetics, gastrointestinal protectants, and low-dose intramuscular crystalline insulin administration resulted in improvement. After 36 hours, insulin was changed to a porcine lente formulation at a decreasing dosage based on blood glucose response. Insulin treatment was discontinued after seven days, and the dog has remained healthy and euglycemic for 18 months.

**Conclusions:** Pregnancy can contribute to development of diabetes mellitus that may be transient or permanent.

### ◆ CLINICAL IMPACT:

The first dog in this report had clinical signs of acromegaly in addition to diabetes mellitus. Thickened skin, widened interdental spaces, and respiratory stridor in a bitch in diestrus or one that is pregnant or has received progestin therapy should alert the clinician to the possibility of acromegaly. While these signs were absent in the second dog, measurement

of blood glucose at the time it presented for dystocia likely would have identified hyperglycemia consistent with diabetes mellitus. Hypoglycemia is more likely to develop in a bitch in the periparturient period. So, blood glucose should be assessed routinely in cases of dystocia or elective Caesarean sections. Removal of the source of progestin should be accomplished since secondary diabetes mellitus is often transient if treated appropriately.

**blood glucose should be assessed routinely in cases of dystocia or elective Caesarean sections**



## Gastrin-Secreting Neoplasia

*Diroff JS, Sanders NA, McDonough SP, et al. Gastrin-secreting neoplasia in a cat. J Vet Intern Med 2006;20:1245-1247.*

### \* INTRODUCTION:

**Background:** Gastrin is a hormone that is produced by the G cells of the stomach and duodenum in adult animals. It works with histamine to stimulate the release of gastric acid. Gastrinomas occur in the pancreatic islets or duodenum and secrete excesses of gastrin leading to gastroduodenal ulceration.

Gastrinomas can cause vomiting with and without blood, anorexia, weight loss, and diarrhea. They are not palpable, not visible on radiography, and rarely apparent on abdominal ultrasonograms. Diagnosis is based on ruling out more common causes of vomiting and renal insufficiency and finding gastroduodenal ulceration with the presence of fasting hypergastrinemia. Gastrinomas have rarely been reported in cats.

**Objectives:** The purpose of this report was to describe a gastrinoma in a cat.

### ▲ SUMMARY:

**Case Report:** An 8-year-old, castrated male, domestic shorthaired cat was presented with a history of poor appetite and intermittent vomiting for the preceding six weeks. Results of routine hemogram, serum chemistries, and abdominal and thoracic radiographs were within normal limits. Gastroduodenoscopy revealed suppurative esophagitis and duodenitis.

A percutaneous gastrostomy (PEG) tube was placed and symptomatic therapy was begun with enrofloxacin, metoclopramide, famotidine, and sucralfate. Clinical improvement was noted during the subsequent three weeks although appetite did not return. Another gastroduodenoscopy was performed. Focal duodenal ulcers were observed. All

previous treatment was continued, except for enrofloxacin.

Three weeks later, the cat was still anorectic and vomiting. Serum cortisol concentrations before and after adrenocorticotrophic hormone stimulation were within normal limits. Prednisone was administered to treat enteritis. Low-dose erythromycin and cyproheptadine were administered as a promotility agent and appetite stimulant, respectively.

**Abnormally elevated, fasting, serum gastrin concentration in a cat with normal renal function is diagnostic of gastrinoma.**

Vomiting had worsened after two months of treatment. Serum chemistries were compatible with chronic vomiting of gastric acid (metabolic alkalosis, hypochloridemia, hypokalemia). Mild anemia was also present. Abdominal ultrasonography showed an image of a 1 cm hypoechoic mass within the right lobe of the pancreas. Exploratory laparotomy revealed a 3-cm mass in the distal right limb of the pancreas which was excised. Histopathologic examination findings were consistent with an islet cell tumor. Immunohistochemical evaluation demonstrated intense staining of 40 to 60% of neoplastic cell cytoplasmic granules for gastrin.

Post surgery treatment included ranitidine, sucralfate, omeprazole, and iron supplement. Three weeks after surgery, the PEG tube was removed. Omeprazole was continued indefinitely. Seventeen months after surgery, the cat was clinically healthy.

**Conclusions:** Cats that have a history of vomiting without response to conservative treatment should be examined for gastroduodenal ulceration. If idiopathic gastroduodenal ulceration is confirmed, fasting serum gastrin levels should be determined.

### ◆ CLINICAL IMPACT:

The findings in this cat with a gastrinoma were consistent with those seen in dogs and humans with gastrinomas. Any older cat with persistent vomiting, unresponsive to conservative symptomatic therapies, should have gastroduodenoscopy performed. If gastric or duodenal ulcers, or both, are found, fasting serum gastrin concentrations should be determined. Abnormally elevated, fasting, serum gastrin concentration in a cat with normal renal function is diagnostic of gastrinoma. Gastrinomas are not palpable, radiographically evident, and rarely imaged by ultrasonography.



## Canine Gastrinoma

Hughes SM. Canine gastrinoma: A case study and literature review of therapeutic options. *N Zealand Vet J* 2006;54:242-247.

### \* INTRODUCTION:

**Background:** Gastrinomas are gastrin-secreting tumors which most commonly occur in the pancreatic islets (non-beta cells). Gastrin stimulates the secretion of hydrochloric acid from the gastric parietal cells. Excessive gastrin secretion can cause gastric hyperacidity, anorexia, weight loss, gastric or duodenal ulcerations, vomiting with or without blood, and diarrhea.

**Objectives:** The purpose of this report was to describe a case of gastrinoma in a dog.

### ▲ SUMMARY:

**Case Report:** An 8-year-old, spayed female Australian terrier was presented with anorexia, weight loss, and lethargy. Vomiting had occurred intermittently for two days. Clinical findings included signs of pain in the cranial abdominal abdomen. Melena was evident after digital rectal examination. Laboratory findings included a hemogram with leukocytosis with a left shift. The serum biochemistries revealed a slight decrease in calcium, albumin, potassium, and chloride concentrations. Occult blood was present in the feces.

