THE 30TH ANNUAL

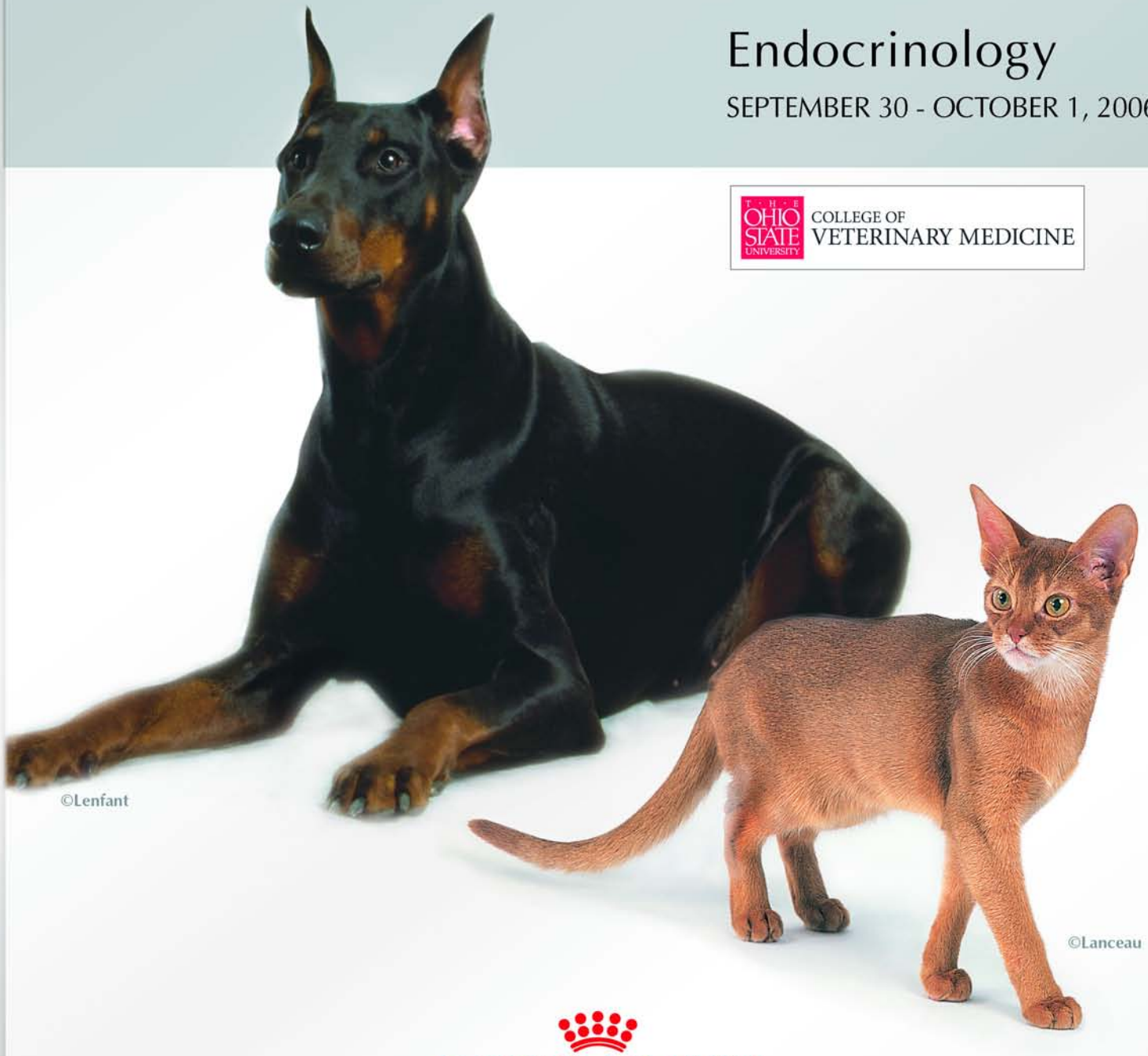
ROYAL CANIN / OSU Symposium

FOR THE TREATMENT OF SMALL ANIMAL DISEASES

Endocrinology

SEPTEMBER 30 - OCTOBER 1, 2006

THE OHIO STATE UNIVERSITY COLLEGE OF VETERINARY MEDICINE



ROYAL CANIN
VETERINARY DIET™

The 30th Annual

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SCHEDULE OF EVENTS

Saturday September 30, 2006

7:30 am **Registration/Continental Breakfast**

8:00 am **Welcome**
Dr. Dennis Chew

8:05 am **Approach to Polyuria and Polydipsia - Diabetes Insipidus, Psychogenic Polydipsia**
Dr. Dennis Chew

8:55 am **Alopecia - Is an Endocrine Disorder Responsible?**
Dr. Andrew Hillier

9:45 am **Coffee Break**

10:15 am **Diagnosis of Hyperadrenocorticism (Cushing's Syndrome) - Which Tests are Best?**
Dr. Ed Feldman

11:05 am **Trilostane - 5 Years of Clinical Experience for the Treatment of Cushing's Disease**
Dr. Claudia Reusch

Noon **Question and Answer Panel**
Drs. Chew, Hillier, Feldman, Reusch

12:30 **Lunch on Your Own**

2:00 pm **Hypoadrenocorticism (Addison's Disease) in Dogs**
Dr. Mark Peterson

2:50 pm **Hypothyroidism in Dogs - How Many Diagnostic Indices Do You Need to be Sure?**
Dr. Ray Nachreiner

3:40 pm **Refreshment Break**

4:10 pm **Challenging Issues in the Diagnosis and Treatment of Feline Hyperthyroidism**
Dr. Thomas Graves

5:00 pm **Question and Answer Panel**
Drs. Peterson, Nachreiner, Graves

5:30 pm **Adjourn**

Sunday October 1, 2006

8:00 am **Welcome**
Dr. Dennis Chew

8:05 am **Feeding the Diabetic Patient**
Dr. Denise Elliott

8:55 am **Monitoring of Glycemia in Dogs and Cats with Diabetes Mellitus**
Dr. Reusch

9:45 am **Coffee Break**

10:15 am **Selecting an Insulin for Treating Diabetes Mellitus in Dogs and Cats**
Dr. Richard Nelson

11:05 am **Unusual Endocrine Disorders in Dogs and Cats**
Dr. Richard Nelson

Noon **Question and Answer Panel**
Drs. Elliott, Reusch, Nelson

12:30 pm **Lunch on Your Own**

2:00 pm **Laboratory Assessment for Disorders of Calcium: Special Considerations for Sample Handling and Interpretation of Results**
Dr. Patricia Schenck

2:50 pm **Hypercalcemia and Primary Hyperparathyroidism (PHP) in Dogs**
Dr. Ed Feldman

3:40 pm **Refreshment Break**

4:10 pm **Idiopathic Hypercalcemia in Cats - When to Intervene?**
Dr. Dennis Chew

5:00 pm **Question and Answer Panel**
Drs. Schenck, Feldman, Chew

5:30 pm **Adjourn**

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Proceedings Editor
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Denise Elliott, BVSc, PhD, Dipl ACVIM, Dipl ACVN

OBJECTIVES:

Royal Canin and OSU proudly present a 10 member panel of internationally recognized experts from 7 different academic institutions with presentations spanning two information-filled days of continuing education in veterinary medicine.

The 2006 Royal Canin/OSU Symposium will provide an overview of diseases of the endocrine system of dogs and cats designed for the progressive primary care veterinarian. These topics have been carefully chosen to reflect common problems in small animal practice and to familiarize the practitioner with new information on the diagnosis and treatment of endocrine disorders.

Topics include the approach to to patients with polyuria and polydipsia, hyper and hypofunction of the adrenal gland, hyper and hypofunction of the thyroid gland, hyper and hypofunction of the parathyroid glands, diabetes mellitus, and idiopathic hypercalcemia.

CONTENTS

Approach to Polyuria and Polydipsia - Diabetes Insipidus, Psychogenic Polydipsia **4**
Dennis J. Chew, DVM, Dipl ACVIM, Patricia A. Schenck, DVM, PhD, Lawren Durocher, DVM

Alopecia - Is an Endocrine Disorder Responsible? **10**
Andrew Hillier, BVSc, MACVSc, Dipl ACVD

Diagnosis of Hyperadrenocorticism (Cushing's Syndrome) - Which Tests are Best? **14**
Edward C. Feldman, DVM, Dipl ACVIM

Trilostane - 5 Years of Clinical Experience for the Treatment of Cushing's Disease **17**
Claudia E. Reusch, DVM, Prof, Dipl ECVIM-CA

Hypoadrenocorticism (Addison's Disease) in Dogs **20**
Mark E. Peterson, DVM, Dipl ACVIM, Peter P. Kintzer, DVM, Dipl ACVIM

Hypothyroidism in Dogs - How Many Diagnostic Indices Do You Need to be Sure? **26**
Raymond F. Nachreiner, DVM, PhD

Challenging Issues in the Diagnosis and Treatment of Feline Hyperthyroidism **29**
Thomas K. Graves, DVM, PhD, Dipl ACVIM, Melissa R. Riensche, DVM

Feeding the Diabetic Patient **33**
Denise A. Elliott, BVSc, PhD, Dipl ACVIM, Dipl ACVN

Monitoring of Glycemia in Dogs and Cats with Diabetes Mellitus **36**
Claudia E. Reusch, DVM, Prof, Dipl ECVIM-CA

Selecting an Insulin for Treating Diabetes Mellitus in Dogs and Cats **39**
Richard W. Nelson, DVM, Dipl ACVIM

Unusual Endocrine Disorders in Dogs and Cats **43**
Richard W. Nelson, DVM, Dipl ACVIM

Laboratory Assessment for Disorders of Calcium: Special Considerations for Sample Handling and Interpretation of Results **47**
Patricia A. Schenck, DVM, PhD

Hypercalcemia and Primary Hyperparathyroidism (PHP) in Dogs **52**
Edward C. Feldman, DVM, Dipl ACVIM

Idiopathic Hypercalcemia in Cats - When to Intervene? **56**
Dennis J. Chew, DVM, Dipl ACVIM, Patricia A. Schenck, DVM, PhD

Approach to Polyuria and Polydipsia - Diabetes Insipidus, Psychogenic Polydipsia

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Patricia A. Schenck, DVM, PhD
Lawren Durocher, DVM

Normal water intake for dogs can be as high as 90 mL/kg/day but is often 60 mL/kg/day or lower. Maximal water intake for normal cats is much lower, at 45 mL/kg/day. Water intake at higher levels indicates the presence of polydipsia (pD) which is typically linked to polyuria (pU). Measurement of water intake at home can be helpful to determine if pUpD is really present, but this is most practical for dogs. Finding isolated pU or pD in the history usually means that the owner has failed to observe the other linked abnormality, or that the initially obtained history is incorrect.

There are numerous potential causes for pUpD (Table 1). The cause of the pUpD may be obvious after a detailed history and physical examination. The most common causes for pUpD in the dog are chronic kidney disease/failure, diabetes mellitus, and hyperadrenocorticism. In the cat, the most common causes are chronic renal disease/failure, hyperthyroidism, and diabetes mellitus. In the history, it is important to make sure that drugs that impair the urinary concentrating mechanism are not being given to the affected animal. Glucocorticosteroid administration, either topical or systemic, can create a profound pUpD in dogs[1,2]; this effect is less pronounced in cats. Also, owners and attending veterinarians occasionally confuse pollakiuria from lower urinary tract urgency with polyuria.

Table 1. Eponym for Differential Diagnoses of Polyuria and Polydipsia.
Used with Permission of Dr. Patricia Schenck and Dr. Dennis Chew 2005

C = Calcium, Cushing's, Cancer, Corticosteroids
L = Liver Insufficiency, Leptospirosis (subacute)
A = Adrenal (hyperadrenocorticism & hypoadrenocorticism)
M = Metabolic, Mellitus, Malignancy
P = Psychogenic, Pituitary, Polycythemia, Pyometra, Porto-Systemic Shunt, Partial Urinary Obstruction, Paraneoplastic (hypoglycemia)
E = Endocrine, Electrolytes (↓↑Calcium, ↓Potassium)
D = Drugs, Diabetes, Diuresis (post-obstructive)

R = Renal Insufficiency/Failure
I = Insipidus (Nephrogenic, Central)
B = Brain

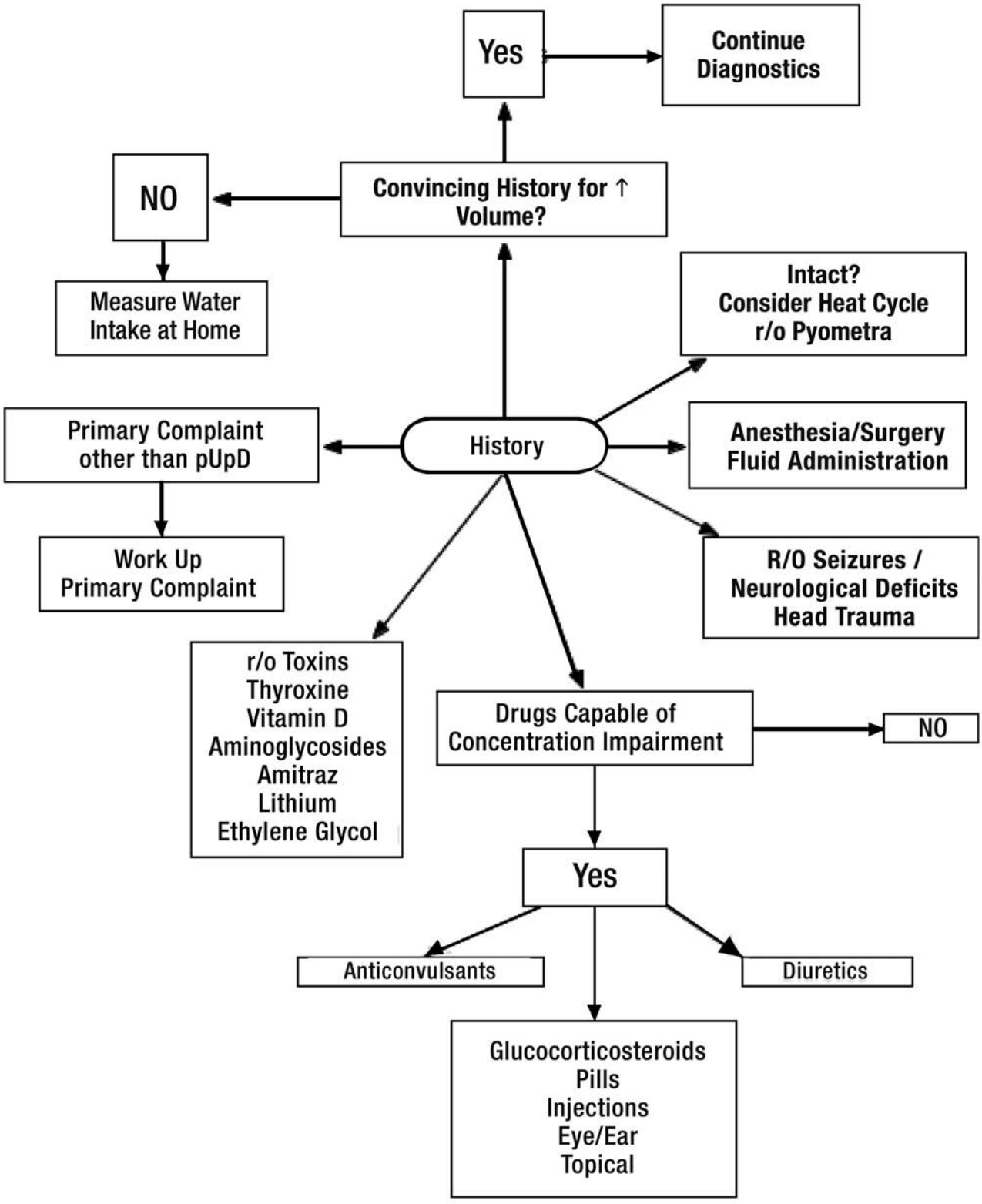
A complete physical examination is important in those patients with pUpD, as small irregular kidneys may be noted suggesting renal disease, or a neck mass in a cat may indicate hyperthyroidism. Diagnostic evaluation in these instances is directed at the primary underlying disease rather than the urinary concentrating defect.

Evaluation of a minimum database (CBC, serum biochemical panel, and urinalysis) should be performed in all cases in which pUpD has been verified. Assessment of thyroid function should be included as part of the minimum data base for cats with pUpD. Frequently, various organ failures or disorders are exposed by evaluation of the minimum data base (e.g. renal failure, hepatopathy, hypercalcemia, hyperthyroidism). If the diagnosis is not obvious after evaluation of the history, physical examination, and minimum database, then further diagnostic evaluation is indicated. In dogs this evaluation will include testing to rule out hyperadrenocorticism. Approaches to the evaluation of history and diagnosis are presented in Figures 1, 2 and 3.

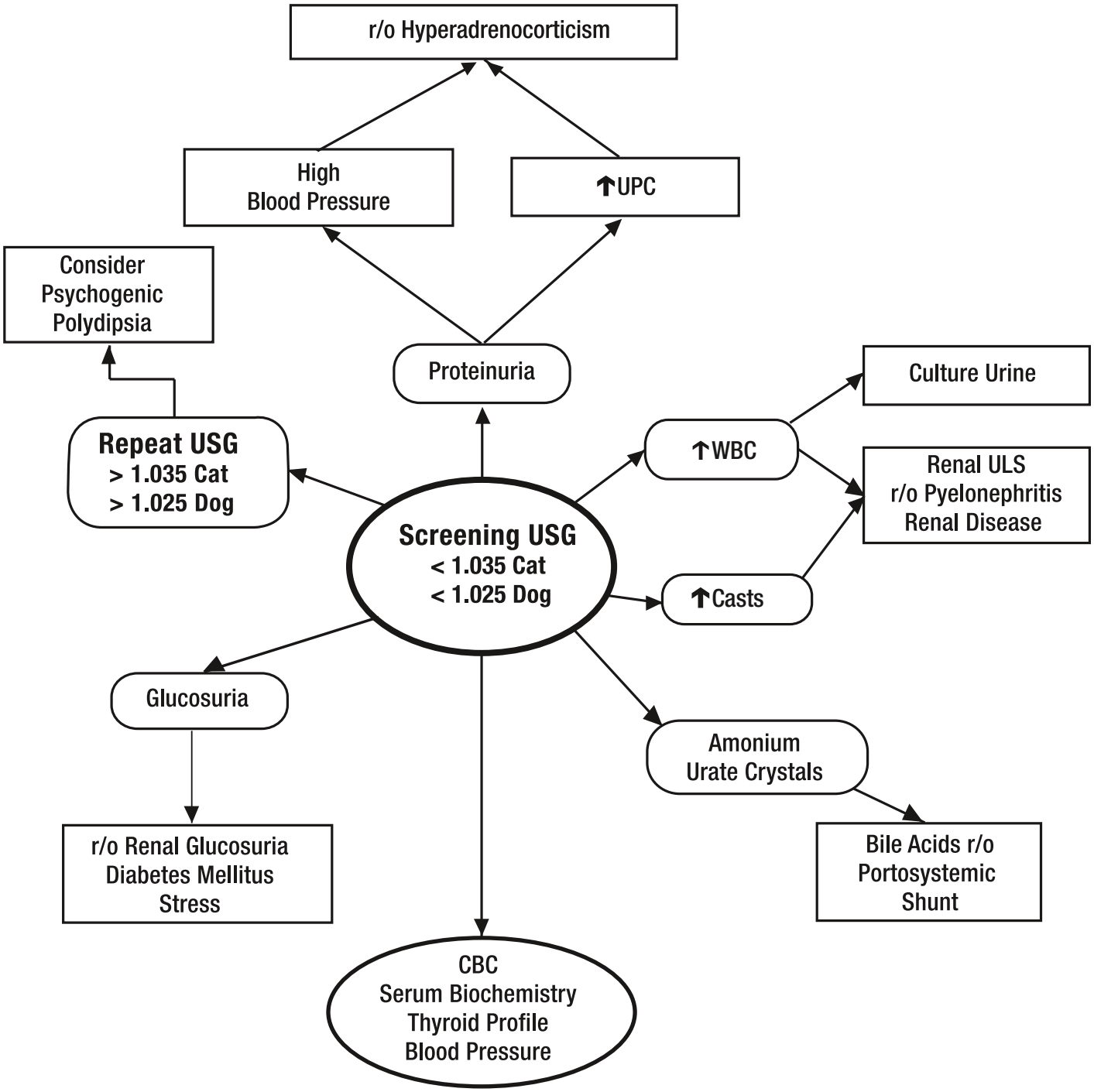
Urine concentration is most often evaluated using urinary specific gravity (USG) estimated by refractometry. Though urine osmolality is the gold standard for evaluation of urine concentration, excellent correlation between USG by refractometry and urinary osmolality has been reported in dogs[3,4]. The dipstrip evaluation is not reliable for estimation of USG in either dogs[4,5] or in cats[6]. Estimates of USG determined by refractometer may differ by type and brand of refractometer, depending on temperature compensation and scales that are used to make the reading. Refractometers should be chosen that use temperature compensation and that use different scales to determine the USG of dogs and cats[7].

The USG of normal animals (normal brain-pituitary-renal-adrenal axis) depends on dietary intake, hydration status, ambient temperature and humidity, and activity level. Dogs can produce urine of widely varying concentration throughout the day. Urine should be collected in the morning prior to eating and drinking, as this urine is most likely to have the highest USG of urine obtained during the day. USG was 1.035 ± 0.010; 1.009 - >1.050) in one study of 62 dogs; morning USG was higher in morning samples than in the evening and USG declined with age[8]. The median USG was 1.042 and mean USG was 1.038 in 51 urine samples taken weekly from 13 apparently normal dogs eating a variety of foods[9]. In that study, the USG ranged from 1.003 to 1.068; 37 of the 51 samples had USG > 1.030. Pooled 24 hour urine samples from normal dogs usually have USG of 1.020 or greater; the same dog can vary USG from 1.006 to > 1.040 during a 24 hour period[8].

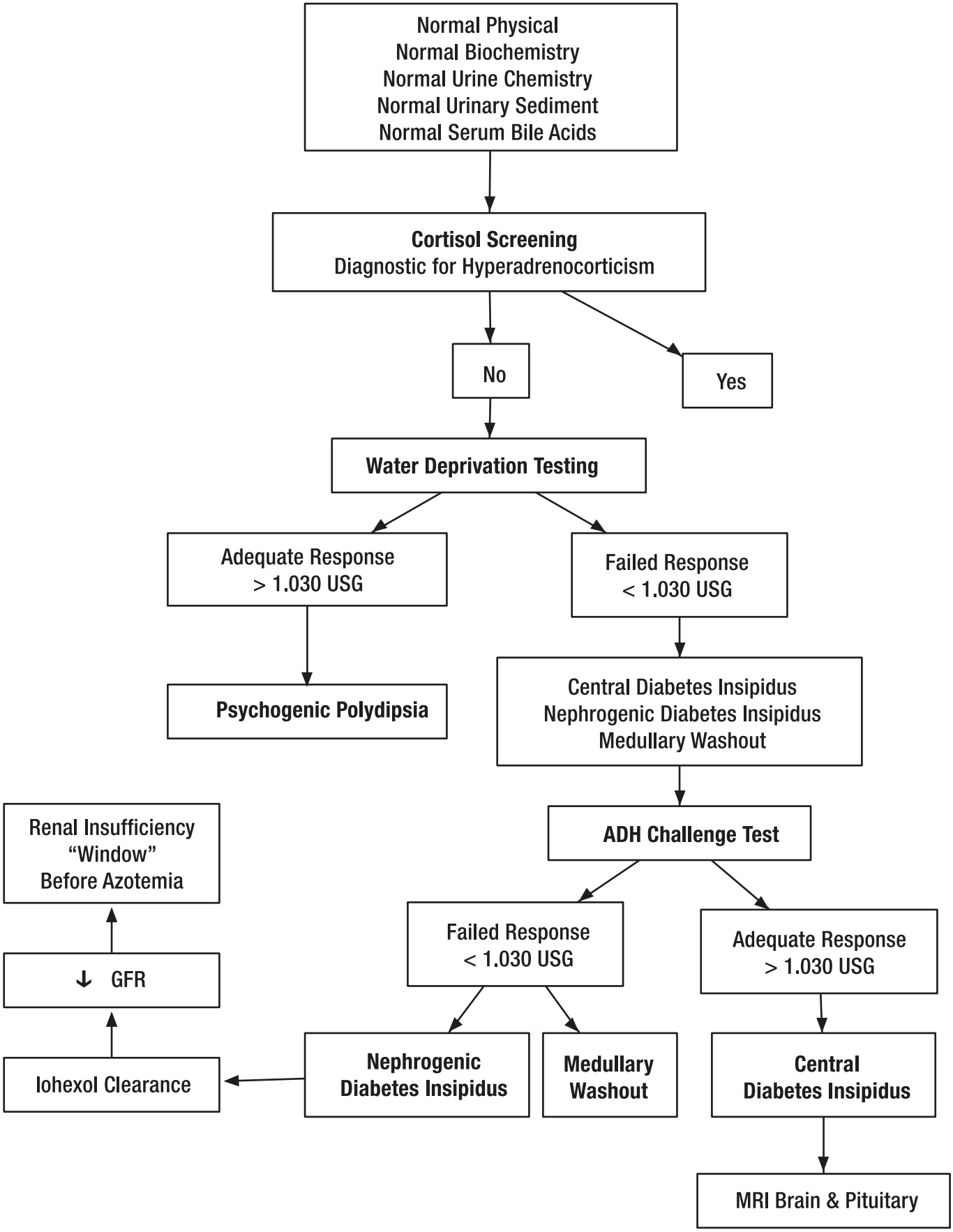
Appproach to Polyuria and Polydipsia - History



Approach to Polyuria and Polydipsia
Based on Initial USG



Approach to Polyuria and Polydipsia
When Cause is Not Obvious
After History, Examination, and Minimum Data Base



The USG of normal cats varies far less throughout the day than that of dogs. Normal cats housed under laboratory conditions in our hospital produce urine with a minimum USG of 1.035 when eating dry food and 1.025 when eating canned food[10]. Submaximal concentration of urine is expected in those with pUpD. The USG from young normal dogs or cats that are dehydrated should be 1.050-1.076 in dogs[11] and 1.047-1.087 in cats[12]. A USG of 1.040 is used as the minimum concentration expected of sick dogs or cats that are dehydrated. Although healthy dogs and cats can make urine with USG as low as 1.001, this is not common.

In dogs with pUpD, water deprivation testing is the next step after hyperadrenocorticism has been ruled out. Water deprivation testing (WDT) is a way to establish the patient's physiologic response to hypertonic plasma perfusing the hypothalamus, which would usually signal the release of antidiuretic hormone (ADH; vasopressin) from the posterior pituitary. Mild dehydration stimulates ADH secretion into the peripheral circulation, where it can exert its effects on the collecting tubule to concentrate urine and raise USG[11,13,14]. USG should be determined by the same operator using the same refractometer to ensure consistency of reported readings. It is important to carefully monitor the progress during the WDT so that the patient does not become too dehydrated. WDT should not be performed in patients that are already dehydrated, as they have already failed the challenge to concentrate their urine. WDT should also not be performed in those with azotemia, as dehydration may cause further injury to the kidneys. WDT should not be performed in those with hypercalcemia because the magnitude of hypercalcemia will be increased. Though not contraindicated, it is not necessary to perform WDT in those animals with other organ dysfunctions or metabolic disorders that easily account for the lack of urine concentration.

Unfortunately, measurement of ADH is not routinely performed due to methodological and handling issues that limit its usefulness. Even when this measurement is available, pulsatile secretion of ADH in dogs makes interpretation difficult. Measurement of urinary aquaporins could preclude the need to measure serum or plasma ADH but its clinical utility as a diagnostic tool has not yet been established.

The abrupt WDT involves the abrupt removal of all water intake and is performed in the hospital. We recommend no food be fed during this time since moisture content and solute load for renal excretion will influence urine concentration. The patient is weighed prior to the start of the test, and abrupt WDT is stopped if the patient loses 5% of the body weight, or if 'adequately' concentrated urine is produced. Body weight and USG should be evaluated every two hours in those with severe polyuria, or every 4 hours in those with less severe polyuria. Urine concentration with USG > 1.040 is adequate, but USG > 1.030 is considered adequate in those that have had longstanding pUpD. Prolonged pUpD will lead to medullary washout, making concentration of urine difficult until tonicity of the medulla has been restored. Measuring sequential USG is facilitated by placement of an indwelling urinary catheter; otherwise urine previously formed will admix with newly formed urine, which confuses interpretation of results. The effects of WDT and ADH challenge in various conditions are presented in Figure 4.

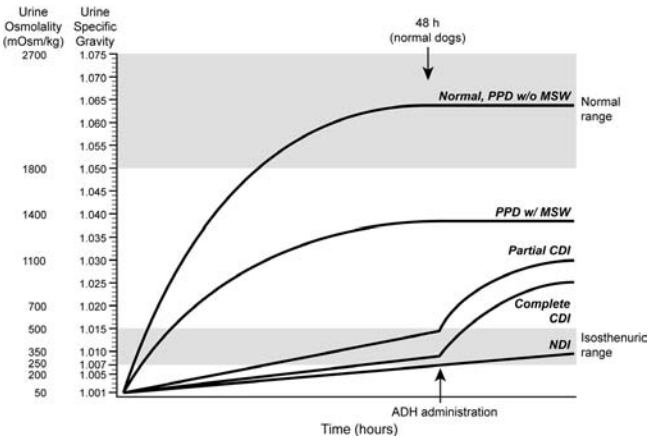


Figure 4. Hypothetical response to water deprivation testing and then to ADH testing. PPD = psychogenic polydipsia; MSW = medullary solute washout; CDI = central diabetes insipidus; NDI = nephrogenic diabetes insipidus. From "Disorders of Sodium and Water:Hypernatremia and Hyponatremia" Figure 3-16 In *Fluid and Electrolyte and Acid-Base Disorders in Small Animal Medicine* 3rd edition SP Dibartola Editor, Elsevier 2006. Used with permission.

If the USG changes from submaximally concentrated urine to USG > 1.030 following WDT, the diagnosis is psychogenic polydipsia. Psychogenic polydipsia may be a form of a behavioral disorder or neurosis, but can also be secondary to portosystemic shunting, advancing liver disease, polycythemia, paraneoplastic hypoglycemia, hypoparathyroidism with hypocalcemia, or hyperadrenocorticism. Rarely, psychogenic polydipsia will be encountered with primary brain lesions. Psychogenic polydipsia is reported to be rare in dogs, but is relatively common in our hospital setting. German Shepherd dogs may be over represented with this diagnosis. Psychogenic water drinking is very rare in cats.

The WDT is terminated when the USG is relatively unchanged when mild dehydration has been created to ensure release of ADH. This is defined as a < 10% increase in the USG on 3 consecutive urine samples at two hour intervals. The WDT is also terminated when > 5% body weight has been lost regardless of USG. Failure to adequately respond to WDT occurs in those with central diabetes insipidus (lack of ADH release), nephrogenic diabetes insipidus (lack of response to adequate circulating ADH), and in those with medullary washout of solutes (circulating ADH and ADH receptor interactions are normal, but water fails to move out of the collecting tubules due to lack of an osmotic gradient that otherwise favors this movement).

In those that fail to produce concentrated urine following WDT, exogenous ADH is then given to ensure that the kidneys cannot respond to ADH. If the animal is not obviously dehydrated, ADH testing can begin immediately

after the WDT fails to result in the production of concentrated urine. Desmopressin (dDAVP) is an aqueous form of synthetic ADH with minimal pressor activity and enhanced antidiuretic properties compared to native ADH. One to 5 micrograms of the nasal formulation is given subcutaneously and USG is checked at 30, 60, 90, and 120 minutes after administration to determine the effect[14]. A dramatic increase in USG following exogenous administration of ADH typically occurs in those with central diabetes insipidus. Failure to respond to WDT followed by failure to respond to ADH testing is consistent with the diagnoses of nephrogenic diabetes insipidus or medullary washout.

In some cases in which there is very dilute urine and the suspicion is high for central diabetes insipidus, ADH testing instead of WDT can be performed while the animal is at home with the owner. Oral dDAVP (either a 0.1 or 0.2 mg tablet) can be given every 8 hours for several days up to a week. A 0.1 mg tablet provides 5 micrograms of dDAVP (oral dDAVP has much less bioavailability than does the nasal spray formulation). Urine samples should be collected several times throughout the day to measure USG and determine the effect of exogenous ADH. However, some medullary washout likely exists initially, so USG should be measured after a few days of dDAVP treatments. Alternatively, 1 to 4 drops of the nasal spray (1 drop provides 1.5 to 4 micrograms dDAVP) can be placed into the conjunctival sac twice daily and USG monitored. Although the nasal spray is not sterile, 2 to 5 micrograms (100 microgram/mL; 0.05 mL = 5 micrograms) can be administered by subcutaneous injection twice daily after filtering, and the effects monitored[14].

All forms of dDAVP are costly. Twice daily treatment with dDAVP is needed to adequately minimize polyuria, although it can be given once daily biased toward the sleeping hours to minimize costs to the owners. Larger doses may increase the magnitude of urinary concentration and its duration of effect. Treatment with dDAVP is not required if the animal has free access to water, stays hydrated, and is allowed to urinate large volumes frequently in spaces acceptable to the owners. Water restriction in the absence of dDAVP treatment can result in large losses of urinary free water and rapid increases in serum sodium and osmolality that may have severe neurologic consequences for the patient.

In those patients that fail both the abrupt WDT and ADH testing, washout of medullary solutes should be considered. In these instances, gradual WDT, either alone or in conjunction with dDAVP, may allow repletion of the medullary solutes. Gradual water deprivation entails progressive water restriction over several days. The water intake is gradually decreased from its previous level to 100 mL/kg/day. The gradual WDT is discontinued if the animal becomes sick or daily body weight decreases by more than 5%. After this gradual WDT, abrupt WDT is again performed; if the patient fails to adequately concentrate urine during this abrupt WDT, medullary washout is excluded from further consideration. Those animals that now concentrate urine have either a diagnosis of CDI or psychogenic polydipsia with medullary washout that has been corrected.

In conclusion, pUpD can be diagnostically challenging. However, by following a logical train of thought and diagnostic work up, the clinician usually can determine the underlying cause and appropriate course of treatment.

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Alopecia: Is An Endocrine Disorder Responsible?

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Introduction

Alopecia (loss of hair, aka hypotrichosis) may occur for a wide variety of reasons and may be a primary or secondary lesion of skin disease. In the majority of dogs with alopecia, hair loss is a consequence of self-trauma and in this case is a secondary event. In contrast, the hair loss associated with endocrine disease is a consequence of hair cycle arrest and is a primary lesion. This paper will present an algorithm and decision-making process that should aid and guide the general practitioner towards an etiologic diagnosis in dogs presenting with alopecia. The main focus will be on a discussion of the causes, diagnosis and treatment of dogs presenting with the classic endocrine-like alopecia, namely non-pruritic hair loss affecting the trunk but sparing the head and distal limbs.

Diagnostic approach

First, answer the question, "Is the dog pruritic or not, i.e. is the hair loss due to self-trauma or is it just falling out?" Most alopecia is secondary to self-trauma and is associated with allergic, parasitic, or infectious disease. A point of possible confusion may arise when alopecia is due to a non-pruritic disease yet a secondary bacterial or yeast infection is present that induces pruritus. In this case, answering the question, "What came first, pruritus or hair loss?" is critical, with alopecia preceding pruritus as the initial event when the primary disease is non-pruritic.

Second, once it is established that hair is falling out and not associated with self-trauma, the clinician should try and determine whether the alopecia is inflammatory or not. This may be evident from the physical examination, although some inflammatory causes of hair falling out may not have erythema on physical examination. Thus, in addition to the presence or absence of inflammation, the author considers the *pattern of hair loss* as helpful in distinguishing between inflammatory and non-inflammatory disease. Typically, inflammatory diseases result in patchy, focal-to-multifocal "moth-eaten" alopecia that may or may not be bilaterally symmetrical and may also affect the head and extremities as well as the trunk. In contrast, non-inflammatory causes typically result in diffuse, mostly bilaterally symmetrical alopecia confined to the trunk (black hair follicle dysplasia and congenital hypotrichosis may be exceptions).

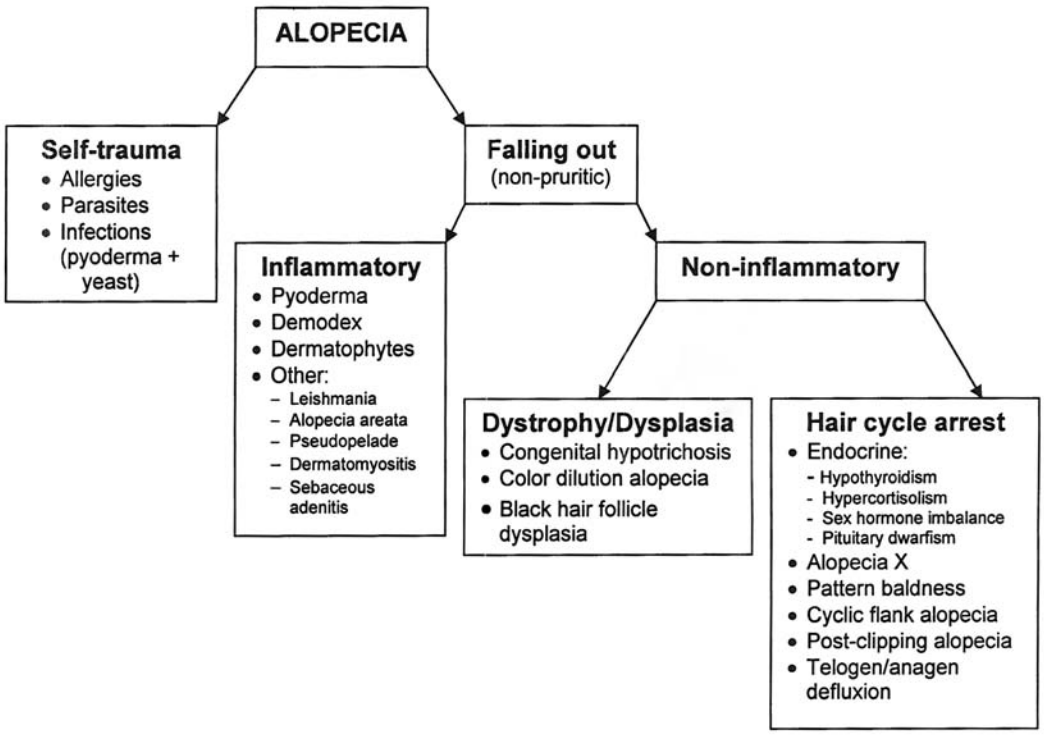
Third, if a non-inflammatory alopecia is suspected, consider whether other cutaneous and systemic clinical signs are present, which is usually the case with endocrine disorders. Consider breed (congenital hypotrichosis, color dilution alopecia, Alopecia X, pattern baldness and cyclic flank alopecia all have breed predilections), age, sexual status (intact or sterilized for sex hormone abnormalities), and the color of the affected hair coat (black hair follicle dysplasia, color dilution alopecia). In the majority of dogs with a primary problem of alopecia, following these guidelines will allow the clinician to focus on one, or a few, conditions for further, more specific, diagnostic tests.

Diagnostic procedures

In the case of inflammatory, patchy, focal-to-multifocal alopecia, perform cytology (cocci), deep skin scrapes (demodicosis), and DTM culture (dermatophytosis) first. Once these conditions are ruled out, other inflammatory alopecias require collection of skin samples by biopsy for histopathologic diagnosis.

In the case of non-inflammatory diffuse symmetrical alopecia, biopsy of skin for histopathology is indicated if the breed, age, and coat color are suggestive of congenital hypotrichosis, color dilution alopecia, black hair follicle dysplasia, pattern baldness, or cyclic flank alopecia. However, if there is uncertainty regarding the possibility of these disorders, or whenever an "endocrine" pattern is present, a minimum data base of CBC, biochemistry panel and UA, and more specific tests for hypothyroidism and hypercortisolism (Cushing's disease) should be pursued first (see other presentations in these proceedings for details on the diagnosis of these diseases). Most importantly, a diagnosis of Alopecia X should not be made without performance of adequate testing to rule out the more common endocrinopathies such as hypothyroidism and hypercortisolism.

A Diagnostic Approach to Alopecia



Microscopic lesions seen on skin histopathology may sometimes be helpful in distinguishing between non-inflammatory "endocrine" causes of alopecia. For example: hyperplasia of the follicular epithelium in hypothyroidism and hyperestrogenism; mucinosis in hypothyroidism; pronounced epithelial, follicular, and sebaceous atrophy or calcinosis cutis in hypercortisolism; and, striking flame follicles (excessive tricholemmal keratinization) in Alopecia X. However, it must be emphasized that the typical microscopic features of "generic" endocrine alopecia are seen in many cases and a definitive diagnosis is rarely made on the basis of histopathology alone. Caution should also be exercised when considering the significance of an abundance of telogen hairs either on a trichogram or on histopathology. Unlike humans who have anagen-dependent hair cycles, great breed variability exists in dogs. Poodles have anagen-dominant hair cycles, but most dog breeds appear to have telogen-dominant hair cycles. The duration of telogen is highly variable between breeds, with Nordic breeds having telogen that lasts for years. Thus, the significance of a predominance of telogen hairs should only be made in consideration of the breed of dog, and unfortunately, little information is known about the normal hair cycle of most breeds.

Dermatologic features

Non-cutaneous features of the following disorders, as well as detailed analysis of diagnostic tests and treatments is presented by other authors in these proceedings.

Hypothyroidism

Skin and coat changes are variable and may precede other clinical signs of hypothyroidism. Classic cutaneous lesions include non-pruritic symmetric truncal alopecia, with a dull dry hair coat and seborrhea. Alopecia may be patchy and multifocal, especially initially, and areas of increased friction may be the earliest sites of hair loss e.g. on the neck around the collar, elbows and hips, tail ("rat's tail"), and on the bridge of the nose. The hair coat may become lighter (due to bleaching) and in some cases there is a preferential loss of primary guard hairs, leaving behind a "puppy coat," with later loss of all hair. Seborrhea is typically greasy when present but may also be dry with excessive scaling. Ceruminous otitis may be prominent with secondary bacterial and yeast otitis. Secondary skin infections with staphylococcal and yeast organisms are common and may cause secondary pruritus, especially with yeast infections. Large calluses may form on the elbows and hocks and poor wound healing may be noted. Acral lick dermatitis ("lick granuloma") may be a feature; the author notes this more commonly in Dobermans and Retriever breeds with hypothyroidism. Myxedema (accumulation of glycosaminoglycans in the dermis causing skin thickening) is occasionally seen affecting the head and face and leading to a "tragic expression." Adult-onset generalized demodicosis is associated with underlying hypothyroidism and alopecic dogs should always have deep skin scrapings performed.

Hypercortisolism

Skin and coat changes are variable and may precede other clinical signs of hypercortisolism. Classic cutaneous lesions include non-pruritic symmetric truncal alopecia with thin hypotonic skin. Focal or patchy alopecia may be noted initially. Secondary staphylococcal pyoderma is common, and sometimes pustules may be large and non-follicular, and reminiscent of bullous impetigo. The thin skin bruises easily and wound healing may be poor. Hypercortisolism is the most common underlying cause of adult-onset generalized demodicosis (especially iatrogenic hypercortisolism) and the lesions associated with demodicosis may override the typical lesions of hypercortisolism. Calcinosis cutis is a feature in some cases and occurs most commonly over the dorsal neck, rump, axilla and inguinal area. The clinical lesions of calcinosis cutis are variable and may include hard white cyst-like lesions, firm erythematous plaque-like lesions, or hemorrhagic bullae with ulceration and crusts.

Alopecia X

Also referred to as pseudo-Cushing's, adult-onset hyposomatotropism, growth hormone-responsive alopecia, castration-responsive alopecia, biopsy-responsive alopecia, adrenal sex hormone imbalance, adrenal sex hormone hyperplasia, black skin disease, etc. What does this tell us? Probably that there are a number of disorders with very similar clinical presentation, possibly with overlapping etiology, and likely multifactorial in some instances.

The condition is best described in Pomeranians, plush-coated Nordic breeds, Miniature Poodles, and Chow-Chows, although Alopecia X has been recorded in other breeds as well. The condition occurs in male and female dogs, sterilized or intact, and usually starts in early to mid-adulthood. Alopecia is non-pruritic and truncal, and may affect frictional areas initially with progression to more generalized alopecia. Primary hairs may be lost first in some cases, exposing a fluffy "puppy coat," but eventually secondary hairs are also lost. The underlying skin tends to become markedly hyperpigmented, and mild scaling may be present, as well as occasional comedones. Hair fails to grow in shaved areas. A feature of this condition is the regrowth of hair at sites of trauma (biopsy, skin scrapes, wounds). There are no reports of noncutaneous disease or progression of disease to involve other organs associated with Alopecia X.

Diagnosis of Alopecia X is based on history, clinical signs, breed, and the rule out of other endocrinopathies (hypothyroidism, hypercortisolism, functional gonadal neoplasms). Histopathology of the skin is typically reported as "endocrine-like," although the presence of significant numbers of flame figures may be supportive of Alopecia X. Specific tests of adrenal sex hormones and their intermediaries via ACTH stimulation testing can be performed; the assays are performed at the University of Tennessee. However, current reports indicate that abnormal values may be found in clinically normal dogs, normal values may be found in clinically affected dogs and there appears to be breed variability. Further research is needed before the true value and accuracy of ACTH stimulation tests for sex hormone intermediaries can be determined, and currently, it may be most valuable in ruling out other diseases (such as hypercortisolism).

Numerous treatments have been suggested for Alopecia X with variable results. If the dog is intact, castration or spay may result in hair regrowth. This is a benign cosmetic disorder and benign neglect should be considered as a reasonable option. The risks associated with drug therapy should always be considered and discussed with the owner before embarking of specific treatments. Hormone replacement therapy with growth hormone (0.15 IU/kg of porcine growth hormone SC 2x weekly for 6 weeks), estrogen, methyltestosterone (1 mg/kg to a maximum of 30mg PO q 48 hrs, or 1-2 mg/kg of injectable repositol testosterone q 30 days) and thyroxine ($0.5mg/M^2$)have been used to stimulate hair regrowth with variable results. Adrenolytic drugs such as mitotane have been reported to be efficacious: induction doses of 15-25 mg/kg q 24 hrs are lower than those used to treat hypercortisolism. Trilostane (Modrenal® or Vetoryl®), which blocks adrenal steroid hormone synthesis, has been reported to be efficacious at 10 mg/kg q 24 hrs initially then tapering to q 48 hrs (depending on results of ACTH stimulation tests 2-6 hours post-pill). The drug is currently unavailable in the USA but may be obtained from another country once FDA approval is obtained. Melatonin is a relatively safe form of therapy and is administered at a dose of 3-6 mg q 8-12 hours. Irrespective of the treatment, the owner should understand that results are variable and may stimulate partial or complete hair regrowth that may be permanent or transient.