Intravenous fluids and electrolyte replacement were administered, as well as amoxicillin with clavulanic acid. Another hemogram and serum chemistry panel were performed. Severe anemia and hypoalbuminemia were found. Twenty-four hours after administering omeprazole, vomiting had ceased, and the dog's attitude had improved. Exploratory surgery was recommended based on a tentative diagnosis of gastrinoma but declined by the owners. A fasting plasma gastrin concentration was determined one month after omeprazole treatment had begun and was

approximately 20 times the concentration of a healthy dog's (826 ng/L and 48 ng/L, respectively). After a 14-month asymptomatic period, vomiting recurred but was controlled by ranitidine, sucralfate, and omeprazole.

Twenty-six months after the tentative diagnosis of gastrinoma, vomiting recurred again while still receiving ranitidine, sucralfate, and omeprazole. Fasting plasma gastrin concentration was high (9,514 ng/ml). A healthy dog's fasting plasma gastrin concentration was 30 ng/ml. An exploratory

laparotomy was permitted. Multiple nodules were present throughout the pancreas with additional ones on the ileum and in the omentum. The dog was euthanized and necropsied. Immunohistochemical staining of the nodules was positive for gastrin.

**Conclusions:** Omeprazole administration can be effective in controlling the signs of gastrinoma in dogs for up to several months.

### ◆ CLINICAL IMPACT:

The dog of this report had typical gastrinoma findings, and the diagnosis was confirmed at necropsy with immunohistochemistry staining. However, plasma gastrin levels were confusing and inconsistent: ng/L then ng/ml in the dog with the gastrinoma and the healthy dog. Treatment with proton pump inhibitors and type-2 histamine receptor antagonists may have also affected the plasma gastrin concentrations.

Gastrinomas should be suspected in cases of vomiting that do not respond to conventional therapy. Finding gastric or duodenal ulcers during gastroduodenoscopy is highly suggestive of gastrinoma when other causes are not evident. The clinical diagnosis is then

based on finding an elevated fasting plasma gastrin concentration. Excision of the tumor should be attempted whenever, and as early as, possible.

**Finding gastric or duodenal ulcers during gastroduodenoscopy is highly suggestive of gastrinoma when other causes are not evident.**



## Plasma Cortisol Changes Associated with Diagnostic Imaging Procedures

*Cavallone E, Secchiero B, Di Giancamillo M, et al. Plasma cortisol levels in dogs undergoing diagnostic imaging procedures. Vet Rec 2006;159:749.*

### \* INTRODUCTION:

**Background:** The neuroendocrine response to stress is complex, but includes secretion of cortisol. Plasma cortisol concentration in dogs with nonadrenal illness is 2-3 times that of healthy dogs. Cortisol secretion is abruptly increased by in-hospital stresses including abdominal ultrasound, general anesthesia, and surgery.

**Objectives:** This study investigated the effects of various radiologic procedures on cortisol secretion in dogs that were administered general anesthesia.

### ▲ SUMMARY:

**Methods:** Blood samples were obtained for measurement of cortisol in 13 dogs on admission to the hospital, after induction of anesthesia with propofol and isoflurane, and 15 minutes after intravenous or intrathecal administration of a contrast agent. Computed tomography (CT) with contrast was performed in eight dogs and without contrast in one dog, myelography in three dogs, and plain radiographs of the elbows in one dog. Dogs were classified as stressed if serum cortisol concentrations were elevated on admission or non-stressed if serum cortisol concentration were not elevated on admission.

**Results:** All seven dogs in the stressed group had neurologic or orthopedic abnormalities that necessitated imaging and had serum cortisol concentrations above the reference range, i.e., more than 3.0 µg/dl. All six dogs in the non-stressed group had serum cortisol concentrations within the reference range at the time of admission. Three of the six dogs in the non-stressed group were healthy, and the other three had neurologic abnormalities that necessitated imaging. The serum cortisol concentration did not change at either sam-

pling time during procedures compared with the level at the time of admission in the non-stressed group of dogs. Five of the seven dogs in the stressed group showed an increase in serum cortisol concentration of 40% or more when the final blood sample was compared with either the admission or post-induction sample.

**Conclusions:** Elevated cortisol concentrations in the stressed dogs may represent anxiety or pain, and dogs exhibiting either should be under a deeper plane of anesthesia during diagnostic imaging procedures.

### ◆ CLINICAL IMPACT:

Cortisol secretion is increased by pain and by emotional or physical stress. It seems likely that the elevation in cortisol noted in many dogs of this study was the result of pain associated with positioning for imaging. However, some dogs in the non-stressed group had disorders similar to those with elevated cortisol concentration, making it difficult to predict dogs that might need additional analgesia during imaging procedures. When supplementing glucocorticoids in dogs with hypoadrenocorticism that are undergoing general anesthesia and potentially painful procedures, additional glucocorticoids should be administered in addition to that routinely provided for non-stressed dogs with hypoadrenocorticism.

**Cortisol secretion is increased by pain and by emotional or physical stress.**



## ACTH Stimulated Cortisol and Progesterone in Intact and Spayed Cats

Chatdarong K, Ponglowhapan S, Karlsson A, et al. The effect of ACTH stimulation on cortisol and progesterone concentrations in intact and ovariobysterectomized domestic cats. *Theriogenol* 2006;66:1482-1487.

### \* INTRODUCTION:

**Background:** Adrenocorticotrophic hormone (ACTH) stimulates the steroidogenesis pathway to progesterone and cortisol. ACTH administration increases plasma cortisol and progesterone concentrations in cats. The effects of ovarian hormones on the response in cats to ACTH stimulation of cortisol and progesterone production are not known.

**Objectives:** The aim of this investigation was to evaluate the ACTH-stimulated production of cortisol and progesterone in sexually intact anestrus, and spayed, female cats.

### ▲ SUMMARY:

**Methods:** Five sexually intact, young adult, anestrus female cats were evaluated before and after being spayed in four trials: intact saline treated (control), intact ACTH-stimulated, spayed control, and spayed ACTH-stimulated. Blood samples were collected at -30, 0, 60, 90, 120, and 180 minutes relative to ACTH administration.

**Results:** Basal serum cortisol and progesterone concentrations were unchanged by saline administration. ACTH administration produced significantly correlated increases in serum cortisol and progesterone concentrations. Both hormones' serum concentrations peaked at 90 minutes and returned to basal levels 180 minutes after ACTH administration. Stress of restraint caused increases in both hormones of similar magnitude.

**Conclusions:** Spaying has no significant effect on serum cortisol and anestrus progesterone concentration responses to ACTH stimulation. Stress of restraint during artificial insemination of cats could reduce fertilization.

### ◆ CLINICAL IMPACT:

ACTH stimulates pathways to the production of progesterone and cortisol. Although it is logical that there would be no significant difference in ACTH-stimulated serum cortisol and progesterone before and after spaying, the results of this study confirm the lack of difference.

More important, baseline concentrations of serum cortisol and progesterone were 3- to 4-fold higher after being spayed. This is probably the stress of being returned to the hospital environment and restraint for venapuncture. The authors speculate that stress hormone responses of this magnitude to restraint and hospital environment could impair the conception rates from artificial insemination in cats. Whether or not this is true, the increase in baseline cortisol and progesterone after handling during hospitalization indicates the need for minimizing stress in cats from being handling whenever possible.

**the increase in baseline cortisol and progesterone after handling during hospitalization indicates the need for minimizing stress in cats from being handling**



## Canine Primary Hyperaldosteronism

Johnson KD, Henry CJ, McCaw DL, et al. Primary hyperaldosteronism in a dog with concurrent lymphoma. *J Vet Med A* 2006;53:467-470.

### \* INTRODUCTION:

**Background:** Primary hyperaldosteronism is a rare disease in the dog resulting in excessive secretion of aldosterone. Clinical signs are generally related to hypokalemia and hypertension. All reported canine cases of primary hyperaldosteronism have been the result of a functional adrenocortical neoplasm. The diagnosis is based on finding markedly elevated serum aldosterone concentration, suppressed plasma renin activity, and an adrenal mass in a dog with appropriate clinical and clinicopathologic abnormalities.

**Objectives:** The intent of this report was to describe the clinical findings and diagnosis of primary hyperaldosteronism in a dog undergoing chemotherapy treatment for lymphoma.

### ▲ SUMMARY:

**Case Report:** An 11-year-old, neutered male, English springer spaniel that was being treated with cyclophosphamide, prednisone, and vincristine for stage IV lymphoma was evaluated for weakness, lethargy, and anorexia. Marked hypokalemia (2.3 mEq/L) as well as mild hypoalbuminemia, hypochloremia, and azotemia were present. Treatment consisted of oral potassium gluconate and continued chemotherapy. Multiple measurements of potassium over the next 10 weeks showed consistent hypokalemia despite treatment. At that time, the dog was evaluated for depression, bradycardia, polyuria, and polydipsia. Serum aldosterone was elevated when hypokalemia (2.9 mEq/L) was documented, suggestive of primary hyperaldosteronism. A large soft tissue mass located cranial to the left kidney was identified on abdominal radiographs and an adrenal mass was confirmed by abdominal ultrasound. Multiple masses were found

in the liver as well on ultrasound. Pre- and post-adrenocorticotrophic hormone-stimulated serum aldosterone concentrations were elevated and considered diagnostic of primary hyperaldosteronism, while serum cortisol concentrations were low, consistent with long-term administration of prednisone. An adrenocortical carcinoma with hepatic metastasis was diagnosed by surgical adrenalectomy and liver biopsy. The neoplastic tissue stained strongly for aldosterone on immunohistochemistry. The dog died 48 hours after surgery due to progressive, severe pulmonary disease.

**Conclusions:** Persistent unexplained hypokalemia should prompt evaluation for hyperaldosteronism.

### ◆ CLINICAL IMPACT:

Although rare in the dog, primary hyperaldosteronism should be considered as a differential diagnosis in any dog with persistent hypokalemia. Additional findings that would support hyperaldosteronism include hypertension, metabolic alkalosis, and an adrenal mass. Although blood pressure was apparently not measured in the current case, hypertension can be severe and can result in serious complications. Abdominal imaging is an important test when evaluating a dog for hyperaldosteronism since an adrenal tumor should be present. Because serum aldosterone should be suppressed in a normovolemic dog with a low potassium level and normal renal function, elevated serum aldosterone with hypokalemia is highly suggestive of primary hyperaldosteronism.

**elevated serum aldosterone with hypokalemia is highly suggestive of primary hyperaldosteronism**



## Adrenocortical Stimulation Testing with Intramuscular, Low Dose ACTH

Sieber-Ruckstuhl NS, Boretti FS, Wenger M, et al. Cortisol, aldosterone, cortisol precursor, androgen and endogenous ACTH concentrations in dogs with pituitary-dependent hyperadrenocorticism treated with trilostane. *Dom Anim Endocrinol* 2006;31:63-75.

### \* INTRODUCTION:

**Background:** Trilostane is a competitive inhibitor of 3 $\beta$ -hydroxysteroid dehydrogenase, the enzyme responsible for catalyzing the conversion of pregnenolone, dehydroepiandrosterone (DHEA), and 17 $\alpha$ -OH-pregnenolone to sex steroids, cortisol, and aldosterone. It has been reported in a few cases that trilostane administration does not decrease serum 17 $\alpha$ -OH-progesterone concentrations in dogs with hyperadrenocorticism, while cortisol decreases consistently. Because some dogs with hyperadrenocorticism can have a normal plasma cortisol concentration but elevated non-cortisol steroid hormone concentrations in response to adrenocorticotropic hormone (ACTH), it is important to address the effect of trilostane on adrenocortical hormones other than cortisol.