Disorders most similar to endocrine alopecia

Pattern Baldness

Usually starts in juvenile (about 6 months old) or young adult dogs, and has variable progression. Patterns include: pinnal alopecia in Dachshunds; ventral alopecia of Dachshunds, Boston Terriers, Chihuahuas, Miniature Pinschers, Whippets, and Boxers; pattern alopecia of Curly Coated retrievers, Portuguese Water dogs, and American Water Spaniels; and bald thigh syndrome and ventral alopecia in Greyhounds. Melatonin may stimulate hair regrowth in some dogs.

Color Dilution Alopecia

An autosomal recessive disorder in some dogs with dilute (blue or fawn) hair coats. Most recognized in Dobermans but also reported in Dachshunds, Great Danes, Whippets, Italian Greyhounds, Chow Chows, Yorkshire Terriers, and Chihuahuas. Diagnosis is based on breed and coat color predisposition and abnormal melanin clumping in the hair shafts (trichogram and histopathology) and in the epidermal and follicular basal epithelial cells (histopathology). Treatment with oral retinoids and fatty acid supplementation may be beneficial. Recently, melatonin has also been used with variable results.

Recurrent flank alopecia

Usually acute-onset alopecia in the thoracolumbar region, but may be associated with more widespread truncal alopecia. The lesions are usually well demarcated and there is striking hyperpigmentation. The course of the disease is highly variable and may occur only once or a few times, it may be seasonally recurrent, or may be non-seasonally progressive. It is most often seen in Boxers, English Bulldogs, Airedale Terriers, and Schnauzers. As this is a benign disease and the course of the disease is unpredictable, no treatment is indicated initially. Melatonin may be helpful in some cases.

Sebaceous adenitis

Inflammation and destruction of the sebaceous glands results in alopecia and scaling that usually involves the trunk in a symmetrical pattern, but also tends to involve the head and pinna as well. Breeds at high risk are the Standard Poodle and Akita, but the disease has been reported in many pure-bred and cross-breed dogs. The hair coat is dry, brittle and dull and characteristic hair casts are seen at the base of hairs (so-called "candle wax" appearance). Diagnosis is by histopathology of skin specimens. Treatments include anti-seborrheic and moisturizing shampoos, topical propylene glycol, and various systemic treatments (cyclosporine, retinoids, and fatty acids).

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Diagnosis of Hyperadrenocorticism (Cushing's Syndrome) in Dogs - Which Tests are Best?

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HISTORY

Dogs chronically exposed to excess cortisol usually develop a classic combination of clinical signs, some of which may be dramatic. These common signs include polydipsia, polyuria, polyphagia, abdominal enlargement, alopecia, pyoderma, panting, muscle weakness, thin skin, and lethargy. It must be remembered, however, that not all dogs with hyperadrenocorticism develop the same signs. From this long list of potential signs (plus others), most dogs exhibit several (but not all) of these problems. Hyperadrenocorticism is a *clinical disorder*, and animals afflicted with this disease must have at least some clinical signs or the diagnosis must be questioned. Clinical signs result from the combined gluconeogenic, lipolytic, protein catabolic, anti inflammatory, and immunosuppressive effects of glucocorticoids.

Typically, the course of the disease is insidious and slowly progressive. Owners usually report observing some alterations typical of hyperadrenocorticism in their pet for 6 months to as long as 6 years before they seek veterinary attention for their animal, since these changes are quite gradual in onset and are often believed to be a result of simple "aging." Commonly, only after signs become intolerable to the client or after abnormalities are pointed out by people who see a pet infrequently (therefore objectively noting obvious changes that have developed so slowly the owners do not observe them) that professional opinion is sought. The most common reasons that owners give for finally seeking veterinary help are usually polydipsia/polyuria, polyphagia, lethargy, panting, and/or hair coat changes. It should be pointed out that dogs with Cushing's syndrome do not have vomiting, diarrhea, anorexia, weight loss, or other signs that would cause many owners to quickly seek veterinary care.

PHYSICAL EXAMINATION

The physical examination on a typical "Cushing's" dog reveals an animal that is stable, hydrated, has good mucous membrane color and is not in distress. Veterinarians will usually observe, during the physical examination, many of the signs seen by owners. Among these abnormalities are abdominal enlargement (truncal obesity), panting, bilaterally symmetrical alopecia, skin infections, and comedones. Hyperpigmentation, testicular atrophy, and hepatomegaly are commonly identified on physical examination. Ectopic calcification (calcinosis cutis), clitoral hypertrophy, and easy bruisability are much less common. There is, however, remarkable variation in the number and severity of abnormalities noted. These dogs may have a single dominant sign or 10 signs.

SENSITIVITY AND SPECIFICITY (WHICH TEST IS BEST?)

Sensitivity of a particular test refers to the number of patients with a condition whose test results are abnormal. Specificity of a particular test refers to the number of patients that do not have a condition but their test results are positive for that condition. Medicine would be much easier if our tests were 100% sensitive and 100% specific. Since this is never the situation, the most commonly asked question regarding naturally occurring hyperadrenocorticism is: "which test is best?" There is no doubt that the most specific and sensitive tests for this condition are history and physical examination. Therefore, all test interpretations must be done in the context of these two parameters.

"ROUTINE" DATA BASE

Any dog suspected of having hyperadrenocorticism from the history and physical examination should be thoroughly evaluated before specific endocrine testing is undertaken. These initial tests should include clinicopathologic studies (complete blood count [CBC]; urinalysis with culture; and a serum chemistry profile). In addition to blood and urine testing, abdominal ultrasonography (preferred over radiography) should be completed. Finding a large percentage of abnormalities on initial screening tests that are consistent with hyperadrenocorticism further allows the veterinarian to establish a diagnosis that was initially based on history and physical examination. Typical abnormalities include dramatic increases in serum alkaline phosphatase activity, mild-to-moderate increases in ALT and serum cholesterol, low-normal or low BUN, urine specific gravity <1.020 on a sample caught by the owner at home, and bacteriuria. The more expensive and sophisticated studies needed to "confirm" a diagnosis and localize the cause of Cushing's syndrome can be recommended to the client if the dog is still believed to have this condition. Initial data base results not only ensure that the veterinarian is pursing the correct diagnosis but also might alert the clinician to any concomitant medical problems. These problems may be common for hyperadrenocorticism (urinary tract infection) or unexpected (renal failure), but in any case may require specific therapy.

"SCREENING" TESTS

Background

After establishing a presumptive diagnosis of canine hyperadrenocorticism from a review of owner observations, physical examination, and laboratory data base, one usually proceeds to attempt "confirmation" of the diagnosis. When necessary, and if possible, an attempt can also be made to determine whether the pet has pituitary dependent hyperadrenocorticism (PDH) or an adrenocortical tumor (ACT). Choosing a screening test for Cushing's syndrome is important because that test result may determine whether or not a dog is treated. Routinely used screening tests include ACTH stimulation, low dose dexamethasone, and the urine cortisol : creatinine ratio. The decision to treat a dog for Cushing's syndrome should never be based solely on laboratory information. Cushing's syndrome is a clinical disorder with clinical signs. If a dog has no clinical signs of Cushing's syndrome, treatment is not recommended. This concept gains importance when it is understood that no screening test is correct all of the time, i.e., as previously stated, sensitivity and specificity is never 100%. Some dogs with non-adrenal disease and many with polyuria and polydipsia due to a condition other than Cushing's syndrome can have false positive screening test results for hyperadrenocorticism. Because false positive test results have been observed with any commonly used screening test, the definitive diagnosis of Cushing's syndrome should never be solely on screening test results, especially in dogs without classical clinical signs or in those with known non-adrenal disease. In our experience, the most sensitive, specific, and reliable screening tests for hyperadrenocorticism in dogs are history and physical examination. The most sensitive, specific, and reliable hospital study is the low dose dexamethasone test.

Low Dose Dexamethasone Test (LDDS)

The protocol utilized for this test is obtaining plasma samples for cortisol before and 4 and 8 hours after I.V. administration of 0.01 mg/kg dexamethasone. The 8-hour plasma cortisol is used as a screening test for hyperadrenocorticism, with concentrations >1.4 μg/dl being consistent with (not confirming) the diagnosis of Cushing's syndrome. This test is relatively sensitive and specific, but not perfect. Approximately 90% of dogs with Cushing's syndrome have an 8 hour post-dexamethasone plasma cortisol concentration >1.4 μg/dl and another 6 to 8% have values of 0.9 - 1.3 μg/dl. The results of a low dose test can also aid in discriminating PDH from ACT, using three criteria: 1) an 8 hour plasma cortisol >1.4 μg/dl but <50% of the basal value; 2) a 4 hour plasma cortisol concentration <1.0 μg/dl; and 3) a 4 hour plasma cortisol concentration <50% of the basal value. If a dog has Cushing's and it meets any of these three criteria, it most likely has PDH. Approximately 65% of dogs with naturally occurring PDH demonstrate suppression, as defined by these three criteria. A dog with Cushing's that fails to meet any of these three criteria could have either PDH or ACT. However, if it has two relatively equal sized adrenals on abdominal ultrasonography, it most likely has PDH.

ACTH Stimulation (NO LONGER RECOMMENDED)

The ACTH stimulation test has been popular for decades in veterinary medicine. It is simple to complete and takes little time. The other significant feature regarding results of an ACTH stimulation test is that this is the only study which reliably demonstrates the effect of o,p' DDD on the adrenal cortex. Thus, some veterinarians want results of an ACTH stimulation test, prior to initiating o,p' DDD therapy, because the results are used as "baseline" information to objectively monitor effects of o,p' DDD. Regardless of the protocol chosen, it must be appreciated that 20 - 30% of dogs with Cushing's syndrome have test results within the reference range (in our laboratory: post ACTH plasma cortisol concentrations of 6 to 17 μg/dl). An additional 20 - 30% of dogs with Cushing's have test results described as "borderline" (plasma cortisol concentrations >17 but <22 μg/dl). Therefore, the test is not considered sensitive but is relatively specific, i.e., those dogs with plasma cortisol concentrations >22 μg/dl frequently have Cushing's. However, specificity of an exaggerated response to ACTH is also not perfect. Therefore, test results should never be interpreted without knowing results of history, physical examination, and routine data base testing. There are no features of ACTH stimulation test result that allow discrimination between PDH and ACT. As ACTH has become more and more expensive, this test is losing popularity. ACTH gel is effective and synthetic ACTH can be given at 0.05 mg/kg (IV or IM) instead of using 0.25 mg (one vial) per dog. Excess cortrosyn can be frozen while maintaining potency for about 6 months. In our opinion, the lack of sensitivity of the ACTH stimulation test makes it a test that the profession should abandon. The situations in which ACTH stimulation testing would be indicated include monitoring therapy for naturally occurring hyperadrenocorticism, to aid in the diagnosis of iatrogenic Cushing's syndrome, and as the "gold standard" for the diagnosis of naturally occurring hypoadrenocorticism.

Urine Cortisol: Creatinine Ratio (UC:CR)

The urine UC:CR ratio is easily performed (simply have the owner collect and deliver urine to the hospital and submit it to the laboratory) and, therefore, it is usually less expensive than other screening tests. Most dogs (~97%) with naturally occurring Cushing's syndrome have an abnormal result (the test is sensitive) but a significant percentage of dogs with polyuria / polydipsia due to other conditions and those with non-endocrine illness also have abnormal results (the test is not specific). It has been suggested that the UC:CR be routinely performed only on urine collected by an owner at home, rather than having it collected in-hospital. Since this protocol eliminates travel or hospital stress from altering test results, it seems reasonable to follow this concept. We do not utilize this test with the same degree of confidence with which we use the low dose dexamethasone screening test. However, a normal result is quite uncommon in a dog with Cushing's syndrome while an abnormal result could be used to prompt further testing. Therefore, this test can be used as a prompt to recommend abdominal ultrasonography and a low dose dexamethasone test to an owner.

17 αHydroxyProgesterone (17OHP) Testing
The use of 17OHP has been recommended as a screening test for dogs with "atypical Cushing's syndrome." The definition of "atypical" is a dog with clinical signs and routine laboratory testing consistent with hyperadrenocorticism but with normal low dose dexamethasone screening test results, normal ACTH stimulation test results, and normal urine cortisol : creatinine ratio test results. Human beings, dogs and cats with adrenocortical tumors have been reported in which the primary hormone secreted by such tumors has been 17OHP. Adrenocortical tumors have long been known to synthesize and secrete a myriad of steroids and it is not surprising to learn that some primarily produce steroids other than cortisol. Such dogs and cats, in our experience, do not have "normal" screening tests results, but their results may be relatively low in cortisol. It is extremely rare for a dog or cat with PDH to produce only 17OHP. Further, the recommendation regarding use of this hormone involves assaying 17OHP after ACTH stimulation. Our recommendation would be repeating a low dose dexamethasone test if results are <0.9 μg/dl at the 8-hour sample, since the most common explanation for such a result would be administration of 0.1 instead of 0.01 mg/kg of dexamethasone. If one is convinced that a dog has naturally occurring hyperadrenocorticism, and if that dog persistently has a non-diagnostic low dose dexamethasone test result, use of ACTH stimulation and assessment of 17OHP can be considered. This is an extremely unusual situation, however.

DISCRIMINATION TESTS

Low Dose Dexamethasone Test
Please see previous discussion.

Endogenous ACTH
This test is relatively difficult to perform because the plasma must be handled with care, the test is not routinely available, and it is expensive. Having used this test for more than 30 years, we have found it to be highly specific and sensitive (normals: 10 to 100 pg/ml; PDH: 45 to 450 pg/ml; ACT: results are undetectable). There is some overlap in results, however. Most specifically, some dogs with PDH and some with ACT have results that range from 10 - 45 pg/ml. Our experience with the LDDS and abdominal ultrasonography has limited the need for assaying the endogenous ACTH concentration. This test is most commonly utilized when other discrimination test results provide conflicting information.

High Dose Dexamethasone Suppression (HDDS)
The HDDS test is relatively easy to perform (plasma obtained before and 4 or 8 hours after I.V. administration of 0.1 mg/kg dexamethasone), readily available and inexpensive. If a dog has Cushing's syndrome and the plasma cortisol, 8 hours post dex, is <50% of the basal value, the dog has PDH. However, our experience with the LDDS and abdominal ultrasonography has limited the need and use of HDDS. Approximately 75% of dogs with PDH demonstrate suppression with the HDDS. Realizing that approximately 65% of PDH dogs demonstrate "suppression" consistent with PDH on the LDDS limits the value of this test by only identifying an additional 10% of afflicted dogs.

Abdominal Ultrasonography
In dogs suspected as having hyperadrenocorticism, abdominal ultrasonography serves three major functions. First, it is part of the "routine data base" utilized to evaluate the abdomen for any unexpected abnormalities (urinary calculi, masses, etc.). Second, the study is used to evaluate the size and shape of the adrenals. If the adrenal glands appear to be bilaterally normal sized or large in a dog or cat otherwise diagnosed as having Cushing's, this is considered strong evidence of adrenal hyperplasia due to pituitary dependent disease (PDH). If one, large, irregular and/or invasive adrenal is visualized and the opposite is small or not seen, adrenal tumor must be suspected. Some dogs with ACT have one adrenal that appears to be a "mass" and the other may be normal or enlarged. One must consider the possibility of PDH with irregular adrenals or PDH in a dog that also has a pheochromocytoma. Third, if an adrenal tumor is identified, ultrasound is an excellent screening test to identify hepatic or other organ metastasis, compression of adjacent tissues by a tumor, or tumor invasion into the vena cava or other vascular structures. It must be emphasized that interpretation of abdominal ultrasonography is completely operator dependent. Radiologists at our school routinely visualize both adrenals in healthy dogs and cats. The only limitations to successfully visualizing the adrenals are: 1) the pet's willingness to remain still and 2) air in the intestinal tract. Neither of these problems is common and both adrenals are usually visualized. In dogs and cats with PDH, both adrenals are also routinely visualized. The adrenals in PDH are usually described as relatively equal in size. Approximately 50% of dogs with PDH have adrenals that appear to be "normal" in size and about 50% have adrenal glands that appear to be enlarged. Adrenal size is best determined using the width of the left adrenal (7.5 mm represents the upper limit of normal).

Trilostane - 5 Years of Clinical Experience for the Treatment of Cushing's Disease

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The standard medical treatment for hyperadrenocorticism (HAC) in dogs has long been mitotane. Mitotane leads to selective, progressive necrosis of the adrenal cortex, which may be partially or completely destroyed, depending on the treatment protocol. The efficacy of mitotane is favorable, and in dogs with pituitary-dependent hyperadrenocorticism (PDH), more than 80% of the dogs have a good to excellent response. Disadvantages of mitotane include potential development of adrenocortical insufficiency, possible drug intolerance, and a relatively high frequency of relapses during therapy. Due to these problems, a variety of other drugs have been investigated. Several of them have been shown to have limited efficacy. However, trilostane, an orally active steroid analogue, has gained wide popularity, especially in Europe, after its first report in 1998.[a] So far, three prospective studies evaluated the effects of trilostane in dogs with pituitary-dependent hyperadrenocorticism (PDH) and they all came to the conclusion that it is an effective and safe medication. A total of 119 dogs with PDH were included in those studies and 70, 90, and 97% showed marked improvement or resolution of clinical signs.[1,2,3]

In some European countries, trilostane is now officially registered for use in dogs with HAC under the name of Vetoryl® (Dechra Veterinary Products) and therefore has to be used as a fist line treatment.

From studies in humans and other species, the assumption has been made that trilostane is a competitive inhibitor of 3β-hydroxysteroid-dehydrogenase in dogs. This enzyme system mediates the conversion of pregnenolone to progesterone in the adrenal gland. Cortisol, aldosterone, and androstendione are produced from progesterone via various biochemical pathways. Since trilostane inhibits progesterone synthesis it blocks the synthesis of its end products. Recently, we have proven that trilostane definitively has an inhibitory effect on the 3β-hydroxysteroid dehydrogenase enzyme system in dogs. However, inhibition is incomplete and there are additional effects more distal in the enzyme cascade, either on the 11β-hydroxylase or the 11β-hydroxysteroid dehydrogenase (Fig. 1).[4]

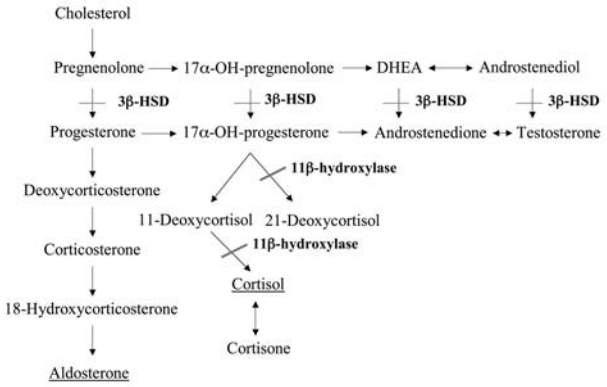

Fig. 1 Steroid synthesis pathway and sites of action of trilostane (inhibition of 3ß-HSD and 11ß-hydroxylase) Sieber-Ruckstuhl et al, 2005

In Zurich we have been using trilostane since 1999, and in dogs with PDH it has replaced the use of mitotane completely. Over the years, between 80 - 90% of dogs with PDH have shown a good to excellent response. The time required for a noticeable improvement is similar to that of mitotane. There is a rapid decrease in polydipsia, polyuria, polyphagia, an increase in activity level, and a delayed improvement in hair coat, skin condition, and abdominal muscle tone. Some dogs may have transient worsening of their dermatologic problems before clinical improvement becomes obvious; this may also occur with mitotane.[1]

Initially, only 60 mg capsules were available rendering dosing per kg bodyweight impossible. Dose therefore was determined on the basis of three categories of bodyweight: dogs less than 5 kg received 30 mg SID (1/2 capsule), dogs 5 to 20 kg received 60 mg SID (1 capsule) and dogs greater than 20 kg received 120 mg SID (2 capsules). Today 30 mg, 60 mg and 120 mg capsules are available. The recommended starting dose, although slightly altered by the company, is still according to weight categories. Initially, re-evaluations and dose adjustments have to be performed frequently. After several months, dosing becomes relatively stable in the majority of cases.

According to a recent consensus statement of endocrinologists from seven European countries (Amsterdam, 4-19-2006), initial dose should be according to bodyweight and should be in the range of 2 - 5 mg/kg (dogs ≤ 5 kg at the lower end of the dose range). Applications should be SID, in the morning with food. Re-evaluations should be performed after 1-2 weeks, 4 weeks, 12 weeks and then every 3 months. They should include history, physical

examination, the most important blood parameters (kidney parameters, liver enzymes, electrolytes) and an ACTH stimulation test. The latter test determines adrenal reserve and is therefore suitable for evaluating the extent of enzyme inhibition during treatment and for calculating dosage adjustments. It is important that testing is performed always at the same time. It should be performed 2 to 3 hours after drug administration, which corresponds to the peak effect of trilostane. According to the consensus, meeting the target range of the post ACTH cortisol level at 2-3 hours post pill should be 40 to 150 nmol/l (1.4 - 5.4 μg/dl).

Several of our dogs had post-ACTH cortisol levels < 27 nmol/l (1 μg/dl) for months without showing signs of hypoadrenocorticism. Several reasons may explain this phenomenon: (1) It is known that trilostane decreases cortisol concentration for only a few hours (up to 13 hours). It has been demonstrated that post ACTH cortisol concentrations are significantly higher 24 hours post dosing than after 4 hours. Therefore, those dogs probably have acceptable cortisol levels during many hours of the day. (2) Steroid precursors, which have accumulated as a result of enzyme inhibition, may have glucocorticoid-like effects that prevent signs of hypocortisolism, even though the cortisol concentration is low.

Trilostane also inhibits the synthesis of aldosterone, however, to a lesser extent than cortisol. Some dogs show a slight increase of potassium after initiating treatment, which could theoretically be due to reduced aldosterone availability. However, we were unable to detect a correlation between potassium and aldosterone levels. Therefore, the reason for the increase in potassium is currently unknown.[5] Adjustments of trilostane dose should be made in increments of 10 to 30 mg/dog. The effective dosage of trilostane differs markedly among dogs with PDH. In our most recent study in 29 dogs with PDH, initial dose was 3.0 - 13.0 mg/kg (median 6.1); after 6 months the dose ranged from 1.8 - 16.0 mg/kg (median 4.7).[b] The reason for the differences may be a significant variation in 3β-hydroxysteroid dehydrogenase activity in adrenal glands among individuals. Additionally, it is likely that absorption of trilostane differs between individuals. Dogs fed after dosing absorb trilostane at a higher rate and to a greater extent than fasted animals; however, it is not known to what extent the type of food influences absorption.

Trilostane is well tolerated by most dogs. Adverse effects are seen in 10 - 20% of dogs and may be due to a direct drug effect, glucocorticoid withdrawal, or hypoadrenocorticism. In case of direct drug effect or glucocorticoid withdrawal, severity is usually mild and signs may be self-limiting. Hypoadrenocorticism, however, may cause serious signs. In case of adverse effects, it is advisable to perform an ACTH stimulation test to exclude hypoadrenocorticism. While awaiting the results, trilostane administration should be stopped and symptomatic treatment (IV fluids, glucocorticoids) should be considered. After recovery trilostane should be restarted at a lower dose.

Dogs treated with trilostane develop distinct changes in the ultrasonographic appearance of the adrenal glands.[1,6] In almost all dogs, there is a marked increase in thickness. Shape of the adrenal glands may become irregular and the echogenicity of the parenchyma heterogenous. Histopathological studies have shown that these lesions are consistent with diffuse and/or nodular hyperplasia, most likely due to chronic ACTH hypersecretion.[7]

In previous years, a few cases of sudden unexplained deaths have been seen and recently adrenal necrosis has been described in a dog receiving trilostane.[2,8,9] Currently, there is some debate on the phenomenon that trilostane may lead to adrenal necrosis, which can not be explained by the current knowledge about the actions of trilostane. We recently studied the histopathology of adrenal glands from seven dogs treated with trilostane, and which had died due to different reasons.[7] In 5 of the 7 dogs, adrenal necrosis and hemorrhage was demonstrated. In 2 of the dogs necrosis was judged to be severe and multifocal throughout the adrenal cortex, in the other 3 dogs lesions were mild to moderate and either focal or multifocal.
Some dogs experience prolonged suppression of adrenal function at variable time intervals (most often after a few months) after starting trilostane therapy. Currently the reason is not known, however, we assume that it may be due to partial adrenal necrosis.