**Objectives:** The purpose of this study was to evaluate the effect of trilostane treatment on adrenocortical steroid hormones throughout the biosynthetic pathway of steroid hormone synthesis.

### ▲ SUMMARY:

**Methods:** Fifteen dogs with pituitary-dependent hyperadrenocorticism (PDH) had plasma endogenous ACTH concentrations and serum concentrations, before and after administration of synthetic ACTH of cortisol, aldosterone, 17 $\alpha$ -OH-pregnenolone, DHEA, 17 $\alpha$ -OH-progesterone, androstenedione, 11-deoxycortisol, and 21-deoxycortisol. Clinical assessments and concentrations of these hormones were made before and 1 to 2 and 3 to 7 weeks after oral administration of trilostane. The ACTH response test was performed 2 to 6 hours after administration of the previous dose of trilostane. The once

daily trilostane dosage was adjusted to obtain post-ACTH cortisol concentrations of 1 to 2.5  $\mu$ g/dl.

**Results:** Clinical signs of hyperadrenocorticism improved in all dogs within the first 1-3 weeks of treatment. Basal and post-ACTH serum cortisol decreased at both treatment times. Basal aldosterone concentrations increased at both times during trilostane administration, and the post-ACTH aldosterone concentrations were significantly decreased at the first post-treatment time compared with that prior to treatment. Basal and post-ACTH concentrations of hormones early in the biosynthetic pathway prior to the action of 3 $\beta$ -hydroxysteroid dehydrogenase, 17 $\alpha$ -OH-pregnenolone and DHEA, increased during trilostane treatment. Trilostane treatment did not alter basal or post-ACTH concentrations of 17 $\alpha$ -OH-progesterone or androstenedione. Basal 21-deoxycortisol did not change during treatment, while the post-ACTH 21-deoxycortisol concentration was significantly lower during trilostane administration. Concentrations of basal but not post-ACTH 11-deoxycortisol increased during treatment. Plasma endogenous ACTH concentration was significantly higher at the second treatment time compared with before treatment.

**Conclusions:** While trilostane appears to inhibit 3 $\beta$ -hydroxysteroid dehydrogenase, it also appears to alter activity of other enzymes in the pathway.

### ◆ CLINICAL IMPACT:

The elevation of 17 $\alpha$ -OH-pregnenolone and DHEA, both hormones that are catalyzed by 3 $\beta$ -hydroxysteroid dehydrogenase, is consistent with inhibition of this enzyme and accumulation of these hormones because

of decreased metabolism. The finding that trilostane decreases cortisol but not its precursor, 17 $\alpha$ -OH-progesterone, indicates that trilostane inhibits other enzymes as well, such as 11 $\beta$ -hydroxylase. The clinical importance of this finding is that post-ACTH cortisol concentration is probably the most reliable tool to monitor the hormonal response to treatment in dogs receiving trilostane. Because 17 $\alpha$ -OH-progesterone was not altered by trilostane treatment (an effective treatment for hyperadrenocorticism), it seems unlikely 17 $\alpha$ -OH-progesterone is involved in the pathogenesis of clinical signs of hyperadrenocorticism. This is important because cases of hyperadrenocorticism have been identified where post-ACTH cortisol is normal but the respective 17 $\alpha$ -OH-progesterone concentration is elevated. While it might be a useful tool for diagnosing hyperadrenocorticism in some cases, it is not likely to be of benefit for monitoring response to treatment.

it seems unlikely  
17 $\alpha$ -OH-progesterone  
is involved in the  
pathogenesis of  
clinical signs of  
hyperadrenocorticism



## Acute Hepatopathy Associated with Mitotane Administration

Webb CB, Twedt DC. Acute hepatopathy associated with mitotane administration in a dog. *J Am Anim Hosp Assoc* 2006;42:298-301.

### \* INTRODUCTION:

**Background:** Mitotane is an adrenocorticolytic drug used to control hyperadrenocorticism in the dog. Reported adverse effects of mitotane are anorexia, lethargy, vomiting, diarrhea, and hypoadrenocorticism. Steroid hepatopathy from hyperadrenocorticism is usually reversed by mitotane therapy.

**Objective:** The purpose of this report was to describe acute hepatopathy associated with mitotane administration in a dog.

### ▲ SUMMARY:

**Case Report:** An 8-year-old, spayed female, mixed-breed dog was referred for liver failure. The referring veterinarian had previously found elevated serum alkaline phosphatase activities on two occasions (most recent of 922 IU/L), although no clinical signs of liver disease or hyperadrenocorticism were noted. Baseline and post-adrenocorticotrophic hormone (ACTH) serum cortisol concentrations were determined. Baseline cortisol concentration was within normal limits, but the post-ACTH cortisol concentration was abnormally elevated (23.5 µg/dl, reference - 6 to 18 µg/dl) consistent with a laboratory diagnosis of hyperadrenocorticism. Mitotane was prescribed at the conventional loading dose for five days and then the dog was placed on weekly maintenance dosages divided four times per week.

Two weeks later, the dog had anorexia. Mitotane administration was discontinued and prednisone was prescribed. After an additional two weeks, the dog continued to have a poor appetite, vomited intermittently, developed icterus, and had hemorrhages on the ventral abdomen. A hemogram revealed lymphopenia and thrombocytopenia. Serum biochemistries showed hypoglycemia, low

blood urea nitrogen, hyperbilirubinemia, and elevated serum alkaline phosphatase activity (2,371 IU/L) as well as other routinely measured liver enzymes. An ACTH stimulation test confirmed suppression of the adrenal cortex (post-ACTH cortisol of 4.4 µg/dl). Prothrombin time was prolonged, and ultrasonography of the abdomen revealed a small liver. Laparoscopy and liver biopsies were performed. The biopsy revealed diffuse,

hydropic, and fatty changes. Two days later, the dog was discharged on S-adenosylmethionine, ursodiol, and prednisone. Three months after discharge, the owners considered the dog to be normal, although serum alkaline phosphatase activity was still elevated (1,931 IU/L).

**Conclusions:** Extensive evaluations of adrenocortical function are necessary when dogs without clinical signs of hyperadrenocorticism are found to have exaggerated response to ACTH stimulation due to the potential risks of adverse effects from mitotane therapy.

### ◆ CLINICAL IMPACT:

Mitotane is an organochlorine that is cytolytic to the adrenal cortex. It has been used clinically in thousands of dogs over the last 30 years. Known common adverse effects include digestive dysfunction signs of anorexia, depression, and vomiting. The most serious potential adverse effect is iatrogenic acute primary hypoadrenocorticism resulting in hypotensive shock. Acute hepatopathy from mitotane therapy has not been previously reported.

This was a singular case of acute hepatopathy concurrent with mitotane administration in a dog. Recovery coincided with withdrawal from mitotane administration, but re-exposure to confirm the relationship

between acute hepatopathy and mitotane administration was not attempted. Therefore, acute hepatopathy may have been due to another cause during the same time frame as the mitotane administration.

An exaggerated response to ACTH administration is indicative of adrenocortical hyperplasia usually due to a corticotropic microadenoma, but prolonged stress, such as hepatic dysfunction, could lead to stress-induced adrenocortical hyperplasia.

**acute hepatopathy may have been due to another cause during the same time frame as the mitotane administration**





## Physical Exercise in Dogs with Primary Adrenocortical Insufficiency

*Zeugschwetter F, Willmann M, Teinfalt M, et al. Physical exercise in dogs with primary adrenocortical insufficiency. Wien Tierarztl Mschr 2006;93:29-31.*

### \* INTRODUCTION:

**Background:** Dogs with hypoadrenocorticism have an impaired ability to respond to stress due to the absence of secretion of cortisol from the adrenal glands. Therefore it is generally recommended to increase the dosage of glucocorticoid supplementation when a stressful event such as exercise, boarding, surgery, and other stressors are expected. While earlier studies= results are conflicting, anesthesia and surgery transiently increase plasma cortisol concentrations, while dogs with non-adrenal illness have plasma cortisol concentration 2-3 times that of normal dogs.

**Objectives:** The purpose of this study was to evaluate dogs with hypoadrenocorticism on standard replacement dosages of glucocorticoids for adverse effects of exercise.

### ▲ SUMMARY:

**Methods:** Six dogs with naturally-occurring hypoadrenocorticism were treated with fludrocortisone and, when necessary to control clinical signs, prednisolone (required in 3 dogs). Seven healthy dogs acted as controls. Venous blood gas, white and red blood cell counts, serum chemistries, electrocardiogram (ECG), blood pressure, and skin temperature were measured prior to and after running for 5 km at a speed of 10 km/minute.

**Results:** All dogs in both groups finished the run despite signs of exhaustion. Clinical signs and laboratory evidence of glucocorticoid deficiency or abnormalities in an ECG were not present after exercise in any dog. No significant differences between groups prior to, or following, exercise were noted between the hypoadrenocorticoid and control groups in

lactate, glucose, or diastolic blood pressure.

The Na:K ratio was significantly lower in dogs with hypoadrenocorticism prior to exercise, but not after exercise. There were no differences between measurements before and after exercise within either group. No abnormalities were reported by owners in the days following exercise.

**Conclusions:** Dogs with treated hypoadrenocorticism can tolerate moderate exercise without adverse effects.

### ◆ CLINICAL IMPACT:

The results of this study show that a brief period of stress (modeled by 30 minutes of exercise) does not overtly affect the well-being of dogs on maintenance therapy for hypoadrenocorticism. However, many stresses that dogs are exposed to are much more prolonged in duration than that induced in this study. Glucocorticoid doses up to three times the physiologic replacement dose are still recommended for dogs expected to undergo more prolonged stress until the stress is eliminated.

**Glucocorticoid doses up to three times the physiologic replacement dose are still recommended for dogs expected to undergo more prolonged stress.**

## Comparison of the Effects of IM and IV Triamcinolone Acetonide

*Abraham G, Demiraj F, Ungemach FR. Comparison of the hypothalamic-pituitary-adrenal axis susceptibility upon single-dose i.m. depot versus long-acting i.v. triamcinolone acetonide therapy: a direct pharmacokinetic correlation. J Endocrinol 2006;191:491-496.*

### \* INTRODUCTION:

**Background:** Triamcinolone is a synthetic glucocorticoid with eight times more anti-inflammatory potency per mg than prednisone. Intramuscular injections of the depot (crystalline) form, triamcinolone acetonide (TAA), are absorbed slowly and have long-lasting effects. An intravenous water-soluble ester, triamcinolone acetonide-dihydrophosphate (TAA-DHP) is rapidly eliminated. Several studies have been performed to assess the duration of adrenocortical suppression from TAA in humans and dogs with a wide range of results.

**Objectives:** The goal of this study was to compare the suppression on the HPA axis in dogs by two forms of triamcinolone.

### ▲ SUMMARY:

**Methods:** Four castrated male beagles and six spayed female beagles were administered triamcinolone and evaluated twice. The first treatment was a single intravenous administration of 0.2 mg/kg of TAA-DHP. Basal plasma cortisol concentrations were determined at 0, 0.5, 1, 1.5, 2, 4, 8, 12, 24, 36, 48, 72, and 96 hours as well as 8 and 10 days after injection. Adrenocorticotropic hormone (ACTH)-stimulated plasma cortisol concentrations were determined at 0 and 48 hours and 10 days after administration. Plasma concentrations of triamcinolone were also assayed for pharmacokinetic assessments.