Recently, survival times of dogs treated with mitotane or trilostane for PDH were compared and were found to be not different.[10] In dogs treated with mitotane, survival times ranged between 33 and 1399 days (median 708 days); in dogs treated with trilostane, survival times between 8 and 1971 days (median 662 days).

Trilostane has also been successfully used in dogs with functional adrenocortical tumors.[11] In Zurich, the treatment modality of choice for dogs with adrenocortical tumors is adrenalectomy. In dogs with inoperable tumors we prefer mitotane to trilostane using a protocol aiming for complete adrenocortical destruction. In some dogs, this treatment regimen results in complete tumor remission and disappearance of metastasis.[12]

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Hypoadrenocorticism (Addison's Disease) in Dogs

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Hypoadrenocorticism is an uncommon condition in dogs characterized by a severe deficiency in adrenocortical hormone secretion. Although the disorder may develop as a result of dysfunction of any part of the hypothalamic-pituitary-adrenal axis, most dogs with hypoadrenocorticism have disease of adrenocortical tissue itself. Although even mild destruction or atrophy of adrenocortical tissue may impair adrenocortical reserve, at least 90% of the adrenal cortex needs to be non-functional before associated clinical signs are observed under non-stressful conditions.[1,2]

Etiology

The major adrenocortical hormones are synthesized in three distinct zones of the adrenal cortex. The outer *zona glomerulosa* produces aldosterone, the principal mineralocorticoid of the dog. The middle *zona fasciculata* is the thickest of the three adrenocortical layers and produces cortisol, the principal glucocorticoid in the dogs, as well as a variety of adrenal androgens. The zona fasciculata functions as a unit with the narrow, inner *zona reticularis*, which also produces cortisol and androgens.

Primary hypoadrenocorticism (Addison's disease) results from the destruction or atrophy of all three zones of the adrenal cortex, with subsequent loss of both glucocorticoid and mineralocorticoid secretion. In most dogs with naturally-occurring hypoadrenocorticism, the cause is idiopathic, thought to be the end result of immune-mediated destruction of adrenocortical tissue in the vast majority of cases.[1-3] Rare causes of adrenocortical destruction include infiltrative granulomatous disease (eg, blastomycosis), lymphoma or other metastatic neoplasia to the adrenal glands, and adrenal hemorrhage.[1-3] Iatrogenic hypoadrenocorticm is relatively common in dogs with hyperadrenocorticism treated with either mitotane or trilostane therapy.[1,2] Such iatrogenic primary hypoadrenocorticism is usually reversible with cessation of the mitotane or trilostane administration, but may be permanent in some dogs.

A subset of dogs with primary hypoadrenocorticism appear to develop a selective glucocorticoid deficiency with apparently normal mineralocorticoid secretion, based upon the findings of low basal and ACTH-stimulated serum cortisol values with normal concentrations of serum electrolytes. This type of hypoadrenocorticism is commonly referred to as "atypical" hypoadrenocorticism.[4,5] In most of these dogs, mineralocorticoid deficiency eventually develops, but a few dogs do not develop deficient mineralocorticoid secretion or serum electrolyte changes when followed for many months or years.[2] In man, several naturally occurring mutations of the ACTH receptor gene have been identified which lead to hereditary unresponsiveness to ACTH and isolated glucocorticoid deficiency without mineralocorticoid deficiency.[6] It is possible that some dogs with atypical hypoadrenocorticism have similar mutations of the ACTH receptor gene, but this syndrome has not yet been documented in dogs.

Secondary hypoadrenocorticism is caused by insufficient pituitary ACTH secretion. Without circulating ACTH, the inner zones of the adrenal cortex responsible for glucocorticoid production (ie, zonae fasciculata and reticularis) atrophy, with a subsequent fall in glucocorticoid secretion. Because aldosterone secretion is principally controlled by plasma concentrations of renin and potassium rather than by circulating ACTH, mineralocorticoid secretion (as well as normal serum electrolyte concentrations) are preserved in these dogs with secondary hypoadrenocorticism. The most common cause of secondary hypoadrenocorticism is iatrogenic, resulting from overly rapid discontinuation of long-term and / or high-dose glucocorticoid therapy. Very rare spontaneous or natural causes in the dog include pituitary or hypothalamic lesions or idiopathic isolated ACTH deficiency.[1-3,7]

Clinical Features

Naturally occurring hypoadrenocorticism has been reported in dogs ranging from 2 months to 14 years of age, although most affected dogs present in young to middle age.[1-3,7] A genetic predilection has been confirmed in Standard Poodles and Bearded Collies and suggested in certain breeds such as Nova Scotia Duck Tolling Retrievers, Leonbergers, Portugese Water Spaniels, Great Danes, Rottweilers and Wheaten and West Highland White Terriers.[1,2] Female dogs are about twice as likely to develop naturally occurring hypoadrenocorticism as males.

The clinical features of hypoadrenocorticism vary from acute collapse with generalized underperfusion to a more chronic clinical course with vague, non-specific signs. Dogs presenting with acute collapse usually have

evidence of generalized marked hypovolemia and dehydration, together with vomiting, diarrhea, abdominal pain, and hypothermia. Some may have severe gastrointestinal hemorrhage with melena and occasional hematemesis.[2,7,8] Many affected dogs will have an inappropriately low heart rate for their degree of circulatory collapse and about a quarter of dogs will have absolute bradycardia. These dogs are obviously unstable and require initial stabilization with rapid parenteral fluid and glucocorticoid therapy.

The majority of dogs with the chronic forms of primary and secondary hypoadrenocorticism present with vague and non-specific clinical features, usually attributable to variable impairment of the gastrointestinal, renal, and neurological systems. These may include any combination of lethargy, weakness, depression, inappetance, vomiting, and diarrhea. Polydipsia and polyuria are rarely primary owner complaints but may be reported. It is not uncommon for these dogs to have a waxing and waning illness characterized by vague illness interspersed with periods of apparent normality.

Routine Laboratory Findings

In the presence of appropriate clinical signs, suspicion for hypoadrenocorticism is dramatically increased by the presence of lymphocytosis or eosinophilia in a clearly sick dog. More commonly, simply the absence of a stress leukogram (ie, lymphopenia and eosinopenia) may alert the clinician to the potential for hypoadrenocorticism.

As with all hypovolemic conditions, most dogs with primary hypoadrenocorticism commonly develop prerenal azotemia as a consequence of renal underperfusion.[2-4,7] However, unlike other hypovolemic conditions where renal concentrating ability is maintained, dogs with primary hypoadrenocorticism are generally unable to concentrate their urine effectively. Impaired urine concentrating ability is due to mineralocorticoid deficiency and resultant chronic renal sodium loss, depletion of normal renal medullary sodium concentration gradient, and impaired water resorption from the renal collecting ducts. As a consequence, the prerenal azotemia is usually accompanied by inappropriately dilute urine, increasing the potential for affected dogs to be misdiagnosed with primary renal disease.

The classic electrolyte abnormalities associated with primary hypoadrenocorticism are hyperkalemia and hyponatremia. In our experience, one or both are present in over 90% of affected dogs.[2-4,7] Dogs with secondary hypoadrenocorticism (ACTH deficiency) can develop hyponatremia; however, because circulating ACTH is not the major stimulus for mineralocorticoid secretion, these cases do not develop hyperkalemia and do not require mineralocorticoid supplementation.

Although the presence of hyponatremia, hyperkalemia, hypochloremia, and a low sodium-to-potassium ratio all support a diagnosis of primary hypoadrenocorticism, these changes can occur in a variety of other conditions. Non-adrenal diseases associated with moderate to marked hyponatremia and hyperkalemia include acute and chronic urinary tract disease, various gastrointestinal disorders (eg, pancreatitis, secretory enteropathies, or diffuse small bowel disease), chronic end-stage heart or liver failure, pleural and peritoneal effusions, neoplasia, and uncomplicated pregnancy.[1,2,9-11] In addition, artefactual hyperkalemia may be a confusing consequence of post-collection hemolysis, particularly in Japanese Akitas,[12] or of marked leucocytosis or thrombocytosis.[13]

Approximately 5% to 10% of dogs with primary hypoadrenocorticism have normal serum electrolyte concentrations or only mild hyponatremia without hyperkalemia at the time of diagnosis.[2-4,7] These dogs presumably have either early or mild primary hypoadrenocorticism or selective glucocorticoid deficient hypoadrenocorticism and are commonly referred to as having "atypical Addison's disease.[4,5] Prior treatment with fluids or steroids or both may also mask any serum electrolyte changes. Therefore, one should never exclude a diagnosis of primary hypoadrenocorticism in a dog suspected of having hypoadrenocorticism on a basis of normal serum electrolyte concentrations alone.

Diagnostic Adrenal Function Tests

ACTH Stimulation testing (Gold Standard): A definitive diagnosis of hypoadrenocorticism requires the demonstration of inadequate adrenal reserve.[1-3,7] The preferred method for ACTH stimulation testing in dogs is to determine serum cortisol concentrations before and 1 hour after the intravenous administration of at least 5 μg/kg of cosyntropin (Cortrosyn, Amphastar Pharmaceuticals, Rancho Cucamonga, CA 91730). Following reconstitution, the solution appears to be stable for at least 4 weeks when refrigerated. Otherwise, the remaining solution can be divided into aliquots and frozen.[14]

If cosyntropin is not available, the ACTH stimulation test can also be performed by determining the serum cortisol concentration before and after the intramuscular injection of 2.2 U/kg of ACTH gel.[1-3,7] Acthar Gel (80 U/ml; Questcor Pharmaceuticals, Union City, CA, 94587) is available but very expensive. If this product is used, the post-ACTH serum cortisol sample is collected at 2 hours.

Alternatively, compounded forms of ACTH (usually 40 U/ml) can be purchased from several veterinary pharmacies. It should be noted, however, that the bioavailability and reproducibility of all of these compounded formulations have yet to be carefully evaluated. A recent study in dogs evaluated four compounded ACTH preparations and compared their cortisol responses to that of cosyntropin.[15] The data of that study showed that injection of the four compounded forms of ACTH increased serum cortisol concentrations to a similar magnitude as cosyntropin in samples collected 30 and 60 minutes after ACTH administration. However, serum cortisol

concentrations at 90 and 120 minutes post-ACTH varied considerably, depending on the preparation of ACTH injected, with two compounded forms of ACTH producing much lower serum cortisol concentrations. Based upon such variability in cortisol responses between compounded forms of ACTH, these investigators recommended determining serum cortisol concentrations at both 1 and 2 hours after ACTH administration when using a compounded preparation.[15] Overall, the determination of a third cortisol concentration would likely offset any presumed cost-saving derived from using a compounded ACTH product. In addition, because the potential for lot-to-lot variability in compounded ACTH formulations has not been evaluated, one should consider assessing the activity of each new vial by performing an ACTH stimulation test on a normal dog.

In normal dogs, administration of a supraphysiological dose of ACTH produces a rise in serum cortisol to values usually greater than 10 μg/dl (>300 nmol/L). In contrast, dogs with hypoadrenocorticism have an absent or blunted response to ACTH administration. Basal and post-ACTH serum cortisol concentrations are less than 1 μg/dl (<25 nmol/L) in over 75% of dogs and less than 2 μg/dl (<50 nmol/L) in virtually all dogs with primary hypoadrenocorticism.[1-3,7] Although the post-ACTH serum cortisol concentration may be as high as 2 to 3 μg/dl (50-80 nmol/L) in a few dogs with secondary hypoadrenocorticism, the great majority of these dogs also have ACTH-stimulated cortisol concentrations of less than 2 μg/dl (<50 nmol/L).[1-3,7]

Prednisone, prednisolone, hydrocortisone, and cortisone all cross-react with serum cortisol assays and should be withheld until completion of ACTH response testing. On the other hand, dexamethasone does not interfere with cortisol determination and can be used in the initial treatment of acute adrenocortical insufficiency without interfering with ACTH response testing. In those dogs that have received prednisone, prednisolone, hydrocortisone, or cortisone treatment, glucocorticoid therapy must be switched to dexamethasone for at least 24 hours before an ACTH response test can be performed. ACTH gel cannot be used in dehydrated or hypovolemic dogs since impaired absorption may lead to inaccurate results. Alternatively, testing can be delayed until after the dog is stabilized.

Although the ACTH response test is the gold standard for confirming a diagnosis of hypoadrenocorticism, its major limitation is that the test can not reliably differentiate dogs with primary adrenocortical disease from those with chronic atypical or secondary adrenal insufficiency

Basal and ACTH-Stimulated Aldosterone Concentrations: Determining plasma aldosterone concentrations before and after ACTH administration theoretically should be helpful in differentiating primary from secondary hypoadrenocorticism. As one might expect, dogs with primary hypoadrenocorticism generally have low basal and ACTH-stimulated plasma aldosterone concentrations, since these dogs have serum electrolyte abnormalities and are presumed to have complete adrenocortical destruction (including zona glomerulosa). On the other hand, because atrophy or destruction of the zona glomerulosa does not occur in secondary hypoadrenocorticism, one might expect these dogs to maintain normal aldosterone values. However, the circulating aldosterone concentrations in dogs with secondary hypoadrenocorticism are reported to be quite variable, with many having low basal and ACTH-stimulated values.[2] This variability and overlap in aldosterone values between dogs with primary or secondary forms of hypoadrenocorticism severely limits the usefulness of circulating plasma aldosterone measurements in differentiating primary from secondary hypoadrenocorticism,[2] unless measured in conjunction with plasma renin activity (see Aldosterone-to-Renin Ratios).

Plasma ACTH Concentrations: Measuring the basal plasma ACTH concentration is the most reliable means of differentiating dogs with primary from those with secondary hypoadrenocorticism. The plasma ACTH concentration is high (>500 pg/ml; > 100 pmol/L) in dogs with primary hypoadrenocorticism (both typical and atypical cases).[1-3,7,16] In contrast, plasma ACTH concentrations are low to low-normal in dogs with secondary hypoadrenocorticism. ACTH is labile and, therefore, the diagnostic laboratory performing the assay should be consulted for appropriate sample handling instructions.

Plasma for ACTH determination must be collected prior to instituting therapy, especially glucocorticoid treatment. Even a relatively low dose of glucocorticoid may lower high ACTH concentrations into the normal to low reference range, so the results must be interpreted in conjunction with a careful drug history. To properly evaluate the endogenous ACTH test result, a dog ideally should not have received any form of steroid treatment in the weeks preceding the diagnosis. If plasma ACTH is measured in a dog that has received recent glucocorticoid treatment, a false-positive diagnosis of secondary hypoadrenocorticism may be made.

Cortisol-to-ACTH and Aldosterone-to-Renin Ratios: Recently, an alternate approach was proposed in dogs for assessing the pituitary-glucocorticoid axis by measuring basal cortisol and plasma ACTH concentrations, and then calculating a cortisol-to-ACTH ratio.[17] Similarly, the renin-angiotensin-aldosterone system was assessed by the determining the basal plasma concentrations of aldosterone and plasma renin activity, and then calculating an aldosterone-to-renin ratio.[17,18]

Dogs with primary hypoadrenocorticism have low basal concentrations of cortisol with high plasma ACTH concentrations.[16,17] In contrast, dogs with secondary hypoadrenocorticism have low plasma cortisol concentrations with low plasma ACTH concentrations. Therefore, dogs with primary hypoadrenocorticism have much lower cortisol-to-ACTH ratios than do normal dogs or dogs with secondary hypoadrenocorticism, with little to no overlap in ratio values.[16,17]

In states of aldosterone deficiency, such as primary hypoadrenocorticism, the inability to retain sodium leads to hypovolemia, which subsequently stimulated renin release.[17,18] Thus, dogs with primary hypoadrenocorticism have low basal concentrations of aldosterone with high plasma renin activity.[17] In secondary hypoadrenocorticism, aldosterone secretion is not decreased; therefore, plasma renin activity remains relatively normal.[18] Accordingly, dogs with primary hypoadrenocorticism have much lower aldosterone-to-renin ratios than do normal dogs or dogs with secondary hypoadrenocorticism, again with little to no overlap in ratio values.

The advantage of the use of cortisol-to-ACTH and aldosterone-to-renin ratios is that such measurement of endogenous hormone variables in a single blood sample allows for the specific diagnosis of primary hypocortisolism and primary hypoaldosteronism. A dynamic stimulation test is not required. The use of these paired-hormone ratios allows for clear differentiation between primary and secondary hypoadrenocorticism, and this dual assessment is particularly relevant when isolated hormone deficiency is suspected (ie, isolated glucocorticoid deficiency or isolated mineralocorticoid deficiency).

Disadvantages of this approach to diagnosis include the considerable expense to measure plasma concentrations of cortisol, ACTH, aldosterone, and renin activity, as well as the absolute necessity of collecting the blood sample for measurement of the hormone and renin concentrations prior to any fluid or steroid treatment. In addition, it may be difficult to find a laboratory that can accurately measure plasma renin activity in dogs.

Treatment of Primary Hypoadrenocorticism (Addison's Disease)

Acute hypoadrenocorticism (Addisonian crisis): If the clinical presentation is consistent with an Addisonian crisis, treatment must be instituted immediately. Prior to treatment, however, one should collect routine samples for CBC, serum biochemistry profile, and urinalysis. Furthermore, for the endocrine diagnostic workup, pretreatment samples should also be collected for basal cortisol and endogenous ACTH (and aldosterone and renin if one wishes to calculate the aldosterone-to-renin ratio). Goals of therapy are to correct hypovolemia and electrolyte and acid-base disturbances, improve vascular integrity, and provide an immediate source of rapid-acting glucocorticoid.

Of primary importance in therapy for acute hypoadrenocorticism is the rapid infusion of large volumes of intravenous fluids, preferably 0.9% NaCl, at an initial rate of 60–80 ml/kg/hr for 1–2 hours.[1-3] This initial rate of infusion helps to quickly address hypotension and hypovolemia. In addition, it rapidly decreases serum potassium concentration by dilution, as well as by increasing renal perfusion and thereby potassium excretion. The rate of saline infusion is then gradually reduced to a maintenance rate and eventually discontinued over a few days based on the dog's clinical response and laboratory parameters including serial blood pressure and serum electrolyte measurements.

Also critically important in treatment of acute hypoadrenocorticism is the intravenous administration of a rapid-acting glucocorticoid. Dexamethasone sodium phosphate (0.5-2.0 mg/kg) or methylprednisolone sodium succinate (1-2 mg/kg) are generally preferred; again, dexamethasone must be used if the ACTH stimulation test is in progress. These initial doses can be repeated in 2 to 6 hours if needed. Alternatively, one can give hydrocortisone sodium succinate as the parenteral steroid replacement, which has the advantage of containing both glucocorticoid and mineralocorticoid activity. However, the disadvantage of using hydrocortisone sodium succinate is that this steroid is best administered as an IV infusion (0.5 mg/kg/hour).[1,2] As the dog's condition improves, the daily parenteral glucocorticoid supplementation should be continued (eg, prednisone or prednisolone, 0.5 to 1.0 mg/kg, IM). The dose is gradually reduced over the next three to five days until a maintenance oral dosage of prednisone or prednisolone (0.2 mg/kg/day) can be tolerated without risk of vomiting.

No rapid-acting parenteral mineralocorticoid preparation is currently available for treatment of acute hypoadrenocorticism (other than hydrocortisone sodium succinate). This does not constitute a significant clinical problem, as prompt aggressive treatment as described above is sufficient to stabilize a dog suffering an addisonian crisis. Nonetheless, we typically give a desoxycorticosterone pivilate (DOCP; Percorten-V, Novartis Animal Health, Greensboro, NC) injection as soon as the diagnosis of primary hypoadrenocorticism is confirmed (2.2 U/kg, IM). Alternatively, fludrocortisone acetate (Florinef, Bristol-Myers Squibb Company, Princeton, NJ) can be administered orally at an initial daily dose of 0.01-0.02 mg/kg body weight. Such mineralocorticoid supplementation will do no harm and may help correct serum electrolyte abnormalities.

Chronic hypoadrenocorticism: Dogs with chronic hypoadrenocorticism present with clinical signs of varying severity and duration and do not require the aggressive therapy described above for cases of acute hypoadrenocorticism. However, fluid therapy and parenteral glucocorticoid supplementation may be indicated in some cases, particularly if azotemia, dehydration, hypotension, or severe vomiting and diarrhea are present. If the endocrine diagnostic workup has not yet been completed, it is again extremely important that one collect pretreatment samples for basal cortisol and endogenous ACTH (and aldosterone and renin if one wishes to calculate the aldosterone-to-renin ratio) before instituting any steroid replacement therapy.

Dogs with naturally-occurring primary hypoadrenocorticism typically require both glucocorticoid and mineralocorticoid replacement therapy for life.[1-3, 19-21] Dogs with "atypical" primary hypoadrenocorticism can be started on glucocorticoid replacement therapy alone. However, one should monitor their serum electrolyte concentrations frequently, since most of these dogs with atypical disease will develop serum electrolyte abnormalities within weeks to months of initial diagnosis and require mineralocorticoid supplementation as well.[1-3]

Either desoxycorticosterone pivilate (DOCP) or fludrocortisone can be used for chronic mineralocorticoid replacement. In that regard, the veterinarian and owner have a choice between giving monthly injections of DOCP or administering daily oral fludrocortisone for the rest of the dog's life.

We typically institute treatment with DOCP at a dosage of 2.2 mg/kg, SQ or IM, every 25 to 30 days.[3, 21] Side effects associated with DOCP therapy are rare. This dosage interval is effective in almost all dogs, and most are well-controlled with a DOCP injection every 4 weeks. Until well-stabilized, serum creatinine and electrolyte concentrations should be monitored at approximately 2-weeks intervals after DOCP injection in order to determine the drug's peak effect and to help make necessary dosage adjustments.[1-3,19-21] Serum creatinine and electrolyte concentrations should also be monitored prior to the each DOCP injection to help determine the duration of action of the drug. Once stabilized, serum electrolyte and creatinine concentrations are checked every 3 to 6 months. Inasmuch as DOCP has no glucocorticoid activity, it is essential that dogs receive concurrent glucocorticoid supplementation (see below).

Although a DOCP dose of less than 2.2 mg/kg will be sufficient in some dogs, a dosage of 2.2 mg/kg is still recommended at least for the initial treatment. Less than 10% of dogs require a DOCP dosage greater than 2.2 mg/kg.[21] Use of a starting dose of 2.2 mg/kg eliminates the need for the clinician to incrementally increase the DOCP dosage over the first several months of therapy, which is often seen in dogs started on a lower initial DOCP dose. However, if financial constraints are a factor, one can attempt to gradually reduce the monthly dose of DOCP to the lowest effective dose, based on close monitoring of serum electrolyte concentrations.[21]

Fludrocortisone acetate is a synthetic corticosteroid that possesses moderate glucocorticoid activity as well as having marked mineralocorticoid potency.[1] By comparison, fludrocortisone has 10 times the glucocorticoid activity and 125 times the mineralocorticoid activity of cortisol. In this regard, fludrocortisone is very different than DOCP, which possess no glucocorticoid activity.