The second treatment was performed after a two-week washout period. TAA was then administered intramuscularly. Basal plasma cortisol concentrations were determined at 0, 0.5, 1, 1.5, 2, 4, 8, 12, 24, 36, 48, 72, and 96 hours as well as 8, 10, 15, 17, 22, and 29 days

after injection. ACTH-stimulated plasma cortisol concentrations were determined at 0 and 48 hours and 10 and 29 days after administration.

**Results:** Intravenous TAA-DHP suppressed basal cortisol concentrations for 12 hours. Hypothalamic-pituitary-adrenal suppression lasted less than 10 days after TAA-DHP based on ACTH stimulation responses in plasma cortisol concentration, but HPA suppression lasted at least four weeks after intramuscular TAA administration. The terminal half-life of TAA-DHP was 13.9  $\forall$  1.3 hours, while it was 125.9  $\forall$  15.8 hours. Mean resident times were 11 and 160 hours for TAA-DHP and TAA, respectively.

**Conclusions:** Regular weekly use of TAA can worsen suppression of the HPA axis.

### ◆ CLINICAL IMPACT:

Relatively insoluble glucocorticoid preparations administered intramuscularly or subcutaneously have prolonged suppressive effects on the HPA axis. This has been known, but underappreciated, for many years. This study demonstrated a longer than expected suppression of the HPA axis from a single intramuscular administration of TAA. Whenever glucocorticoid effects are required for longer than two weeks, a soluble parenteral form of short-acting glucocorticoid or an oral preparation should be administered at the lowest possible dose as infrequently as possible. Prednisone, prednisolone, and methylprednisone are short-acting and economical glucocorticoids that can be administered more than two weeks in conservative, infrequent doses with minimal effects on the HPA axis. Repeated intramuscular injections of TAA or any other depot glucocorticoid more often than six months apart are inadvisable.

**HPA suppression lasted at least four weeks after intramuscular TAA administration**

## Management of Canine Respiratory Disease with Inhaled Corticosteroids

*Bexfield NH, Foale RD, Davison LJ, et al. Management of 13 cases of canine respiratory disease using inhaled corticosteroids. J Sm Anim Pract 2006;47:377-382.*

### \* INTRODUCTION:

**Background:** Most chronic respiratory diseases are inflammatory and respond at least symptomatically to corticosteroids. Oral or parenteral corticosteroid treatment for chronic respiratory disease often requires a dose or duration of treatment, or both, sufficient to cause adverse effects of iatrogenic hypoadrenocorticism and, in some cases, concurrent iatrogenic hyperadrenocorticism caused by supra-physiologic doses of exogenous glucocorticoids.

Inhaled corticosteroids are preferred treatment for chronic inflammatory respiratory diseases in humans. The inhaled route of administration has the potential of being more effective and causing fewer adverse effects than oral or parenteral corticosteroid treatment. The benefits and risks of inhaled corticosteroid therapy in dogs with chronic respiratory disease are not known.

**Objectives:** The purpose of this study was to assess the usefulness of inhaled corticosteroids in treating chronic inflammatory airway disease in dogs.

### ▲ SUMMARY:

**Methods:** The medical records of 13 dogs presented for respiratory disease examined with a resulting diagnosis of the underlying disease, treated with inhaled corticosteroids, and followed up for at least two months were reviewed. Follow-up evaluations were performed by the owners and results obtained by telephone.

**Results:** Ten dogs were diagnosed with chronic bronchitis. Three dogs had eosinophilic bronchopneumopathy. Using a spacer device to direct spray from a distance to the nose, 10 dogs were treated with inhaled beclomethasone dipropionate at a dose of 250

µg, twice per day, and three dogs were treated with fluticasone propionate at 125 µg, twice per day. Inhaled corticosteroids were administered for at least two months. Nine dogs had received oral or parenteral corticosteroids during previous attempted management of their respiratory problem. Each dog had adverse effects from corticosteroid treatment.

Four dogs that had not previously received corticosteroids did not have adverse effects from inhaled corticosteroids. Of the nine dogs that had received oral or parenteral corticosteroids and experienced adverse effects, five were treated solely with inhaled corticosteroids. Improved respiration without adverse effects occurred. The four remaining dogs were treated with inhaled and oral corticosteroids with a reduction in clinical signs and a reduction in adverse effects.

**Conclusions:** Inhaled corticosteroids can be effective and safe treatment of chronic bronchitis or eosinophilic bronchopneumopathy in dogs.

### ◆ CLINICAL IMPACT:

Inhaled corticosteroids appear to be effective and safe for use in dogs for two months. However, treatment of chronic inflammatory airway diseases is often a lifelong maintenance treatment, and the safety of inhaled corticosteroids in dogs for more than two months is not known. Oral candidiasis is a significant risk in humans treated for long periods with oral inhalers of corticosteroids. Candidiasis could also be a risk to dogs treated for longer than two months with inhaled corticosteroids. The method of administering inhaled corticosteroids to dogs (mask over the muzzle) could put the nasal mucosa as well as the naso-oropharynx at risk for candidiasis.

**the safety of inhaled corticosteroids in dogs for more than two months is not known**



## Methylprednisolone Acetate Administration in Cats

*Ployngam T, Tobias AH, Smith SA, et al. Hemodynamic effects of methylprednisolone acetate administration in cats. Am J Vet Res 2006;67:583-587.*

### \* INTRODUCTION:

**Background:** Corticosteroid administration has been reported to be associated with congestive heart failure in some cats. Corticosteroids can cause volume expansion by sodium retention through any mineralocorticoid activity they possess or by increasing plasma glucose concentration. Congestive heart failure may also be the result of inducing systemic hypertension or activating other mechanisms adversely affecting the myocardium.

**Objectives:** The purpose of this study was to evaluate potential mechanisms whereby methylprednisolone administration could contribute to development of congestive heart failure.

**intramuscular methylprednisolone acetate should be restricted to cats where oral administration is impractical, especially in cats with known, or known risk for, congestive heart failure.**

thoracic radiographs. The only echocardiographic change was a small increase in interventricular septal thickness in diastole at 16 to 24 days. In the seven cats in which valid measurements could be obtained, there was a significant decrease in total body water from baseline at 3 to 6 days but not at 16 to 24 days. Plasma volume increased at 3 to 6 days but not at 16 to 24 days compared with baseline. Plasma volume increased in all 12 cats, and in three cats, it was increased by 44-50%.

**Conclusions:** The increase in plasma volume noted 3 to 6 days after intramuscular methylprednisolone acetate administration is likely the result of fluid shifting into the intravascular space due to hyperglycemia.

### ▲ SUMMARY:

**Methods:** Twelve cats with a variety of dermatologic diseases, but without other significant abnormalities were studied before and 3 to 6 and 16 to 24 days after intramuscular administration of 5 mg/kg methylprednisolone acetate. At each study period, cats underwent a physical examination, systolic blood pressure, complete blood count, serum chemistries, thoracic radiographs, echocardiogram, and total body water and plasma volume measured by bioimpedance analysis.

**Results:** Body weight decreased slightly at 3 to 6 days but returned to baseline at 16 to 24 days. Blood pressure and heart rates were unchanged at all times. The mean serum glucose concentration increased significantly at 3 to 6 days (187 mg/dl) compared with the pretreatment level (136 mg/dl) and returned to 133 mg/dl at 16-24 days. The hematocrit, red blood cell count, and sodium, and chloride concentrations decreased significantly at 3 to 6 days and returned to baseline values at 16 to 24 days. No changes were noted on

### ◆ CLINICAL IMPACT:

The results of this study provide information on the mechanism underlying the acute onset of congestive heart failure in some cats without apparent heart disease administered a corticosteroid. The marked and rapid expansion of plasma volume that was noted in several cats in this study likely precipitates heart failure in susceptible cats. While short-acting corticosteroids including prednisolone have been reported to induce heart failure, most cats were administered methylprednisolone acetate similar to this study. Because of the long duration of effect of intramuscular methylprednisolone acetate, its use should be restricted to cats where oral administration is impractical, especially in cats with known, or known risk for, congestive heart failure.



## Androgen Receptors in Hepatoid Glands in the Dog

*Pisani G, Millanta F, Lorenzi D, et al. Androgen receptor expression in normal, hyperplastic and neoplastic hepatoid glands in the dog. Res Vet Sci 2006;81:231-236.*

### \* INTRODUCTION:

**Background:** Perianal (circumanal) glands are modified sebaceous glands unique among domestic animals to the dog. Tumors of the perianal glands are common in older, sexually intact, male dogs. Although these tumors can also occur in females, males are affected 5.6 times more frequently than females. Microscopically, the cells have a hepatocyte-like morphology and are referred to as hepatoid cells. The persistence of androgen receptor expression occurs in adenomas, but perianal gland carcinomas may not have androgen receptors.

**Objectives:** The goal of this study was to investigate the presence of androgen receptors in normal, hyperplastic, and neoplastic hepatoid glands in male dogs.

**Hyperplastic hepatoid cells and hepatoid epitheliomas had a significantly higher percentage of androgen receptors than normal hepatoid cells**

### ▲ SUMMARY:

**Methods:** Tissue from the hepatoid glands in 31 male dogs were classified. Nineteen were hyperplastic tumors, 10 were benign (two epitheliomas and eight adenomas), and 19 were carcinomas. Five samples of normal hepatoid tissue were examined. Androgen receptors were determined by immunohistochemistry and assessed by percent of androgen receptor positive nuclei and intensity of staining.

**Results:** Normal and abnormal hepatoid tissues were positive for androgen receptors. Hyperplastic hepatoid cells and hepatoid epitheliomas had a significantly higher percentage of nuclei that were positive for androgen receptors than normal hepatoid cells. Hepatoid adenomas and carcinomas had just slightly more androgen receptors than normal hepatoid cells.

**Conclusions:** Perianal gland adenomas and carcinomas maintain and enhance the ability to express androgen receptors. Castration or anti-androgen therapy may be beneficial in managing perianal gland tumors in dogs.

### ◆ CLINICAL IMPACT:

Perianal gland hyperplasia and adenomas are androgen-dependent. Castration of older males with perianal hyperplasia and adenomas has been standard treatment to cause regression of adenomas. Excised testes in cases with perianal tumors are often found to contain interstitial adenomas which may produce excesses of androgens that either initiate or enhance the growth of perianal gland tumors.

Castration of male dogs with perianal carcinomas is also advised since some may have enhanced growth from androgen stimulation. There may also be an increased risk of interstitial cell tumors in dogs with perianal gland carcinoma. However, the primary tumor should also be excised as completely as possible due to the potential invasiveness and frequent recurrence of perianal gland carcinomas.

The role that adrenal androgens might play in the recurrence of perianal gland tumors is not known. However, suppression of adrenal androgen production using physiologic glucocorticoid replacement doses of prednisone or prednisolone may have value in managing perianal gland recurrences in males. Females with perianal gland tumors should be spayed and consideration should be given to glucocorticoid replacement, as an adrenal androgen production suppression therapy.

# Thyro-Tabs<sup>®</sup>

(levothyroxine sodium tablets, USP)

**Caution:** Federal law restricts this drug to use by or on the order of a licensed veterinarian.

**Description:**

Each Thyro-Tabs<sup>®</sup> tablet provides synthetic crystalline levothyroxine sodium (L-thyroxine).