If fludrocortisone acetate is employed as mineralocorticoid supplementation, we recommend an initial oral dosage of 0.01-0.02 mg/kg/day (10-20 μg/kg/day).[3,21] After initiation of fludrocortisone therapy, serum electrolyte and creatinine concentration should be monitored weekly, with the dosage adjusted by 0.05-0.1 mg/day increments until values have stabilized within the reference range. Once this is achieved, the dogs should be reevaluated monthly for the first 3 to 6 months of therapy, then every 3 to 6 months thereafter. In many dogs in which fludrocortisone is used as long-term mineralocorticoid replacement, the daily dose required to control the disorder gradually increases; this is most evident in the first 6 to 24 months of treatment.[3,21] In most dogs, the final fludrocortisone dosage needed ranges from 0.02-0.03 mg/kg/day (20-30 μg/kg/day). Very few dogs can be controlled on a dosage of 0.01 μg/kg/day (10 mg/kg/day) or less.

There are several potential disadvantages associated with fludrocortisone use in dogs. Because of the drug's potent glucocorticoid activity, its use may produce clinical signs typical of glucocorticoid overdosage (eg, polyuria and polydipsia). This is especially true in dogs treated with concurrent fludrocortisone and glucocorticoid replacement. In such dogs, one should first taper or discontinue the daily glucocorticoid dosage; if signs of polyuria and polydipsia persist, a switch from treatment with fludrocortisone to DOCP should then be strongly considered. Other potential drawbacks to the use of fludrocortisone in some dogs include the development of drug resistance, with larger-than-expected daily dosages of fludrocortisone required to maintain normal serum electrolyte concentrations, as well as the expense to the owner when large daily doses of fludrocortisone are needed.

Many dogs with primary hypoadrenocorticism, particularly those receiving DOCP, will benefit from use of daily glucocorticoid supplementation in addition to mineralocorticoid replacement therapy. In general, all dogs treated with DOCP are started on glucocorticoid replacement with prednisone or prednisolone (0.2 mg/kg/day) in conjunction with mineralocorticoid replacement. Only about half of dogs treated with fludrocortisone appear to require glucocorticoid replacement. If warranted because of the development of side effects, one can taper the glucocorticoid dosage to alternate days or attempt to completely discontinue glucocorticoid supplementation if necessary. In some dogs, glucocorticoids can be discontinued without any ill-effects and mineralocorticoid replacement alone will adequately control signs of hypoadrenocorticism. Nevertheless, glucocorticoid supplementation may still be necessary in these dogs during periods of moderate to severe stress such as illness, trauma, or surgery; therefore, the owner should always have some glucocorticoid on hand and be informed of the situations when the dog might require supplementation.

Treatment of Secondary Hypoadrenocorticism

As aldosterone secretion is principally controlled by plasma concentrations of renin and potassium rather than ACTH, dogs with secondary hypoadrenocorticism (isolated

pituitary ACTH deficiency) do not develop mineralocorticoid deficiency. Consequently, although these dogs may be clinically indistinguishable from animals with primary hypoadrenocorticism, they will not have the classical electrolyte disturbances of hyponatremia and hyperkalemia and they do not require mineralocorticoid supplementations. Therefore, dogs with naturally occurring secondary hypoadrenocorticism can be managed by daily replacement glucocorticoid therapy alone. Oral administration of prednisone or prednisolone at a dosage of 0.2 mg/kg/day will usually suffice, except during periods of stress or illness when higher doses will be necessary.

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Hypothyroidism In Dogs - How Many Diagnostic Indices Do You Need To Be Sure?

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Since 1998, the MSU canine thyroid profile has contained eight indices of thyroid function. These include Total Thyroxine (TT4)[a], Total Triiodothyronine (TT3)[b], an index of Free T4 (FT4E-2S)[a], an index of Free T3 (FT3E)[a], an assessment of T4 autoantibody activity (T4AA)[b], an assessment of T3 autoantibody activity (T3AA)[b], canine TSH (TSH)[c], and an assessment of Thyroglobulin autoantibody (TgAA)[d]. At times the FT4E assay has been an analog procedure (FT4E-A) but the present assay is a 2-step procedure (FT4E-2S) using a solid-phase low affinity T4 antibody to "extract" the free fraction from the serum in the first step, followed by addition of radioactive T4 tracer in the second step. The "gold standard" for free T4, the free T4 by Dialysis (FT4D)[e] is also available for a nominal increase in cost. Are all of these necessary to make a diagnosis? My guess is that 90% of the time they are not, but as a practitioner are you willing to gamble on the health of your client's dog without knowing which 10% need the broad profile?

Examples of the utilization of the components of the profile best illustrate how each is unique, alone or in combination with other components of the profile. Let's assume that all of the following cases have clinical signs which are consistent with a clinical diagnosis of hypothyroidism. Important components of the profile are in bold print.

Profile 1

		REF. RANGE	UNITS
TT4	**8**	**(15-67)**	**nmol/L**
TT3	0.7	(1.0-2.5)	nmol/L
FT4E-A	**6**	**(12-50)**	**pmol/L**
FT3E	3.5	(4.5-12)	pmol/L
T4AA	10	<20	%
T3AA	5	<10	%
TSH	**60**	**(0-37)**	**mU/L**
TgAA	90	(<35)	%

In this dog, low TT4 alone is suggestive of potential hypothyroidism. However, the effects of non-thyroidal illness and glucocorticoids causing low TT4 have been well documented[1,2]. The addition of low Free T4 by dialysis or the 2-step procedure gives additional confidence that hypothyroidism is possible, but they can be falsely lowered in cases of NTI[3] and glucocorticoid effect as well[4]. The addition of TSH to the profile gives enough confidence in this case to diagnosis primary hypothyroidism (i.e. thyroid atrophy). Would TT4 and TSH have been enough to make the diagnosis? The commercially available canine TSH assay is still a first generation assay and apparent falsely low and elevated results have been found[5]. What about the positive titer for TgAA? Though not necessary, it certainly gives one additional confidence that we are dealing with autoimmune thyroiditis which is the major cause of hypothyroidism. TT3 and FT3E also lend support to the diagnosis of hypothyroidism.

Profile 2

		REF. RANGE	UNITS
TT4	155	(15-67)	nmol/L
TT3	**0.5**	**(1.0-2.5)**	**nmol/L**
FT4E-2S	**10**	**(12-50)**	**pmol/L**
FT3E	**0.5**	**(4.5-12)**	**pmol/L**
T4AA	**65**	**<20**	**%**
T3AA	5	<10	%
TSH	**65**	**(0-37)**	**mU/L**
TgAA	**190**	**(<35)**	**%**

In this dog's profile a very relevant finding is the positive T4AA. It caused an artifact in the Total T4 assay and has been reported to occur in 1.66% of the cases of potential hypothyroidism in dogs[6]. In this case, the FT4E-2S and/or FT4D assays were needed to determine an accurate assessment of the number of T4 molecules which were available to the target tissues. TgAA was necessary to confirm the presence of autoimmune thyroid disease. The thyroglobulin (Tg) molecule is the protein which stimulates production of TgAA as well as T4AA and T3AA. About half of the TgAA positive samples also have T4AA and/or T3AA. It appears that there are 10 antibody- stimulating epitopes on the huge Tg molecule and about half of them contain T4 or T3 which stimulates the additional production of the T4AA and/or T3AA. Since T3AA was not significantly elevated, the TT3 and FT3E were also helpful in determining that iodothyronine concentrations were not adequate for normal metabolism in this case.

Profile 3

		REF. RANGE	UNITS
TT4	**5**	**(15-67)**	**nmol/L**
TT3	**0.1**	**(1.0-2.5)**	**nmol/L**
FT4E-A	**2**	**(12-50)**	**pmol/L**
FT3E	**2.6**	**(4.5-12)**	**pmol/L**
T4AA	4	<20	%
T3AA	0	<10	%
TSH	18	(0-37)	mU/L
sTgAA	**106**	**(<35)**	**%**

In this case, T4s and T3s are very low, but the TSH did not elevate as expected from the lack of negative feedback and primary thyroid atrophy[6,7]. However, since there is a very high TgAA titer, primary thyroid disease is present. TgAA can have false positive results, so an adjustment for non-specificity has been added to test for specific TgAA and give additional confidence of thyroiditis. It appears that the TSH assay did not correctly identify the presence of primary hypothyroidism in this dog. The positive TgAA test helped to pinpoint the presence of autoimmune thyroid disease[8] and need for L-thyroxine replacement therapy.

Profile 4

		REF. RANGE	UNITS
TT4	>156	(15-67)	nmol/L
TT3	<0.0	(1.0-2.5)	nmol/L
FT4 dialysis	**5**	**(6-42)**	**pmol/L**
FT3E	>27	(4.5-12)	pmol/L
T4AA	66	<20	%
T3AA	77	<10	%
TSH	15	(0-37)	mU/L
TgAA	**154**	**(<35)**	**%**

This is another case when the TSH assay did not increase as expected. The TgAA, as well as T4AA and T3AA[7], clearly identify the presence of autoimmune thyroid disease and the FT4 by dialysis indicates that inadequate concentrations of iodothyronine are present. Replacement therapy should be helpful. If only T4 was assayed in this case, a laboratory diagnosis of hyperthyroidism would be made. Of course the clinician would know that diagnosis did not correspond with the clinical diagnosis and further assessment would be necessary.

Profile 5

		REF. RANGE	UNITS
TT4	16	(15-67)	nmol/L
TT3	0.0	(1.0-2.5)	nmol/L
FT4 dialysis	14	(6 - 42)	pmol/L
FT3E	20	(4.5-12)	pmol/L
T4AA	2	<20	%
T3AA	73	<10	%
TSH	**45**	**(0-37)**	**mU/L**
TgAA	**146**	**(<35)**	**%**

In this case autoimmune thyroiditis is present. T3AA is positive as well as TgAA. T3AA has been reported to be positive in 5.67 of dogs with potential hypothyroidism[6]. TSH is elevated in this dog, but TT4 and Free T4 by dialysis are not in the hypothyroid range. A laboratory diagnosis of subclinical hypothyroidism would be appropriate, but since the dog was showing clinical signs of hypothyroidism, it is no longer subclinical and L-thyroxine replacement therapy is justified.

Profile 6

		REF. RANGE	UNITS
TT4	**6**	**(15-67)**	**nmol/L**
TT3	**1.1**	**(1.0-2.5)**	**nmol/L**
FT4E-A	**3**	**(12-50)**	**pmol/L**
FT3E	**8.7**	**(4.5-12)**	**pmol/L**
T4AA	8	<20	%
T3AA	6	<10	%
TSH	**53**	**(0-37)**	**mU/L**
TgAA	**61**	**(<35)**	**%**

This dog has evidence of autoimmune thyroid disease as well as thyroid atrophy, based upon the positive TgAA, low T4s and high TSH. T3s are still within the reference interval. This is an example of autoregulation of T4 to T3 conversion by the selanodeiodinase enzymes[9]. Even with low T4, the body is able to more efficiently convert T4 to T3 in an attempt to maintain homeostasis and adequate metabolism. L-thyroxine replacement therapy is necessary in these cases.

Profile 7

		REF. RANGE	UNITS
TT4	**5**	**(15-67)**	**nmol/L**
TT3	**0.7**	**(1.0-2.5)**	**nmol/L**
FT4E	**9**	**(12-50)**	**pmol/L**
FT3E	**2.8**	**(4.5-12)**	**pmol/L**
T4AA	6	<20	%
T3AA	0	<10	%
TSH	**0**	**(0-37)**	**mU/L**
TgAA	12	(<35)	%

This profile is suggestive of thyroid problems, but without an increase in TSH other possibilities must be considered. The dog may have a non-thyroidal illness (the sick euthyroid syndrome)[2,3] or could have Cushing's syndrome or be under the influence of exogenous glucocorticoids[1,5]. A third possibility is hypothalamic or pituitary hypothyroidism since the TSH is inappropriately low for the amount of T4 being produced. Additional history on this case indicated that this 90 lb. dog was receiving 10 mg. of Prednisone daily for over 1 month. Hence, the diagnosis of steroid induced T4 and T3 suppression.

TWO MONTHS LATER—AFTER STOPING PREDNISOLONE THERAPY

		REF. RANGE	UNITS
TT4	**25**	**(15-67)**	**nmol/L**
TT3	**1.7**	**(1.0-2.5)**	**nmol/L**
FT4E	**19**	**(12-50)**	**pmol/L**
FT3E	**4.8**	**(4.5-12)**	**pmol/L**
T4AA	6	<20	%
T3AA	0	<10	%
TSH	**4**	**(0-37)**	**mU/L**
TgAA	12	(<35)	%

By eliminating the glucocorticoid effect, the thyroid hormone profile returned to normal.

Profile 8

		REF. RANGE	UNITS
TT4	**2**	**(15-67)**	**nmol/L**
TT3	**0.1**	**(1.0-2.5)**	**nmol/L**
FT4 dialysis	**1**	**(6 - 42)**	**pmol/L**
FT3E	**3.1**	**(4.5-12)**	**pmol/L**
T4AA	10	<20	%
T3AA	1	<10	%
TSH	**15**	**(0-37)**	**mU/L**
TgAA	9	(<35)	%

The very low T4s and T3s suggest that hypothyroidism is possible. However, without a significant increase in TSH, a non-thyroidal illness (NTI) or glucocorticoid effect is also possible. Even FT4 by dialysis is low, but it can be low in both conditions, so that does not eliminate them as a cause. Further testing and examination are needed to be confident that NTI and the steroid effect are not possibilities. After that, hypothalamic or pituitary hypothyroidism should be considered. Unfortunately, the hypothalamic thyrotropin releasing hormone test has shown inconsistent results in dogs[10], so cannot be used with confidence in testing these potentially pituitary hypothyroid dogs. If clinical signs warrant it, and NTI and the steroid effect have been ruled out, a clinical trial of 6 to 8 weeks duration would be justified to rule in pituitary hypothyroidism.

Profile 9

		REF. RANGE	UNITS
TT4	39	(15-67)	nmol/L
TT3	1.2	(1.0-2.5)	nmol/L
FT4 dialysis	21	(6 - 42)	pmol/L
FT3E	4.8	(4.5-12)	pmol/L
T4AA	8	<20	%
T3AA	0	<10	%
TSH	**94**	**(0-37)**	**mU/L**
TgAA	4	(<35)	%

With only TSH elevated, it could be a false elevation[5] and one does not have confidence that thyroid pathology exists. Repeated analysis of samples from many dogs with profiles similar to this has shown that it is a persistent elevation of TSH (personal observation). Perhaps the assay is detecting isotypes of TSH that are not biologically active.

a. DiaSorin, Stillwater, MN 55082
b. In house procedure, MSU
c. Diagnostic Products Corporation, Los Angeles, CA 90045
d. Nichols Institute Diagnostics, San Juan Capistrano, CA 92675
e. Oxford Laboratories, Oxford, MI 48371

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Challenging Issues in the Diagnosis and Treatment of Feline Hyperthyroidism

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Hyperthyroidism is one of the most commonly diagnosed disorders of domestic cats. As our knowledge and experience in diagnosing and treating the disease has grown, certain challenges have become apparent. Diagnosis is often straightforward, but cases of occult hyperthyroidism are increasingly recognized and can present a diagnostic challenge. Treatment options for feline hyperthyroidism have not changed substantially in recent years, but awareness of adverse effects of treatment has grown, especially regarding the effects of treatment on renal function.

Methimazole Trials

In recent years, investigators have shown consistently that treatment of hyperthyroidism can have profound effects on kidney function in cats, and that feline hyperthyroidism can mask underlying chronic renal insufficiency.[1-4] Post-treatment renal insufficiency is common, occurring in 17% to 38% of cats treated for hyperthyroidism.[1,3,4] Treatment of hyperthyroidism by bilateral surgical thyroidectomy causes a consistent, and sometimes disastrous, drop in glomerular filtration rate (GFR)[1]. The same is true for radioiodine treatment and methimazole.[2-4] For these reasons, the wisdom of treating hyperthyroidism in cats with suspected renal dysfunction has been questioned. Methimazole is the most logical first-line treatment for hyperthyroidism, especially in cats with impaired renal function.[4] Treatment with methimazole can be reversed in the event of exacerbation of renal insufficiency. For this reason, a trial with methimazole is recommended prior to a more permanent treatment for hyperthyroidism.[5]

Unfortunately, there are few published data to guide decisions concerning methimazole trials. Veterinarians, general practitioners and specialists alike, commonly recommend methimazole trials only for cats with questionable renal function. There is a commonly held belief that cats with well-concentrated urine (urine specific gravity > 1.035) have adequate renal function and do not run a significant risk of post-treatment renal insufficiency, and that methimazole trials are not needed in these cats.[6,7] There are no published data to support this opinion, and its wisdom should be questioned. First, urine specific gravity is an unreliable predictor of renal function in cats because of the diuretic effects of thyroid hormone. Second, urine specific gravity is not a measure of GFR, but rather an indicator of renal tubular function. We have asked whether hyperthyroid cats with concentrated urine actually do run a significant risk of post-treatment renal insufficiency, and have gathered preliminary data to investigate this clinical problem. Of the most recent 24 hyperthyroid cats developing overt renal insufficiency within 2-3 months of radioiodine treatment in our hospital, 13 (54%) had urine specific gravity measurements greater than 1.035. Five of those cats (21%) had urine specific gravity measurements above 1.050 (unpublished data). We suspect, therefore, that urine specific gravity should not be used as a predictor of post-treatment renal status in hyperthyroid cats, and that a methimazole trial should be recommended for any hyperthyroid cat that can tolerate the drug.

There are no published studies that have determined the best length of time for a methimazole trial. Studies in which GFR has been measured in cats treated for hyperthyroidism have typically examined renal function before and 30 days after treatment.[1,3,4] It is not known whether there is a further decline in GFR after this initial treatment period, or whether the decline in GFR is permanent. Our opinion is that a 30-day trial with good control of hyperthyroidism is adequate, but that is based on our clinical experience rather than on scientific results. It should also be noted that a good response to a trial with methimazole does not guarantee that a given cat will not experience overt renal insufficiency with subsequent radioiodine treatment. In our hospital we have seen several cats with hyperthyroidism well controlled on methimazole, and with well-concentrated urine and normal serum creatinine and urea nitrogen concentrations, that developed overt renal insufficiency shortly after radioiodine therapy. Some have speculated that a more gradual drop in circulating thyroid hormone concentrations with anti-thyroid drugs vs. radioiodine may explain this situation. Also, methimazole may have some renal protective effects in cats as has been shown in other species.[8,9]

Are There Predictors of Post-Treatment Renal Insufficiency?

As stated previously, we do not support the idea that urine specific gravity predicts the renal response to treatment for hyperthyroidism. Analysis of our unpublished retrospective data, however, supports the notion that cats that develop renal insufficiency after treatment for hyperthyroidism may have lower urine specific gravity measurements than those that do not develop renal insufficiency (Figure 1). Unfortunately, there is probably not enough difference between the two groups of cats to make urine specific gravity a useful predictor.

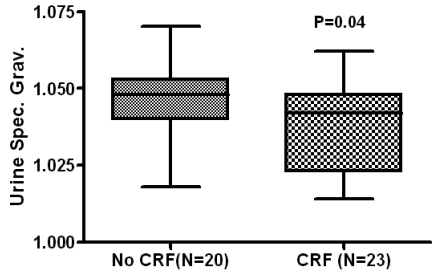

Figure 1 – Box plots showing urine specific gravity measurements in cats that did (CRF) or did not (No CRF) develop overt renal insufficiency within 1-3 months of treatment of hyperthyroidism. The box represents the interquartile range from the 25th to the 75th percentile. The solid horizontal bar through the box represents the mean, and the 10th through 90th percentiles are represented by the capped vertical bars.

Other investigators have reported that pre-treatment GFR measurement may be useful as a predictor of post-treatment renal status in hyperthyroid cats.[3] In that report, cats not experiencing renal insufficiency all had pre-treatment GFRs of greater than 2.25 ml/kg/min, and the authors concluded that pre-treatment GFR was a valuable predictor of post-treatment renal insufficiency. This is in contrast to our report in which 3 of 5 hyperthyroid cats experiencing post-treatment renal insufficiency had pre-treatment GFRs greater than 2.5 ml/kg/min.[1] In that study there was no significant difference between GFR in cats that did or did not experience post-treatment renal insufficiency. Differences in methods of determining GFR may account for these disparate reports, but we do not believe there is adequate published evidence to rely on GFR measurement to predict post-treatment renal insufficiency in hyperthyroid cats. It is well established that GFR is elevated in cats with hyperthyroidism. If this is due to loss of renal autoregulation associated with kidney disease, it is possible that a cat with severe hyperthyroidism and underlying renal disease might have a higher GFR than a cat with a similar degree of hyperthyroidism and more normal kidneys. This possibility bears investigation. The greatest value in using GFR to evaluate hyperthyroid cats prior to treatment is if an abnormally low GFR is found. Because GFR declines consistently in cats treated for hyperthyroidism, a cat with a subnormal pre-treatment GFR would probably have an increased risk of overt renal insufficiency after treatment.

How is Post-Treatment Renal Insufficiency Managed?

If removal of excess thyroid hormone is responsible for the decline in GFR seen in cats treated for hyperthyroidism, can post-treatment renal insufficiency be treated by giving T4 supplementation? Figures 2 and 3 show data from 5 cats with post-radioiodine renal insufficiency treated with 0.05 mg of thyroxine given orally twice daily. T4 supplementation for 30 days, as expected, reliably increased the serum concentration of T4. Body weight remained mostly

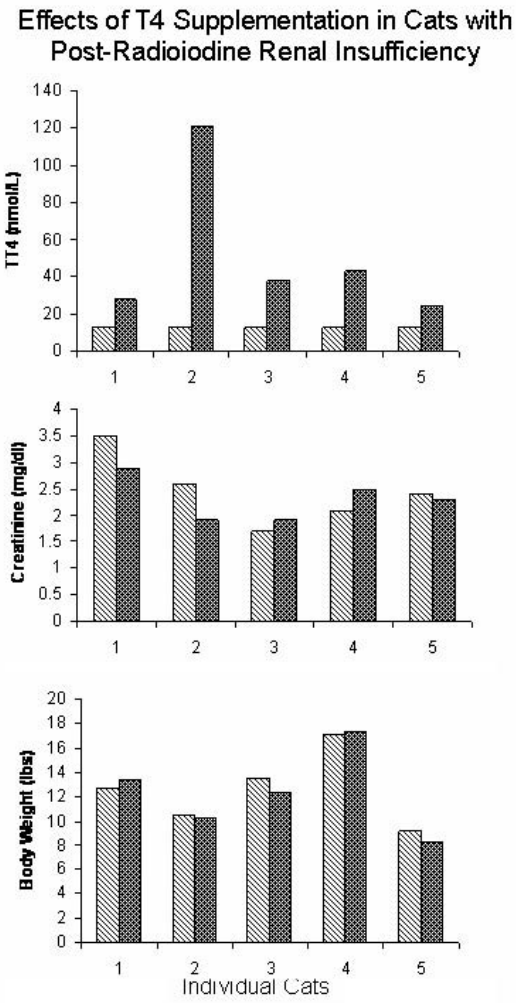

Figure 2 – Data showing the effects thyroid hormone supplementation on serum TT4 concentration (top panel), serum creatinine concentration (middle panel), and body weight (bottom panel) in five individual cats with post-treatment renal disease. The vertically hatched bars represent baseline values at the time oral T4 supplementation (0.05 mg BID) was started, and the darkened bars represent values obtained 30 days later.

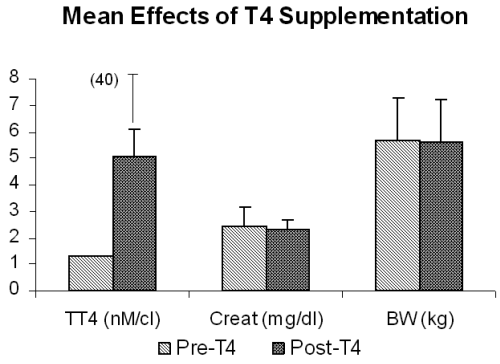

Figure 3 – Mean values and standard deviations (capped bars) of data derived from Figure 2 (see Figure 2 legend for key). Note that TT4 concentrations are expressed in unconventional units of nmol/cl for purposes of comparison.

unchanged. In this preliminary study, serum concentrations of creatinine did not decrease reliably, with 2 of the 5 cats experiencing increases in creatinine despite T4 supplementation. These data provide a hint that T4 supplementation in cats with post-treatment renal failure may prove clinically disappointing with expectations for increases in GFR not being met. Thorough investigation of this treatment strategy is currently underway.