**Indications:**

For use in dogs for correction of conditions associated with low circulating thyroid hormone (hypothyroidism). Low serum circulating T-4 concentrations, coupled with clinical signs, are suggestive of hypothyroidism. The following T-4 concentrations in canine serum have been established:

Normal (euthyroid) – 18 to 32 ng/mL (18 to 32 µg/dL)

Possible hypothyroid - 10 to 18 ng/mL (10 to 18 µg/dL)

Hypothyroid – less than 10 ng/mL (10 µg/dL)

Hypothyroidism is unlikely with a resting serum T-4 concentration of 18 ng/mL or above. A dog exhibiting signs of hypothyroidism with a T-4 below 18 ng/mL should be considered for levothyroxine replacement therapy. Confirmation of the diagnosis could include withdrawal of therapy after which a recurrence of clinical signs further supports the diagnosis. Correct diagnosis of hypothyroidism is important, since such a diagnosis normally commits an animal to life-long replacement therapy. The principle objective of levothyroxine sodium administration is to achieve and maintain normal metabolism in the animal's normal physiologic range. Animal adaptation may necessitate regular monitoring of serum T-4 concentrations during the first several months of treatment to establish maintenance doses. TSH testing may be used to provide a definitive diagnosis in dogs with borderline resting T-4 values.

**Mode of actions:**

Levothyroxine sodium provided by Thyro-Tabs cannot be distinguished from that endogenously secreted by the thyroid gland. The primary regulator of thyroid function is thyroid stimulating hormone (TSH) which is synthesized and secreted by the pars distalis of the adenohypophysis (anterior pituitary). The mediator from the hypothalamus which exerts a continuous influence over the release of TSH is

thyrotropin-releasing hormone (TRH).

**Hypothyroidism in the dog:**

Hypothyroidism usually occurs in older and middle-aged dogs although the condition will sometimes be seen in younger dogs of the larger breeds. Neutered animals of either sex are also frequently affected, regardless of age. The condition is primary failure of the thyroid gland because of lymphocytic thyroiditis or other loss of follicular epithelium and resulting atrophy of the gland. Secondary hypothyroidism is rare and usually due to a destructive pituitary tumor.

**Clinical signs:**

The following list of clinical signs and laboratory findings may vary depending upon the degree of thyroid dysfunction:

**Nerve and muscle function:** lethargy, lack of endurance, increased sleeping, reduced alertness and interest with dulled mental attitude, hypotonus, stiff, slow movements, dragging of forelimbs, head tilt, disturbed balance, unilateral facial paralysis.

**Metabolism:** decreased oxygen consumption and lower metabolic rate, sensitivity and intolerance to cold, low body temperature, cool skin, heat seeking, increased body weight, constipation, poor exercise tolerance, slow heart rate, weak pulse, weak apex heart beat and low voltage on ECG.

**Reproduction:** reproductive failure, abortion, stillbirth, live birth of weak young, delayed puberty, reduced libido, impaired spermatogenesis, irregular estrus and anestrus, galactorrhea.

**Skin and hair:** myxedema of the face, blepharoptosis, atrophy of epidermis, thickening of the dermis, surface and follicular hyperkeratosis, hyperpigmentation, coarse and sparse coat, dry, dull and brittle hair, slow regrowth and retarded turnover of hair and bilateral alopecia.

**Laboratory findings:** low serum T-4 concentrations, hypercholesterolemia, hypertriglyceridemia, elevated serum creatine kinase, normochromic, normocytic anemia.

**Contraindications:**

Therapy is contraindicated in thyrotoxicosis, acute myocardial infarction, and uncorrected adrenal insufficiency. Other conditions in which the use of therapy should be used with caution include primary hypertension, euthyroidism, and pregnancy.

**Precautions:**

The administration of levothyroxine sodium to dogs to be used for breeding purposes or in pregnant bitches has not been evaluated. There is evidence that administration to pregnant bitches may affect the normal development of the thyroid gland in the unborn pups. The clinical effects of therapy are slow in being manifested. Overdosage may produce the signs of thyrotoxicosis including but not limited to: polydipsia, polyuria, polyphagia, reduced heat tolerance and hyperactivity or personality change. Thyro-Tabs 0.1 mg and 0.7 mg tablets contain FD&C yellow #5 (tartrazine) which has been associated with allergic-type reactions (including bronchial asthma) in susceptible humans. It is unknown if such a reaction could also occur in dogs.

**Adverse reactions:**

There are no specific adverse reactions associated with therapy at the recommended dosages. Overdosage will result in thyrotoxicosis.

**Dosages:**

The initial recommended daily dose is 0.1 to 0.2 mg/10 pounds (4.5 kg) body weight in single or divided doses. Dosage is adjusted by monitoring T-4 blood levels of the dog every four weeks until an adequate maintenance dose is established. The usual daily maintenance dose is 0.1 mg/10 pounds (4.5kg). A maximum of 0.8 to 1.0 mg total daily dose will be sufficient in many dogs over 80 pounds in body weight.

**Administration:**

Thyro-Tabs may be administered orally or placed in the food.

**How supplied:**

Available as scored, color-coded caplets in 9 concentrations: 0.1 mg, 0.2 mg, 0.3 mg, 0.4 mg, 0.5 mg, 0.6 mg, 0.7 mg, 0.8 mg and 1.0 mg in 28 tablet strip packs, bottles of 120 and 1,000.

**Storage:**

Store at controlled room temperature; 15°-30°C (59°-86°F) and protect from light.

**References:** See package insert.



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**Journals examined by the editors for article inclusion:**

American Journal of Veterinary Research  
Australian Veterinary Journal  
Canadian Journal of Veterinary Research  
Canadian Veterinary Journal  
Domestic Animal Endocrinology  
Endocrinology  
European Journal of Endocrinology  
Journal of Veterinary Internal Medicine  
Journal of the American Animal Hospital Association  
Journal of Small Animal Practice  
Journal of the American Veterinary Medical Association  
Journal of Veterinary Diagnostic Investigation  
Journal of Veterinary Medical Science  
Journal of Veterinary Medicine, Series A  
Journal of Comparative Pathology  
Journal of Veterinary Pharmacology and Therapeutics  
New Zealand Veterinary Journal  
Research in Veterinary Science  
Veterinary Journal  
Veterinary Pathology  
Veterinary Record  
Veterinary Radiology & Ultrasound  
.....and more than 20 others

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