Diagnosis of Occult Hyperthyroidism

Occult hyperthyroidism is a term that describes clinical hyperthyroidism in which measured serum concentrations of TT4 are within the reference range. Measurement of free T4 (FT4) may be more sensitive in distinguishing cats with occult hyperthyroidism from cats with non-thyroidal disease.[10] Some veterinarians rely on measurement of serum concentrations of free T4 as a first-line diagnostic test for feline hyperthyroidism. We do not recommend this practice for the several reasons. First, most hyperthyroid cats have elevated serum concentrations of total TT4 and FT4. Measurement of FT4 has no added benefit in many cats. The greatest problem arises, however, in evaluating sick cats with non-thyroidal illness. For reasons that are not well explained, around 6-10 percent of cats with non-thyroidal illness have false elevations in serum FT4 concentration.[10,11] This means that a cat with alimentary lymphoma, for example, which could be confused clinically with hyperthyroidism, has a significant chance of having a misdiagnosis of hyperthyroidism based on the serum FT4 concentration alone. In this hypothetical case the TT4 would probably be low because cats with non-thyroidal illness reliably have low serum concentrations of TT4.[12] So, if FT4 is to be used as a diagnostic test for feline hyperthyroidism, it must be interpreted together with the serum TT4 concentration. If the TT4 concentration is low and the FT4 concentration is high, hyperthyroidism is probably not present. If the serum TT4 concentration is in the high end of the normal range and the serum FT4 concentration is high, a diagnosis of hyperthyroidism can probably be made. It should be noted that FT4 assays are fraught with difficulty and are subject to error.[13] While true circulating concentrations of FT4 may more accurately reflect the thyroidal status of a patient than does TT4, measurement of FT4 hormone is more difficult. Furthermore, FT4 assays are not always available. In some cases, occult hyperthyroidism may be best diagnosed through repeated TT4 testing or by use of the tri-iodothyronine suppression test.[14]

Measurement of Feline TSH

Measurement of serum concentrations of thyrotropin (TSH) is a mainstay of diagnosis of thyroid disorders in people, and assays have been available for use in dogs for more than a decade. Recently, investigators have begun evaluating canine TSH assays for use in cats.[15, 16, 17] As expected, serum concentrations of TSH are reportedly very low in cats with hyperthyroidism, but caution should be exercised in interpreting canine TSH assays used in feline serum. Our personal experience using a canine-specific TSH assay to detect TSH in cats has yielded inconsistent results. Recently, Duncan Ferguson and colleagues have cloned the feline TSH protein and have begun development of a feline-specific immunoassay.[18,19] This assay may eventually become an important tool in the diagnosis and management of thyroid disorders in cats.

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Feeding the Diabetic Patient

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Diabetes mellitus is a common endocrine disorder that is characterized by disturbances in carbohydrate, lipid and protein metabolism. Absolute or relative insulin deficiency allows glucagon-driven gluconeogenesis by the liver to proceed uncontrolled. The increased glucose production by the liver in conjunction with reduced glucose up-take by insulin dependent tissues culminates in hyperglycemia and the clinical state of diabetes mellitus characterized by polyuria, polydipsia, and weight loss. In addition to effects on glucose metabolism in the liver, the relative or absolute insulin deficiency stimulates the release of free fatty acids by adipose tissue and triggers protein degradation to release gluconeogenic amino acids.

The main objective of therapy is to achieve adequate glycemic control that minimizes the clinical signs of polyuria, polydipsia and polyphagia, avoids the development of diabetic ketoacidosis, and maintains ideal body weight. In addition, any underlying or concurrent diseases (e.g. pancreatitis, obesity, glucocorticoid or progesterone excess) should be identified and managed. One of the most important aspects of the management of diabetes mellitus is to adequately counsel the client about diabetes mellitus and what to expect with respect to successful management.

Diabetic pets should be provided with clean fresh water at all times. The actual energy requirements of the diabetic pet are not known, however, they are presumed to be the same as for healthy pets. Therefore, diabetic cats with optimal body weight and body condition should be fed at maintenance (50-60 kcal/kg BW/day) and diabetic dogs should be fed at maintenance (132 x $BWkg^{0.73}$). The amount fed should be gradually altered to maintain optimal body condition and ideal body weight. Excess dietary caloric intake and body weight gain should be avoided as obesity contributes to insulin resistance and impairs glucose tolerance.

The primary nutritional goal of the overweight or obese diabetic cat is to institute a weight loss program to achieve ideal body weight. Studies by Biourge et al have demonstrated that healthy cats that gain weight have both higher and more prolonged increases in insulin secretion compared to when they were normal weight. The insulin response to intravenous glucose improves when the cats loose the excessive weight. Therefore, weight reduction is paramount to improve glycemic control. Indeed, diabetes may actually resolve in some diabetic cats upon correction of the obese state. Obese diabetic cats should be fed to achieve a rate of weigh loss not to exceed 1-2% loss per week (30-45 kcal/kg BW/day). Weight reduction may necessitate frequent adjustments in insulin therapy to avoid a hypoglycemic crisis.

The frequency of feeding and the caloric content of each meal should be consistent to enhance the action of insulin and minimize post-prandial hyperglycemia. Ad-libitum feeding can be considered for those cats that are not overweight or obese. Ad-libitum feeding allows the cat to eat numerous small meals per day, which minimizes post-prandial hyperglycemia. For diabetic dogs and diabetic cats that are prone to weight gain, the daily caloric requirements should be divided into two or more equal size meals that are administered either 10-20 minutes prior to or concurrent with insulin. Importantly, every meal should be consistent with respect to the type of food, the calorie content and the time of feeding.

Moderate energy, high protein, low carbohydrate diets are appropriate for the nutritional management of feline diabetes mellitus. Indeed, studies in diabetic cats fed low starch, high protein diets have reported enhanced control of glycemia, a reduction in insulin dosage and greater remission rates compared to traditional high dietary fiber, high dietary carbohydrate diets.

Proteins are a much less efficient energy source compared to carbohydrates, as more energy is lost from the conversion of gross protein to net energy. High protein diets have been shown to be effective in maintaining lean body mass during weight loss. In addition, Nguyen et al have shown that high protein diets are associated with lower blood glucose concentrations following feeding compared with normal protein, high carbohydrate diets. The slower, steadier blood glucose concentrations can be explained by a slow steady release of glucose from the liver via gluconeogenesis from the dietary amino acids, rather than a high more rapid release of glucose form the small intestinal digestion of high carbohydrate diets.

The digestion and absorption of glucose is greatly dependent on the type of carbohydrate. For instance, simple sugars are very rapidly absorbed in the small intestine, leading to rapid increases in blood sugar con-

centrations. Semi-moist diets that are high in simple sugars should be avoided in diets for patients with diabetes mellitus as they perpetuate post-prandial hyperglycemia. Diets high in carbohydrates are not recommended for diabetic cats. Cats do not tolerate high carbohydrate diets because they have lower concentrations of pancreatic amylase and intestinal brush border enzymes. In addition, cats lack hepatic glucokinase and cannot rapidly remove excess glucose from the blood. The blood glucose concentration achieved after the digestion and absorption of starch very much depends on the type of starch in the diet. Feeding a carbohydrate source that is slowly digested results in lower and more prolonged, steady blood glucose concentration. Conversely, carbohydrates that are rapidly digested result in much higher blood glucose concentrations and rapid swings in the blood glucose concentrations. The speed of digestion and rate of glucose absorption is commonly referred to as the glycemic index. Feeding a carbohydrate with a lower glycemic index should result in lower and steadier blood glucose concentrations. Therefore, diets designed for diabetic cats should contain low levels of carbohydrates, and the carbohydrates that are used should have a low glycemic index, such as those from barley and whole grain cereals.

The speed of absorption of glucose can be moderated by mucilages such as psyllium, which has the ability to absorb up to 10 times its weight in water to form a viscous gel. Psyllium has been demonstrated to have an important role in managing the blood glucose concentrations in human diabetic patients. The gel forming effects of psyllium fiber prolong the digestion and absorption of glucose as it takes longer for glucose to diffuse through the gel to the wall of the small intestine for absorption. Psyllium has a substantial effect in lowering the blood glucose concentrations.

Dietary fiber may play in important role in the control of blood glucose concentration in canine diabetic patients. Indeed, several studies have suggested that diabetic dogs fed high fiber diets have improved glycemic control. However, there does seem to be marked variation in the responses of individual dogs to dietary fiber. Fiber slows down glucose absorption and contributes to minimizing post-prandial glycemia. Both soluble and insoluble fibers appear to be beneficial. In addition, the fermentative products of fiber, particularly the short chain fatty acids may modify the secretion of certain gastrointestinal hormones that are involved in metabolism and alter the sensitivity of the tissues to insulin. On the basis of these studies, the dietary management of canine diabetic patients has been to provide a palatable diet of consistent nutrient profile, which is high in complex carbohydrate (starch and dietary fiber), and devoid of simple sugars. However, a recent study failed to demonstrate any clear benefit of a high fiber diet compared with a typical adult maintenance diet (moderate fiber) in dogs with well-controlled diabetes mellitus. Therefore, high fiber diets may not offer any additional advantages for dogs with stable diabetes mellitus.

Carnitine is a quaternary amine that plays a pivotal role in fatty acid metabolism by facilitating the transport of long-chain fatty acids across the mitochondrial membrane. Supplementation with carnitine may enhance energy production from fatty acid oxidation and reduce skeletal muscle catabolism. Dogs with poorly controlled diabetes mellitus experience weight loss, altered fat metabolism, ketogenesis, and hepatic changes, and so are likely to benefit from dietary carnitine supplementation.

Chromium has been suggested to improve peripheral insulin sensitivity and glucose tolerance in rats. However, studies in diabetic dogs and cats have failed to demonstrate improvements in glycemic control hence chromium supplementation can not be recommended at this time.

Oxidative stress may contribute to the chronic complications of diabetes mellitus. Indeed, studies in humans have reported increases in the markers of oxidative stress and decreases in the concentration of antioxidants. Therefore, it seems prudent that diabetic dogs and cats should receive antioxidants to combat free radical damage.

Diabetes mellitus is a complex disorder that alters protein, fat and carbohydrate metabolism. The focus of dietary management is to provide consistent calories to optimize body weight, body condition and glycemic control. Recent studies suggest that the diabetic cats should be fed a moderate energy, high protein diet with controlled levels of low glycemic index carbohydrates. Dogs with poorly-regulated diabetes mellitus may respond to diets with complex carbohydrates and high levels of dietary fiber. Such diets may not provide any additional benefits for dogs with well-controlled diabetes mellitus.

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Monitoring of Glycemia in Dogs and Cats with Diabetes Mellitus

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The aim of therapy in diabetic pets is to eliminate the clinical signs of diabetes mellitus (DM) and to avoid the common complications associated with the disease. It is not necessary to establish near normal blood glucose levels, as is the case in humans. The reason for the different treatment goals is the much shorter life expectancy in animals compared to humans, which prevents the development of the serious complications of diabetes.

History and physical examination are very important parameters to assess the quality of glycemic control. Dogs and cats without clinical signs of DM, stable body weight, and unremarkable physical examination are usually well controlled. In those cases, hospitalization for performing a blood glucose curve may not be warranted. Measurement of serum fructosamine may be helpful to support the judgement of good metabolic control. In Zurich, the reference range of fructosamine is 200 – 340 µmol/l. Fructosamine levels between 300 and 450 µmol/l are considered consistent with excellent to good metabolic control, fructosamine levels < 300 µmol/l point to overregulation (overdose of insulin or oral hypoglycemic agents). Well-controlled dogs and cats usually have blood glucose concentrations between 15 and 5 mmol/l (270 and 90 mg/dl) throughout 24 hours.

In diabetic animals with persistence of clinical signs, ongoing weight loss, and fructosamine levels > 500 µmol/l, single blood glucose measurements are not helpful to characterize the underlying problem. It is the serial blood glucose curve (BGC) which provides guidelines for making rational adjustments in insulin therapy. BGCs enable the assessment of insulin efficacy, the glucose nadir, the time of peak insulin effect, the duration of the effect of insulin, and the degree of fluctuation in blood glucose concentration. BGCs are also needed to recognize the Somogyi phenomenon. Until recently, BGCs were only performed in the hospital, because most owners cannot perform venipuncture at home. However, interpretation of BGCs generated in hospitalized animals may be difficult because of the potential influence of stress, abnormal housing conditions (e.g. lack of exercise) and decreased food intake on blood glucose concentrations. Additionally, BGCs are time consuming and expensive and therefore, are often not performed as frequently as required. Many patients would benefit from more frequent blood glucose determinations. For example, short-notice adjustments of the insulin dosage are necessary in diabetic patients with infections (increased dose) or at times of increased physical activity (mostly decreased dose). Close monitoring of blood glucose concentration is also indicated in diabetic patients that are treated for a concomitant disease, such as hyperadrenocorticism or hypothyroidism. Similarly, bitches may require adjustments of the insulin dosage at the transition from one estrus cycle stage to another. Due to the abolition of the resistance to insulin associated with these conditions, the required insulin dosage may have to be reduced drastically in order to prevent life-threatening hypoglycemia. It is difficult to manage these cases without frequent blood glucose determinations.

In human medicine, problems with diabetic control are in principle similar to veterinary medicine. They have been largely eradicated due to the introduction of self-monitoring of blood glucose concentrations (SMBG) in the late 1970s. For SMBG, human patients obtain a drop of capillary blood by pricking a fingertip with a lancing device. The drop is then placed on a test strip, and the glucose concentration is measured using a portable glucose meter (PBGM). The availability of automated, spring-operated devices makes the finger-pricking process simple and virtually painless.

During the last years, methods analogous to SMBG have been developed for dogs and cats. The method used in Zurich is performed by the use of a lancing device creating a negative pressure (Fig.1). Capillary blood is obtained from the inner aspect of the pinna and blood glucose concentration is determined with a PBGM. The method is relatively inexpensive, fast and easy to perform and can be used by owners of diabetic dogs and cats to determine blood glucose concentrations and to generate BGCs at home.[1,2,3,4]

Fig. 1 Generation of a drop of blood from the inner pinna of a cat using negative pressure created by the lancing device Microlet Vaculance® (Bayer Diagnostics).

Blood sampling is also possible with other techniques, e.g. the marginal ear vein technique.[5] For pet owners, home monitoring of blood glucose (HM) can constitute a challenge and therefore it is important to minimize technical difficulties as much as possible. Owners should be provided with a PBGM that is simple to operate. In our experience the Ascensia Elite® or the latest generation Ascensia Contour® (both Bayer Diagnostics) are very easy to operate: they have no buttons to press, turn on automatically when the test strip is inserted and require a very small amount of blood, which is automatically aspirated into the reaction chamber after contacting the test strip. For the Ascensia Contour® the measurement range is 0.6 – 33.3 mmol/l (10 – 600 mg/dl), the results are displayed within 15 seconds and the last 240 measurements are stored. With the Ascensia Elite® it is of utmost importance that the test strip chamber is filled to the mark, otherwise false low values are displayed.[6,7] This problem has been eliminated in the Ascensia Contour®, in which an additional advantage is the very low amount of required blood (0.6 µl). Blood glucose concentrations that are measured by PBGM almost always vary slightly from those measured by a reference method and quality control of PBGMs prior to their use is extremely important. For more than six years we have been involved in HM of diabetic dogs and cats. The results have been extremely positive. The majority of owners are very interested in measuring blood glucose in their pets, and about 70% have been capable and willing to perform HM on a long-term basis.[8,9]

There are a number of steps that should precede the introduction of HM. The first step is a definitive diagnosis of diabetes mellitus. Additional tests to diagnose concurrent diseases may be indicated at this point. The owner then receives detailed information on various aspects of diabetes mellitus and careful instruction on injection technique, and the concept of HM is mentioned for the first time. This consultation takes approximately 45 minutes. The second step consists of re-evaluation of the patient after one week. Observations made by the owner are discussed, a clinical examination is performed and fructosamine concentration and an in-clinic BGC over 12 hours are determined. Treatment is adjusted if necessary. At the time of discharge, the importance of the BGC in the control of the disease is emphasized. In addition, the advantages of HM for owner and pet are discussed and he/she is informed that this procedure can be started after the next re-evaluation.

The third step follows approximately three weeks after a diagnosis has been made. Once again, owner observations are assessed and a physical examination, a BGC, and fructosamine concentration are determined. The owner is now provided the opportunity to learn the technique of HM. This requires a minimum of 30 minutes and consists of repeated demonstrations of the use of the lancing device and the PBGM. The owner then performs the technique several times in his pet. He is also taught how to calibrate the PBGM (if needed), check its accuracy using the control strips, and record the blood glucose values on forms prepared by us. HM is not started before the third week after a diagnosis of diabetes mellitus. This allows the owner to become familiar with the disease and to gain experience with the injection of insulin. However, introduction of HM is delayed to a later date if the owner does not seem ready for it.
Once the owner is comfortable with the procedure, we request that fasting blood glucose concentration be determined twice weekly and a BGC once monthly. The former serves to detect morning hypoglycemia, in which case the owner is instructed to call us. For determination of a BGC, the blood glucose concentration is measured before the insulin injection (fasting) and every two hours thereafter. Since all our diabetic animals receive insulin BID the BGC is performed for 12 hours. The owner sends the results of the BGC, and appropriate changes in treatment are discussed, if necessary, on the telephone. Periodic re-assessments of the entire procedure in the hospital are mandatory. For the first months the patient is re-assessed at least once a month, later on frequency is reduced to a minimum of twice a year.

It is important that owners have ready access to veterinary support, if required. The majority of our clients call for advice one or more times, especially after the start of HM. Some have specific questions regarding the procedure, while others want reassurance that they are performing the procedure correctly.[4,8] Sometimes support via telephone is not sufficient and additional explanation or demonstration of the technique must be provided. By watching an owner performing the procedure, a veterinarian can immediately identify and correct errors. According to a recently performed study,[3] the most frequently encountered technical problems included inadequate formation of a blood drop due to excessive pressure of the finger behind the ear while lancing the ear, repeated depression of the plunger instead of allowing the negative pressure to slowly build up, and failure to fill the test strip to the mark. These procedural steps therefore require explicit explanation and demonstration. Handling the PBGM usually is not a problem for owners, and most report that their pet tolerates blood collection well. The skin puncture does not seem to be painful, and the puncture sites are barely visible, even after numerous blood collections.

Recently we compared BGC generated at home with those generated in the hospital with regard to treatment decisions.[4,9] In about 60% of cases, treatment decisions would have been the same, and in about 40% treatment decisions would have been different. In the latter, in 3% (dogs) and 8% (cats) of cases, the treatment decisions would have been contrary (increase vs. decrease of insulin dosage). In the others, decisions, although being different, would have had little clinical consequence. It is of course not possible to prove whether hospital or home curves reflected the "true" blood glucose concentrations. Our most recent, so far unpublished study shows that there also is a lot of variability if BGCs are performed at home on consecutive days. Therefore, single curves may not reflect the true glycemic situation independent of where they are performed. However,

one of the major advantages of HM is, that it enables frequent generation of BGCs, which may be of particular importance in animals that are difficult to regulate. In those cases, more than one BGC can be performed at home before a decision is made concerning therapy.

Long-term compliance of pet owners is good; many perform HM for several years. According to a recent retrospective survey in cat owners only a minority adjusted insulin doses independently, most of them called the hospital for advice. All cat owners believed that HM provides major advantages over in-hospital monitoring.[8]

It has been argued that pet owners who are able to perform HM would visit the hospital less frequently. However, our observations over the last years do not support this. Frequency of re-evaluation does not differ between pets with and without home monitoring.

HM is a valuable additional tool in the management of dogs and cats with diabetes mellitus. One of its major advantages is that blood glucose can be measured more frequently than when it has to be done in the hospital. In animals which are difficult to regulate, several BGCs generated at home can be interpreted before a treatment decision is made.

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Selecting an Insulin for Treating Diabetes Mellitus in Dogs and Cats

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Veterinarians often ask which insulin is the best for treating diabetes mellitus in dogs and cats. Unfortunately, this question is difficult to answer. All insulin types currently on the market have the potential to work well in some diabetic dogs and cats but not in others. Recommendations regarding the insulin of choice for treating diabetic dogs and cats are based on personal experiences and vary between clinicians. Some clinicians prefer NPH insulin while others prefer lente insulin for treating diabetic dogs. Some clinicians prefer PZI, some NPH, some lente, and some insulin glargine for treating diabetic cats. Which insulin is ultimately effective in a diabetic is unpredictable. The clinician's role is to identify which type of insulin works best in the diabetic dog or cat currently being treated. Success with insulin therapy requires knowledge of currently available insulin preparations - their intended use, potency, trends regarding duration of effect, and potential impact of species of insulin origin on diabetic control.

Overview of Insulin Types. Commercial insulin is categorized by promptness, duration, intensity of action, and origin. Short-acting prandial insulins include regular crystalline (Humulin R®, Eli Lilly, Indianapolis, IN), insulin lispro (Humulog®, Eli Lilly) and insulin aspart (Novolog®, Novo Nordisk, Princeton, NJ). Regular crystalline insulin is a recombinant human insulin while insulin lispro and insulin aspart are insulin analogs. Recombinant DNA technology has been used to alter the amino acid sequence of the insulin molecule to alter the absorption characteristics of insulin lispro and insulin aspart following subcutaneous (SC) administration. The rate-limiting step in the absorption of human insulin is a hexamer formation of insulin molecules that occurs at high concentrations of insulin such as those obtained in the injectable fluid.[1] After SC administration, the hexamers of insulin molecules slowly dissociate before absorption into the circulation occurs. By replacing certain amino acids in the insulin molecule, the tendency to self-associate into hexamers can be reduced without affecting the insulin-receptor kinetics. Insulin lispro is produced by inverting the natural amino acid sequence of the B-chain at B28 (proline) and B29 (lysine), and insulin aspart is produced by substituting aspartic acid for proline in position B28.[2] As a consequence of these alterations, insulin lispro and insulin aspart exhibit monomeric behavior in solution and display a rapid absorption, faster pharmacodynamic action, and shorter duration of effect than regular crystalline insulin.[3] Insulin lispro and insulin aspart are the current prandial insulins of choice for control of postprandial blood glucose concentrations in human diabetics and are typically administered prior to breakfast, lunch, and dinner. The role, if any, of these insulins for the home treatment of diabetes in dogs or cats remains to be determined.

Mixtures of short- and long-acting insulin have been developed in an attempt to mimic the increase in portal insulin concentrations during and immediately following consumption of a meal, thereby minimizing postprandial hyperglycemia. NPH insulin can be mixed with regular crystalline insulin and, if injected immediately, the regular insulin remains rapid-acting. Stable premixed 70% NPH/30% regular and 50% NPH/50% regular preparations are available (e.g., Humulin 70/30®, Eli Lilly and Co., Indianapolis, IN; Mixtard HM 70/30®, Novo Nordisk, Princeton, NJ). In my experience, these premixed preparations are quite potent, causing a rapid decrease in blood glucose concentration within 60 to 90 minutes of SC administration, and usually have a short duration of effect. I only use these insulin mixtures as a last resort when more conventional insulin preparations have been ineffective in establishing control of glycemia.

Types of insulin typically used for the home treatment of diabetes include intermediate-acting insulin (NPH, lente) and long-acting basal insulin (PZI, insulin glargine). NPH and PZI insulin preparations contain the fish protein protamine and zinc to delay insulin absorption and prolong the duration of insulin effect. Lente insulin relies on alterations in zinc content and the size of zinc-insulin crystals to alter the rate of absorption from the subcutaneous site of deposition. The larger the crystals, the slower the rate of absorption and the longer the duration of effect. Lente insulin contains no foreign protein (i.e., protamine). Lente insulin is a mixture of three parts of short-acting, amorphous insulin and seven parts of long-acting, microcrystalline insulin. Lente insulin is considered an intermediate-acting insulin, although plasma insulin concentrations may remain increased for longer than 14 hours following SC administration in some dogs.[4]

NPH (Humulin N®, Eli Lilly, Indianapolis, IN) is a recombinant human insulin, lente (Vetsulin®, Intervet, Millsboro, DE) is a purified pork-source insulin, and PZI (PZI Vet®, IDEXX, Westbrook, ME) is a beef/pork-source

insulin with approximately 90% being beef-source insulin. Chronic administration of a foreign protein (i.e., insulin) has the potential to induce formation of circulating insulin antibodies; a problem which has been identified in diabetic dogs treated with beef-source insulin. Bovine insulin stimulates formation of insulin antibodies in 40% to 65% of diabetic dogs in which it is used.[5-7] In contrast, development of insulin antibodies following chronic administration of recombinant human or porcine insulin to diabetic dogs appears uncommon[6] and the prevalence of serum insulin antibodies causing problems with control of glycemia is uncommon in diabetic cats regardless of the species of insulin.[8] Differences in the structure and amino acid sequence of the injected insulin relative to the native endogenous insulin influences the development of insulin antibodies. In a recent study evaluating insulin antibody formation in diabetic dogs treated with bovine insulin, the greatest anti-insulin antibody reactivity was directed against the whole insulin protein rather than the A- or B-chain.[7] Serum insulin antibodies may affect the pharmacokinetics and pharmacodynamic response of the exogenously administered insulin. Antibodies may enhance and prolong the pharmacodynamic action by serving as a carrier, or they may reduce insulin action by neutralization.[9,10] Antibodies may also have no apparent clinical effect on insulin dosage or status of glycemic control.[2] In my experience, insulin antibody production in diabetic dogs can alter the duration of insulin activity and prolong its duration of action or have a deleterious impact on insulin effectiveness, ability to maintain control of glycemia and, in extreme cases, cause severe insulin resistance. The current PZI product on the market is predominately a beef-source insulin and is not recommended for diabetic dogs because of concerns for insulin antibody production.

Insulin glargine (Lantus®, Aventis Pharmaceuticals, Bridgewater, NJ) is a long-acting insulin analog that differs from human insulin by replacing asparagine with glycine at position A21 on the A-chain and adding two arginines to the C-terminus of the B-chain of the insulin molecule.[11] These modifications result in a shift of the isoelectric point from a pH of 5.4 toward a neutral pH, which makes insulin glargine more soluble at a slightly acidic pH and less soluble at a physiological pH than native human insulin. As a consequence, insulin glargine forms microprecipitates in the subcutaneous tissue at the site of injection from which small amounts of insulin glargine are slowly released. In humans, the slow sustained release of insulin glargine from these microprecipitates results in a relatively constant concentration/time profile over a 24 hour period with no pronounced peak in serum insulin. Insulin glargine is currently recommended as a basal insulin (i.e., sustained long-acting insulin used to inhibit hepatic glucose production) administered once a day at bedtime and used in conjunction with either prandial insulin analogs or oral hypoglycemic drugs in human diabetics.[12]

In a preliminary study involving healthy cats, most of the pharmacokinetic and pharmacodynamic properties (i.e., onset of action, glucose nadir, time for blood glucose concentration to return to baseline, mean daily blood glucose concentration, and area under the 24-hour blood glucose curve) were similar for insulin glargine and PZI.[13] In my experience, insulin glargine has a duration of effect ranging from 10 to 16 hours in most diabetic dogs and cats.

Insulin recommendations in newly-diagnosed diabetic dogs. In my opinion, recombinant human NPH and porcine lente insulin are the initial choices for treating newly-diagnosed diabetic dogs. My starting dosage for both types of insulin is 0.25 U/kg and I prefer to start with twice a day insulin administration because the overwhelming majority of diabetic dogs require NPH or lente insulin twice a day. Establishing control of glycemia is easier and problems with hypoglycemia and glucose counterregulation (i.e., Somogyi phenomenon) are less likely when twice a day insulin therapy is initiated while the insulin dose is low, i.e., at the time insulin treatment is initiated. A recent study evaluating porcine lente insulin in 53 diabetic dogs supports these recommendations.[14] The starting dosage in the study was 1 U/kg once a day plus an additional 1 to 4 units depending on the size of the dog; a dosage which was too high as attested by the development of clinical signs of hypoglycemia in approximately 40% of dogs and identification of a blood glucose concentration less than 60 mg/dl in 36% of dogs in the study. Sixty-six percent of dogs required insulin twice a day to attain control of glycemia and the authors speculated that more dogs should have been treated twice a day. Finally, the median (range) insulin dosage required to attain control of glycemia was 1.09 (0.43 to 2.18 U/kg) and 0.75 U/kg (0.28 to 1.40 U/kg) in dogs receiving insulin once and twice a day, respectively; findings that support use of a low initial insulin dosage (i.e., 0.25 U/kg) in newly-diagnosed diabetic dogs.

Studies comparing the efficacy of recombinant human NPH versus porcine lente insulin have not been reported. Similarly, studies evaluating the efficacy of insulin glargine in diabetic dogs have not been reported. My experience with insulin glargine in diabetic dogs has been mixed and somewhat disappointing. I currently only use insulin glargine in poorly-controlled diabetic dogs where NPH and lente insulin are ineffective because of problems with short duration of insulin effect. I rarely use beef/pork-source PZI insulin in dogs because of the potential for development of insulin antibodies that may create problems with diabetic control. I consider using PZI in poorly controlled diabetic dogs where the poor control is caused by short duration of effect of NPH and lente insulin and insulin glargine is ineffective in improving control.

Insulin recommendations in newly-diagnosed diabetic cats. Diabetic cats are notoriously unpredictable in their response to exogenous insulin. There is no single type of insulin which is routinely effective in maintaining control of glycemia, even with twice a day administration. The initial insulin of choice ultimately is based on personal preferences and experiences. Commonly used insulin preparations for the long-term management of diabetic cats include NPH, lente, PZI, and insulin glargine. All have potential problems in diabetic cats. Although lente and NPH insulin are consistently and rapidly absorbed following subcutaneous administration, the duration of effect of lente and especially NPH insulin can be considerably shorter than 12 hours, resulting in inadequate control of glycemia despite twice a day administration. Although PZI is a longer acting insulin, the timing of the glucose nadir is quite variable and occurs within 9 hours of PZI administration in greater than 80% of treated diabetic cats. In one study, PZI significantly improved control of glycemia in newly-diagnosed diabetic cats and poorly-controlled diabetic cats previously treated with ultralente or NPH insulin.[15] Comparison of efficacy between PZI and lente insulin has not been reported.

Insulin glargine is the longest acting commercially available insulin for treatment of diabetes in humans and is currently a popular initial choice by veterinarians for the treatment of diabetes in cats. A preliminary study identified better glycemic control and a higher diabetes remission rate in newly-diagnosed diabetic cats treated with glargine twice a day, compared with lente or PZI administered twice a day.[16] Another study found no difference in glycemic control in diabetic cats treated with insulin glargine once a day versus diabetic cats treated with recombinant human lente insulin twice a day, and a higher diabetes remission rate in diabetic cats treated with recombinant human lente insulin.[17] In my experience, the duration of effect of insulin glargine is quite variable, with the glucose nadir occurring as soon as 4 hours and as late as 20 hours after administration. Insulin glargine works well when given once or twice a day in some diabetic cats and does not work very well in others. Problems are usually related to duration of effect.

Currently, my personal preference for the initial treatment of newly-diagnosed diabetes in cats is PZI at an initial dose of one U per cat administered twice a day. Because the majority of diabetic cats require PZI insulin twice a day, I prefer to start with twice a day insulin therapy while the insulin dose is low to avoid problems with hypoglycemia and glucose counterregulation (i.e., Somogyi phenomenon). I switch to porcine lente insulin given twice a day if problems with prolonged duration of PZI effect develop and glycemic control can not be maintained with once a day PZI and I switch to insulin glargine given twice a day if problems with short duration of PZI effect develop. When using insulin glargine for the treatment of newly-diagnosed diabetic cats, I use an initial dose of one unit per cat administered once a day and switch to twice a day therapy if subsequent blood glucose evaluations support a duration of effect of 12 hours or less.

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Unusual Endocrine Disorders in Dogs and Cats

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Insulin-Secreting Beta Cell Tumors

Functional tumors arising from the beta cells of the pancreatic islets are malignant tumors that secrete insulin independent of the typically suppressive effects of hypoglycemia. Beta cell tumors are not completely autonomous and respond to provocative stimuli (e.g., glucose) by secreting insulin, often in excessive amounts. Beta cell tumors are uncommon in dogs and rare in cats. In my experience, virtually all beta cell tumors in dogs are malignant and most dogs have microscopic or grossly visible metastatic lesions at the time of surgery. The most common sites of metastasis are the peripancreatic lymphatics, lymph nodes, mesentery, and the liver. The high prevalence of metastatic lesions is due, in part, to the protracted time it takes for clinical signs to develop and the interval between the time an owner initially observes signs and seeks assistance from a veterinarian. Most dogs are symptomatic for 1 to 6 months before being brought to a veterinarian.

Clinical Features. Beta cell tumors typically occur in middle-aged or older, large breed dogs. There is no sex-related predilection. Clinical signs are caused by neuroglycopenia and increased circulating catecholamine concentrations and include seizures, weakness, collapse, ataxia, muscle fasciculations, and bizarre behavior. The severity of clinical signs depends on the duration and severity of hypoglycemia. Dogs with chronic hypoglycemia tolerate low blood glucose concentrations (i.e., 20 to 30 mg/dl) for prolonged periods without clinical signs and only small additional decreases in blood glucose are required to produce symptomatic episodes. As such, fasting, excitement, exercise, and eating may trigger the development of clinical signs. Because of the compensatory counterregulatory mechanisms that are designed to increase the blood glucose concentration when hypoglycemia develops, clinical signs tend to be episodic and are generally observed for only a few minutes.

Physical examination findings in dogs with beta cell tumors are surprisingly unremarkable; dogs are usually free of visible or palpable abnormalities aside from weakness. Weight gain is evident in some dogs and is probably a result of the anabolic effects of insulin. Peripheral neuropathies have been observed and may be responsible for producing alterations detected during physical examination, including weakness of the rear limbs, proprioception deficits, depressed reflexes, and muscle atrophy. The pathogenesis of the polyneuropathy is not known but may be immune-mediated or secondary to metabolic derangements.

The only consistent abnormality identified in routine blood and urine tests is hypoglycemia, which is typically 30 to 55 mg/dl. Dogs with beta cell tumors may occasionally have a blood glucose concentration of 60 to 70 mg/dl. Fasting with hourly evaluations of the blood glucose concentration should be done in dogs with suspected hypoglycemia. A fast of 12 hours or less is usually successful in demonstrating hypoglycemia in dogs with beta cell tumor.

Diagnosis. The diagnosis of a beta cell tumor requires initial confirmation of hypoglycemia, followed by documentation of inappropriate insulin secretion and identification of a pancreatic mass using ultrasonography or exploratory celiotomy. Considering the potential differential diagnoses for hypoglycemia, a tentative diagnosis of beta cell tumor can often be made on the basis of the history, physical examination findings, and an absence of abnormalities other than hypoglycemia shown by routine blood tests. Abdominal ultrasonography can be used to identify a mass in the region of the pancreas and to look for evidence of metastatic disease; however, failure to identify a beta cell tumor does not rule it out.

The diagnosis of beta cell tumor is established by documenting an excessive serum insulin concentration when hypoglycemia is present. When the blood glucose concentration is less than 60 mg/dl (preferably less than 50 mg/dl), serum should be submitted to a commercial veterinary endocrine laboratory for determination of glucose and insulin. Serum insulin concentrations must be evaluated simultaneously in relation to the blood glucose concentration. A serum insulin concentration in the upper half of, or greater than, the normal range in a dog with a corresponding blood glucose concentration less than 50 mg/dl in combination with appropriate clinical signs and clinicopathologic findings supports the diagnosis of a beta cell tumor. Insulin values in the lower half of the normal range may be found in dogs with other causes of hypoglycemia including beta cell tumor. Careful assessment of the information gathered on the case and possibly repeated serum glucose and insulin measurements will usually

identify the cause of hypoglycemia. Insulin values below the normal range are not consistent with beta cell tumor. Confidence in identifying inappropriate hyperinsulinemia is dependent on the severity of the hypoglycemia; the lower the blood glucose concentration, the more confident the clinician can be in identifying inappropriate serum insulin concentrations.

Treatment. Surgical exploration is the best diagnostic, therapeutic, and prognostic tool in dogs with beta cell tumor. Surgery offers a chance to cure dogs with a resectable solitary mass. In dogs with nonresectable tumors or with obvious metastatic lesions, the removal of as much abnormal tissue as possible has frequently resulted in the remission, or at least alleviation, of clinical signs and an improved response to medical therapy. Survival time is also longer in dogs undergoing surgical exploration and tumor debulking followed by medical therapy, compared with dogs only treated medically. Despite these benefits, surgery remains a relatively aggressive mode of diagnosis and treatment, in part because of the high prevalence of metastatic disease and the older age of many dogs at the time beta cell neoplasia is diagnosed. As a general rule, we are less aggressive about recommending surgery in aged dogs (i.e., 12 years and older), dogs with metastatic disease identified by ultrasonography, and dogs with concurrent disease that enhances the anesthetic risk.

Most dogs with insulin-secreting tumors have masses that can be easily seen by the surgeon inspecting the pancreas. In a minority of dogs, the tumor is not visible but can be palpated during gentle but thorough digital examination of the pancreas. Multiple pancreatic masses may also occur. There is no predisposition for tumor location within the pancreas, and there appears to be little correlation between tumor size and its malignant potential. The most common postoperative complications are pancreatitis, hyperglycemia, and hypoglycemia. Dogs that remain hypoglycemic after surgical removal of a beta cell tumor have functional metastatic lesions. Medical therapy should be initiated in dogs with persistent postoperative hypoglycemia.

Medical treatment includes frequent feedings, limited exercise, and glucocorticoids. The goals of medical treatment are to reduce the frequency and severity of clinical signs and to prevent an acute hypoglycemic crisis, not to establish euglycemia, per se. Frequent feedings provide a constant source of substrate for insulin. Diets that are high in fat, complex carbohydrates and fiber will delay gastric emptying and slow intestinal glucose absorption, helping to minimize the increase in the portal blood glucose concentration and subsequent stimulation of insulin secretion by the tumor. Simple sugars are rapidly absorbed, have a potent stimulatory effect on insulin secretion by neoplastic beta cells and should be avoided. A combination of canned and dry food, fed in three to six small meals daily, is recommended. Daily caloric intake should be controlled to avoid obesity. Exercise should be limited to short walks on a leash.

Glucocorticoid therapy should be initiated when dietary manipulations are no longer effective in preventing clinical signs of hypoglycemia. Glucocorticoids cause insulin resistance, stimulate hepatic glycogenolysis, and indirectly provide substrates for hepatic gluconeogenesis. Prednisone is given at an initial dose of 0.25 mg/kg bid. Adjustments in the dose are done, as needed, to control clinical signs of hypoglycemia. Clinical signs of iatrogenic hyperadrenocorticism will eventually develop and limit the amount of prednisone that can be given. Additional therapy such as diazoxide, somatostatin, and streptozotocin should be considered when prednisone no longer controls clinical signs.

Pheochromocytoma

Pheochromocytoma is a catecholamine-producing tumor derived from the chromaffin cells of the adrenal medulla. The antemortem diagnosis of pheochromocytoma is uncommon in dogs and rare in cats. Pheochromocytoma should be considered a malignant tumor in dogs. Pheochromocytomas commonly invade the adjacent vena cava, phrenicoabdominal vein, kidney and body wall and metastasize to distant sites such as the liver, lung, and regional lymph nodes.

Clinical Features. Pheochromocytomas occur most commonly in older dogs. There is no apparent sex- or breed-related predisposition. Clinical signs and physical examination findings develop as a result of the space-occupying nature of the tumor and its metastatic lesions or as a result of the excessive secretion of catecholamines. The most common clinical signs are generalized weakness and episodic collapse. The most common abnormalities identified during physical examination involve the respiratory (i.e., tachypnea, excessive panting), cardiovascular (i.e., tachycardia, cardiac arrhythmias, weak femoral pulses), and musculoskeletal (i.e., weakness, muscle wasting) systems. Excess catecholamine secretion may also cause severe hypertension. Because catecholamine secretion is sporadic and unpredictable, clinical manifestations and hypertension tend to be paroxysmal and usually not evident at the time the dog is examined.

Diagnosis. A diagnosis of pheochromocytoma requires a high index of suspicion on the part of the clinician. There are no consistent abnormalities in routine blood and urine tests to suggest pheochromocytoma. A history of acute or episodic collapse, weakness, tachypnea, tachycardia or cardia arrhythmias, documentation of systemic hypertension, and identification of an adrenal mass with abdominal ultrasound are suggestive of pheochromocytoma. The contra lateral adrenal gland should be normal in size and tests of adrenocortical function should be normal. Identification of local invasion of the adrenal mass into surrounding structures or presence of a tumor thrombus is not, by itself, indicative of pheochromocytoma; similar findings also occur with adrenocortical tumors. Pheochromocytoma and an adrenocortical

tumor or pheochromocytoma and pituitary-dependent hyperadrenocorticism can occur simultaneously, which can pose a difficult diagnostic and therapeutic challenge. Many of the clinical signs (e.g., panting, weakness) and blood pressure alterations seen in dogs with hyperadrenocorticism are similar to those seen in dogs with pheochromocytoma. Therefore it is important to rule out hyperadrenocorticism before focusing on pheochromocytoma in a dog with an adrenal mass. Measurement of urinary catecholamine concentrations or their metabolites can strengthen the tentative diagnosis of a pheochromocytoma. Unfortunately, these tests are not commonly performed. As a result, the antemortem definitive diagnosis of pheochromocytoma ultimately relies on histologic evaluation of the surgically excised adrenal mass.

Treatment. A period of medical therapy to reverse the effects of excessive adrenergic stimulation followed by surgical removal of the tumor is the treatment of choice for pheochromocytoma. Potentially life-threatening complications are common during the perioperative period, especially during the induction of anesthesia and manipulation of the tumor during surgery. The most worrisome complications include episodes of acute, severe hypertension, episodes of severe tachycardia and arrhythmias, and hemorrhage. Preoperative α-adrenergic blockade is indicated to minimize perioperative complications; phenoxybenzamine is the current drug of choice. I initially start with a low dosage (0.5 mg/kg bid) and gradually increase the dosage every few days until clinical signs of hypotension (e.g., lethargy, weakness, syncope), adverse drug reactions (e.g., vomiting) or a maximum dosage of 2.5 mg/kg bid is attained. Surgery is recommended 1 to 2 weeks later. The drug should be continued until the time of surgery. Complications may still occur despite prior treatment with α-adrenergic blocking drugs; close monitoring of the dog during the perioperative period is critical for a successful outcome. Postoperative complications are common and include hypertension, cardiac arrhythmias, respiratory distress, and hemorrhage.

Feline Acromegaly

Chronic excessive secretion of growth hormone (GH) in adult cats results in acromegaly, a disease characterized by the overgrowth of connective tissue, bone, and viscera. In cats, acromegaly is caused by a functional adenoma of the somatotropic cells of the pituitary pars distalis. In most cats, the pituitary tumor is visible with CT at the time acromegaly is diagnosed. Chronic excessive secretion of GH has anabolic and catabolic effects. Anabolic effects of acromegaly are mediated through insulin-like growth factor-I (IGF-I), which causes proliferation of bone, cartilage, and soft tissues and organomegaly, most notably of the kidney and heart. These anabolic effects are responsible for producing the classic clinical manifestations of acromegaly. The catabolic effects of GH are a direct result of insulin antagonism which ultimately results in insulin-resistant diabetes mellitus. Most but not all cats with acromegaly have diabetes mellitus at the time acromegaly is diagnosed, and most eventually develop severe insulin-resistance.

Clinical Features. Acromegaly typically occurs in older, male domestic short-haired or long-haired cats. The earliest clinical signs are usually polyuria, polydipsia, and polyphagia resulting from concurrent diabetes mellitus. Polyphagia may also develop as a direct result of increased GH independent of diabetes mellitus, and can become quite intense. Weight loss varies and depends in part on whether the anabolic effects of IGF-I, or the catabolic effects of GH predominate. Most cats initially lose weight followed by a period of stabilization and then a slow, progressive gain in body weight as the anabolic effects of IGF-I begin to dominate the clinical picture. Severe insulin resistance eventually develops. Insulin dosages in cats with acromegaly frequently exceed 2 U/kg of body weight twice a day, with no apparent decline in the blood glucose concentration. In most cats, the clinician considers acromegaly only after he or she realizes that insulin therapy is ineffective in controlling the diabetic state.

Clinical signs related to the anabolic actions of excess GH secretion may be evident at the time diabetes mellitus is diagnosed or more commonly become apparent several months after diabetes is diagnosed, often in conjunction with the realization that hyperglycemia is difficult to control with exogenous insulin therapy. Because of the insidious onset and slowly progressive nature of the anabolic clinical signs, owners are often not aware of the subtle changes in the appearance of their cat until the clinical signs are quite obvious. Anabolic changes in acromegalic cats include an increase in body size, enlargement of the abdomen and head, development of prognathia inferior, and weight gain. Weight gain in a cat with poorly regulated diabetes mellitus is an important diagnostic clue to acromegaly. With time, organomegaly, especially of the heart, kidney, liver, and adrenal gland, develop. Diffuse thickening of soft tissues in the pharyngeal region can lead to extrathoracic upper airway obstruction and respiratory distress.

Concurrent, poorly controlled diabetes mellitus is responsible for causing most of the abnormalities identified on routine blood and urine tests, including hyperglycemia, glycosuria, hypercholesterolemia, and a mild increase in liver enzyme activities. Mild erythrocytosis, persistent mild hyperphosphatemia without concurrent azotemia, and persistent hyperproteinemia may also be found. Renal failure is a potential sequelae of acromegaly and, if present, will be associated with azotemia, isosthenuria, and proteinuria.

Diagnosis. A tentative diagnosis of acromegaly is based on the identification of conformational alterations (e.g., increased body size, large head, prognathia inferior, organomegaly) in a cat with insulin-resistant diabetes

mellitus, a persistent increase rather than decrease in the body weight of a cat with poorly controlled diabetes mellitus, and documentation of a pituitary mass by CT or MR scanning. Definitive diagnosis of acromegaly requires documentation of increased serum GH concentrations. GH concentrations in cats with acromegaly typically exceed 10 ng/ml (normal concentration, less than 5 ng/ml). Unfortunately, a commercial test for feline GH is not currently available. A test for serum IGF-I concentration is commercially available for cats and can provide further evidence for acromegaly and can be used as a screening test prior to performing a CT or MR scan. Concentrations are usually increased in acromegalic cats, however, serum IGF-I values may fall in the upper normal range in the early stages of the disease. Repeat measurements should be performed 3 to 4 months later if serum IGF-I is normal and acromegaly is strongly suspected. The increase in serum IGF-I typically coincides with development and growth of the pituitary somatotropic adenoma. The clinical picture and severity of insulin resistance must always be taken into consideration when interpreting serum IGF-I results.

Treatment. Radiation therapy is currently the best treatment option for acromegaly in cats. Unfortunately, the response to cobalt teletherapy is unpredictable and ranges from no response to a dramatic response, characterized by shrinkage of the tumor, elimination of hypersomatotropism, resolution of insulin resistance, and in some cats, reversion to a subclinical diabetic state. Survival time for cats with acromegaly, regardless of treatment, has ranged from 4 to 60 months (typically 1.5 to 3 years) from the time the diagnosis is established. The severity of insulin resistance fluctuates unpredictably in cats with acromegaly and severe, life-threatening hypoglycemia may suddenly develop after months of insulin resistance. As such, administration of large doses of insulin (2 U/kg or more per injection) should be avoided, and owners should be aware of clinical signs of hypoglycemia and know how to respond should signs be observed. Most cats with acromegaly die or are euthanized because of development of heart failure, renal failure, respiratory distress, neurologic signs from an expanding pituitary tumor, or coma caused by severe hypoglycemia.

Laboratory Assessment for Disorders of Calcium: Special Considerations for Sample Handling and Interpretation of Results

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There are a number of measurements that are useful in the assessment of calcium disorders, including serum total calcium (tCa), ionized calcium (iCa), parathyroid hormone (PTH), parathyroid hormone related protein (PTHrP), and calcidiol (25-hydroxyvitamin D). In addition, other measurements including calcitriol (1,25-dihydroxyvitamin D), ionized magnesium (iMg), protein-bound calcium (pCa), or complexed calcium (cCa) may be useful in certain conditions.

Total Calcium

Despite the fact that only the iCa fraction is physiologically active, the calcium status of animals has typically been based on evaluation of serum tCa concentration, assuming that it is directly proportional to iCa. Fasting serum or heparinized plasma samples should be submitted for analysis. Oxalate, citrate, and EDTA anticoagulants should not be used, because calcium is bound to these chemicals and becomes unavailable for analysis.[1] Hemolysis can result in formation of an interfering hemoglobin-chromagen complex that falsely increases measured calcium concentration. High concentrations of bilirubin falsely decrease tCa, and hyperlipidemia can result in spuriously high calcium concentrations.[2] Caution should be exercised in the interpretation of tCa measurements performed on small serum or plasma volumes. If samples are diluted for measurement, serum tCa concentrations may be falsely decreased. Each laboratory should establish normal values. Variability may result from differences in age, diet, duration of fasting before sampling, and time of sampling, in addition to differences in analytical method. Normal serum tCa concentrations in mature dogs and cats are approximately 10.0 and 9.0 mg/dL (2.5 mmol/L and 2.25 mmol/L), respectively. Dogs younger than 3 months of age have slightly higher mean serum calcium concentrations (approximately 11.0 mg/dL or 2.75 mmol/L) than those for dogs older than 1 year (approximately 10.0 mg/dL or 2.5 mmol/L), probably because of normal bone growth. In a small percentage of normal young dogs, serum tCa concentrations may be greater than 12.0 mg/dL (3.0 mmol/L) and as high as 15.0 mg/dL (5.0 mmol/L).[3]

Total calcium is composed of three fractions: ionized, complexed, and protein-bound, and changes in any one fraction will impact the tCa measurement. It has been reported that canine serum tCa concentrations should be "corrected" or "adjusted" relative to the serum total protein or albumin concentration in order to improve diagnostic interpretation.[4] Such correction seemed logical because binding of serum calcium to protein is substantial and 80 to 90% of the calcium bound to proteins is bound to albumin. It has been assumed that serum tCa concentrations that correct into the normal range are associated with normal iCa concentration. Likewise, values that fail to correct into the normal range are presumed to have abnormal iCa concentrations. These formulas, however, were developed without verification by iCa measurements. In a recent study, over 1600 canine cases were retrospectively reviewed, and tCa, and adjusted tCa were compared to anaerobically measured iCa.[5] In dogs, when total calcium was used to predict iCa status, diagnostic discordance was 27%. When total calcium was adjusted to total protein, diagnostic discordance increased to 37%. When total calcium was adjusted to albumin, the diagnostic discordance with iCa measurement was 38%. In a subpopulation of dogs with chronic renal failure, tCa, adjusted tCa to TP, and adjusted tCa to albumin resulted in diagnostic discordance of 36%, 53%, and 54% respectively in the prediction of iCa. In over 400 cats, there was a 40% diagnostic disagreement between serum iCa and tCa measurement. Adjustment formulas perform poorly as they were based solely on the protein-bound fraction of calcium, ignoring cCa. Complexed calcium is not a constant, especially in CRF patients, where cCa can range from 6 to 39% of tCa.[6] Serum tCa or adjusted tCa are unacceptable predictors of iCa status due to the high levels of diagnostic discordance, especially in CRF patients. Changes in serum protein concentration, individual protein binding capacity and affinity, changes in serum pH, and alterations in cCa all interact to change iCa concentration, independent of tCa concentration.

Ionized Calcium

Ionized calcium is the biologically active form of calcium, and for accurate assessment of calcium status, iCa must be measured directly. Use of a calcium ion-selective electrode allows easy and accurate measurement of iCa.[7] Differences among analyzers do exist, and it is recommended that reference ranges be established for each analyzer.[8]

The accurate determination of iCa requires that samples be collected and processed correctly. Acidic pH favors dissociation of calcium from protein and increases the amount of iCa in the sample. Alkaline pH (occurs with loss of CO_2) favors calcium binding to protein and decreases the

amount of iCa. Mixing of serum with air results in decreased iCa and increased pH.[9] Anaerobic collection and separation of serum is the most accurate method for iCa measurement; however, accurate aerobic methods have been developed. Correction formulas can mathematically manipulate the iCa concentration of an aerobic sample to the theoretical iCa concentration at pH 7.4.[10,11] These correction formulas assume that pH and iCa concentration change in a predictable inverse logarithmic manner. Ionized calcium analyzers typically have an internal formula that will make this correction. This internal correction formula should not be used however, since this formula was designed for use in humans. Different species may have different protein-binding properties, and thus formulas must be developed and validated for each species. While not quite as precise as anaerobic measurement, aerobic measurement under proper laboratory conditions offers a diagnostically accurate methodology for iCa determination with simplified shipping and handling requirements.

Ionized calcium can be measured in heparinized whole blood, but measurement is problematic. Concentrations of iCa were lower by about 0.05 mmol/L in heparinized plasma compared to serum in dogs.[12] The amount and type of heparin used also affects iCa measurement. When zinc heparin is used, iCa is overestimated due to a decrease in pH which displaces calcium from proteins.[13,14] Lithium heparin causes an underestimation in iCa,[13] and an electrolyte balanced heparin may under- or overestimate iCa depending on whether hypocalcemia, normocalcemia, or hypercalcemia is present. The amount of heparin used is critical in the measurement of iCa in blood. Using syringes containing a premeasured quantity heparin, iCa measurement was underestimated when a less than recommended quantity of blood was collected.[13,15] When using heparinized whole blood for measurement of iCa, it is imperative to collect the same volume of blood for each sample to avoid dilutional effects. Syringes containing a premeasured amount of dry heparin are preferable to coating a syringe manually with an unknown and variable quantity of liquid heparin.

Ionized calcium and pH are more stable in serum than in whole or heparinized blood. Serum analysis eliminates the potential interference of heparin and allows longer storage period before analysis. Silicone separator tubes are not recommended however, as serum iCa concentration may increase because of release of calcium from the silicone gel.[16]

Recently, portable clinical analyzers have been developed for cage-side analysis of iCa concentration. These analyzers use a disposable cartridge containing an impregnated biosensor for iCa and other analytes. Heparinized whole blood is used for analysis, but caution should be exercised when interpreting these results. Ionized calcium concentrations in dogs are typically 0.05 to 0.26 mmol/L lower, and 0.05 to 0.14 mmol/L lower in cats when heparinized whole blood is compared to serum iCa measurement.[17] The greatest underestimation of iCa concentration occurred when serum iCa concentrations were greater than 1.3 mmol/L. When iCa concentration in heparinized whole blood was measured using both ion-selective electrode methodology and portable clinical analyzer methods, correlation (r) was only 0.71.[18] The portable clinical analyzer method resulted in an iCa concentration that was approximately 2.6% lower than that measured with an ion-selective electrode.[19] Since the quantity and type of heparin used and volume of blood collected also have an effect on iCa measurement, it is best to establish a rigid protocol for blood collection when using a portable clinical analyzer. Reference ranges should also be established for the analyzer using this standard protocol.

The range for serum iCa concentration in normal dogs and cats varies among laboratories but is approximately 5.0 to 5.8 mg/dL (1.25 to 1.45 mmol/L) in adult dogs[20] and 4.6 to 5.4 mg/dL (1.15 to 1.35 mmol/L) in adult cats.[21] An effect of aging has been observed in both the dog and cat. Young dogs and cats (up to 2 years of age) have serum iCa concentrations that are 0.1 to 0.4 mg/dL higher than those reported in older animals.[21,22] Normal values should be established for each laboratory on the basis of age of animal, type of sample, and analyzer used.

Parathyroid Hormone

For measurement of PTH, it is best to measure the intact form since this is the biologically active molecule. Samples should be stored and shipped frozen with overnight delivery to prevent degradation of intact PTH. After 4 days at 4°C, only 65% of the hormone remains, and after 7 days at 24°C, only 19% remains, thus specimen handling and timely transport is imperative. Freezing is best, since PTH is stable up to 2 months at –20°C. Stability is best in EDTA plasma, but serum is adequate if stored frozen after separation. A two-site immunoradiometric (IRMA) assay for intact human PTH has been validated in the dog and cat.[23,24] The two-site assays have the advantage that there is a binding site on both the amino- and carboxyl-terminal end so that intact PTH is measured without interference from the amino-terminal fragment (1-34) and carboxyl-terminal fragments (44-84 and 53-84). The common two-site intact PTH assays actually bind near the tenth amino acid on the amino end, and thus this assay has 90% crossreactivity with the 7-84 fragment. The clinical relevance of this fragment is not known, but may be increased in renal failure. Specific human PTH fragment assays are also available but these have not been investigated in animal species.[25]

Serum PTH concentrations should be evaluated with simultaneous measurement of serum iCa concentration. In primary hyperparathyroidism, both iCa and PTH are elevated. Early in the course of the disease, elevation of iCa may be mild to moderate, with a high normal concentration of PTH. If parathyroid glands are normal, hypercalcemia (parathyroid-independent) should be associated with low PTH concentration, and hypocalcemia should be associated with elevated concentrations of PTH. Animals with renal failure and secondary hyperparathyroidism have increased serum PTH with normal or decreased iCa concentration.[25]

Parathyroid Hormone-Related Protein

Parathyroid hormone-related protein (PTHrP) is not strictly a calcium-regulating hormone; however, it was identified in 1982 as an important PTH-like factor that plays a central role in the pathogenesis of humoral hypercalcemia of malignancy (HHM).[26] PTHrP is a 139-173 amino acid peptide originally isolated from human and animal tumors associated with humoral hypercalcemia of malignancy. PTHrP shares 70% sequence homology with PTH in its first 13 amino acids. The N-terminal region of PTHrP (amino acids 1-34) binds and stimulates PTH receptors in bone and kidney cells with affinity equal to that of PTH and results in PTHrP functioning similarly to PTH in patients with humoral hypercalcemia of malignancy.[27]

Two-site IRMA and N-terminal radioimmunoassays are available for the measurement of human PTHrP.[28,29] These assays are useful for measurement of biologically active PTHrP in the dog and cat because of the high degree of sequence homology in PTHrP between species.[30] The assay is very specific for PTHrP, with no crossreactivity noted to PTH, or any PTH fragment. PTHrP is very susceptible to degradation by serum proteases, and must be measured in fresh or frozen EDTA plasma. EDTA complexes with plasma calcium which is required for function of many proteases. The addition of protease inhibitors may provide further inhibition of proteolysis in plasma.[31] Serum is not recommended for measurement of PTHrP because of the proteolysis that occurs during clotting and sample handling. In a recent study, paired plasma and serum samples were analyzed for PTHrP in 35 dogs with HHM. There was a 50% false negative rate when using serum to measure PTHrP, most likely due to proteolysis of PTHrP in serum.

PTHrP should be measured in all cases when a malignancy is suspected. However, a negative PTHrP result does not rule out the possibility of malignancy as tumors may secrete other factors that can result in hypercalcemia.

Vitamin D Metabolites

Metabolites of vitamin D are chemically identical in all species, thus radioimmunoassays developed for use in humans are satisfactory for the measurement in animals.[32,33] Calcidiol (25-hydroxyvitamin D) concentration is a good indicator of vitamin D ingestion, and can be used to diagnose hypo- or hypervitaminosis D.[25] Either serum or plasma (EDTA or heparin) can be used for measurement of calcidiol, but hemolysis should be avoided. Calcidiol is stable for up to 9 weeks when stored at –20°C, and samples should be shipped on ice using an overnight courier. The assay has little crossreactivity with calciferol, and about 11% cross-reactivity with calcitriol. 25-OH-D_3, 25-OH-D_2, 24,25-$(OH)_2$-D_3, 24,25-$(OH)_2$-D_2, 25,26-$(OH)_2$-D_3, and 25,26-$(OH)_2$-D_3 are completely measured with this assay. Thus, metabolites resulting from the ingestion of cholecalciferol present in rodenticides will be measured with the 25-hydroxyvitamin D assay. Calcipotriene, the vitamin D analog found in antipsoriasis creams, is not measured with the assay for 25-hydroxyvitamin D.

Calcitriol concentration can be used to detect genetic errors in vitamin D metabolism, low concentrations in patients with renal failure, or high concentrations in some patients with humoral hypercalcemia of malignancy.[25] This assay is currently not widely available for clinical use, and further studies are needed to investigate the diagnostic utility. Either serum or EDTA plasma can be used for measurement of calcitriol. Calcitriol is stable for up to 6 months at –15°C, and samples should be shipped on ice using an overnight courier. Young, growing dogs have higher calcitriol concentrations than mature dogs.[34] The assay has very little cross-reactivity with calcidiol, and both 1,25-$(OH)_2$-D_3 and 1,25-$(OH)_2$-D_2 are completely measured with this assay.

Ionized Magnesium

Serum total magnesium is composed of three fractions: iMg, protein-bound magnesium, and complexed calcium.[35] Ionized magnesium does not play a direct role in calcium metabolism, but may have an indirect impact. As serum iCa falls, so does intracellular iCa concentration, which stimulates PTH secretion and synthesis and inhibits calcitonin secretion. As with hypocalcemia, mild acute hypomagnesemia also stimulates PTH secretion because iMg is an agonist of the iCa receptor. However, severe magnesium depletion decreases PTH secretion, increases end-organ resistance to PTH, and may impair calcitriol synthesis. The end-organ resistance to PTH that develops during magnesium depletion may persist for days after magnesium repletion and resumption of normal PTH concentrations. These effects may be partially due to reduced sensitivity of cell membrane receptors to iCa in the presence of low serum iMg concentrations. Hypercalcemia results in decreased PTH and calcitriol synthesis. In the kidney, the iCa receptor is present along the nephron on renal epithelial cells. Stimulation of the iCa receptor due to increased extracellular iCa concentration in the kidney is responsible for decreasing NaCl, iCa, and iMg reabsorption in the proximal convoluted tubule and decreasing water reabsorption in the collecting ducts. This results in greater excretion of iCa and iMg in a more dilute urine, and may lead to a depletion of iMg. Acute hypermagnesemia may also suppress PTH secretion, which may precipitate a fall in iCa concentration.[25]

On the basis of serum tMg concentration, hypomagnesemia is usually defined as a concentration lower than 1.5 mg/dL in dogs and cats. When serum iMg concentration is used, hypomagnesemia is defined as a concentration lower than 1.04 mg/dL (0.43 mmol/L) in both dogs and cats. Hypomagnesemia is not uncommon. At The Ohio State University, 30% (417/1406) of small animal patients exhibited low iMg concentrations. This percentage may be even higher in critically ill patients.

Primary hypoparathyroidism was diagnosed in 357 dogs and 27 cats over a 2 year period.[36] In dogs with hypoparathyroidism, iMg concentration was below the

reference range in 39%, within the reference range in 55%, and above the reference range in 6%. Of the 55% of dogs with iMg within the reference range, 69% had an iMg concentration within the lower half of the reference range, and only 31% had an iMg concentration within the upper half of the reference range. In cats with primary hypoparathyroidism, iMg concentration was below the reference range in 37%, within the reference range in 59%, and above the reference range in 4%. Of 59% of cats with iMg within the reference range, 88% had an iMg concentration within the lower half of the reference range, and only 12% had an iMg concentration within the upper half of the reference range. These results suggest that a large number of dogs and cats with hypoparathyroidism also exhibit subnormal or marginal iMg concentrations. Magnesium depletion can cause functional hypoparathyroidism, and measurement of serum iMg concentration is recommended to exclude or identify this form of hypoparathyroidism, especially in those dogs that appear refractory to treatment for hypoparathyroidism. The impact of magnesium supplementation in the treatment of hypoparathyroidism is under investigation.

Evaluation of Protein-bound Calcium and Complexed Calcium

In addition to measuring the ionized concentration in serum, pCa and cCa can be quantified using fractionation techniques. Ionized calcium and cCa are diffusible and together are referred to as ultrafilterable calcium. To separate protein bound from ultrafilterable serum calcium, a micropartition system based on the filtration method has been used.[20,37] In normal dogs, pCa, iCa, and cCa in serum were 34, 56, and 10%, respectively,[20] and 40, 52, and 8% in normal cats.[38]

Biologic roles of these calcium fractions have been suggested, but they have not been assessed in metabolic disorders associated with abnormal calcium concentrations. Measurement of pCa and cCa in addition to iCa may facilitate detection of disease processes that affect calcium metabolism. In dogs with chronic renal failure, two subgroups have been identified based on calcium fractionation. Dogs with normal to elevated serum tCa concentrations had significantly higher cCa concentration as compared to those dogs with low concentrations of tCa, even though there was no difference in iCa or pCa between groups.[6] Further studies are needed to determine whether prognosis or effectiveness of therapy differs between these groups.

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Hypercalcemia and Primary Hyperparathyroidism (PHP) in Dogs

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DIFFERENTIAL DIAGNOSIS & DIAGNOSTIC APPROACH TO HYPERCALCEMIA

Differential. Hypercalcemia is an abnormality that is usually serendipitously identified on serum biochemical analysis. Disorders associated with hypercalcemia in dogs, in an approximate incidence order as seen at the University of California, include: lymphosarcoma; acute and chronic renal failure; hypoadrenocorticism; primary hyperparathyroidism (PHP); vitamin D toxicosis; apocrine gland carcinoma of the anal sac; multiple myeloma; uncommonly in association with a variety of carcinomas (lung, mammary, nasal, pancreas, thymus, thyroid, vagina, and testicular); and uncommonly in association with certain granulomatous diseases (blastomycosis, histoplasmosis, schistosomiasis). Information from the history, physical examination, CBC, urinalysis, serum biochemistry analysis, thoracic and abdominal radiographs, abdominal ultrasound, and examination of cytology and biopsy specimens usually provide adequate information to establish the diagnosis in dogs.

History and Physical Examination. Since hypercalcemia is almost always an unsuspected finding, it is never a mistake to obtain a second blood sample to be certain that laboratory error has been ruled out. In our experience, laboratory error is extremely rare. With confirmation of hypercalcemia, the veterinarian should review the signalment and history with the owner to identify clues to a definitive diagnosis that may not have been noted initially. From the history, one can attempt to identify a tentative explanation for the hypercalcemia, such as: possible exposure to toxins containing vitamin D (rodenticides; inappropriate supplementation of food, etc); evidence of pain due to a lytic bone lesion (multiple myeloma or mammary tumor); difficulty eating due to oral lesions associated with renal failure; or a waxing/waning course of illness sometimes noted with hypoadrenocorticism. The physical examination should also be repeated in an attempt to identify a tentative explanation for hypercalcemia. The spine and long bones should be palpated to identify bone pain due to a lytic lesion; the mammary chain evaluated for neoplasia; the oral cavity for "rubber jaw" or lesions consistent with renal failure; the rectal and perineal area for apocrine gland carcinoma of the anal sac or other tumor; the heart rate and pulse for abnormalities consistent with hypoadrenocorticism; and the peripheral lymph nodes for enlargement suggestive of lymphoma (most hypercalcemic lymphoma dogs have a mediastinal mass and unremarkable peripheral nodes). Dogs with PHP have unremarkable physical examinations, and parathyroid masses are rarely palpable.

Routine "Data Base." A thorough review of the CBC, serum biochemistry profile and urinalysis should be completed. The urine specific gravity is commonly less than 1.020 in hypercalcemic dogs with renal disease, hypoadrenocorticism, and primary hyperparathyroidism. Urinary tract infection is common in these disorders. The CBC may demonstrate a normocytic normochromic nonregenerative anemia which is relatively common in renal failure, hypoadrenocorticism, and various neoplasias. The serum biochemistry profile should also be reviewed to assess the BUN, creatinine, and serum phosphate for increases consistent with renal failure; hyperkalemia and hyponatremia consistent with hypoadrenocorticism; hyperglobulinemia consistent with myeloma; and abnormal liver enzyme activities in association with a variety of malignancies. To this point, the only "new" expense has been the repeated serum calcium concentration, since all we have done is talk with the owner, repeat a physical examination, and review the laboratory results that were already obtained in order to identify the hypercalcemia in the first place.

Radiographs and Ultrasonography. Assuming the review of the history, physical examination and database has not defined the cause for hypercalcemia, thoracic radiographs are the next diagnostic step. The primary purpose for this study is to assess the cranial mediastinum for a mass consistent with lymphoma. If present, fine needle aspiration or tissue obtained via biopsy should be evaluated to confirm this diagnosis. Radiographs also provide an opportunity to evaluate the perihilar area and lungs for neoplasia or systemic mycoses, the spine and ribs for lytic lesions caused by neoplasia, and the heart for microcardia of hypoadrenocorticism. Abdominal radiographs can also be assessed, although ultrasound examination of the abdomen is preferred. The size and consistency of the liver, spleen, and mesenteric and sublumbar lymph nodes can be evaluated for abnormalities suggestive of malignancy (lymphoma) or other conditions. Diagnostic imaging to evaluate for malignancy

(lymphoma) applies to a variety of tumors located in other organs, but tumors other than lymphoma are an uncommon cause of hypercalcemia. When possible, abnormal areas should be aspirated or biopsied to determine the presence or absence of neoplasia. The size and consistency of the kidneys can be assessed, although renal failure should have been ruled in or out on the initial blood test results. If these studies fail to indicate a diagnosis other than PHP, the index of suspicion for PHP increases. Until a specific cause for hypercalcemia is confirmed, lymphoma should never be ruled out.

SIGNALMENT, HISTORY, AND PHYSICAL EXAMINATION IN DOGS WITH PHP

Dogs with PHP are usually 6 years of age or older. The mean age from our series of 210 dogs with PHP was 11.2 years. Dogs of both genders are almost equally affected, and about 20% of affected dogs are Keeshonds. Dogs with PHP, unlike those afflicted with most other diseases that cause hypercalcemia, are usually not ill or not as ill. Owners of 88 of 210 PHP dogs had observed no abnormalities in their pet related to hypercalcemia. The reason that blood had been obtained from these dogs was as part of a routine geriatric evaluation or as part of a preanesthesia screen prior to a dentistry procedure.

The most common owner-observed abnormalities in dogs with PHP (~50%) were those suggestive of urolithiasis or urinary tract infection, both relatively common in PHP (i.e., straining to urinate, increased frequency of urination, and hematuria). Other clinical signs reported by owners of 210 dogs with PHP included polyuria and polydipsia (48% of dogs), weakness (46%), decreased activity (43%), decreased appetite (37%), weight loss or muscle wasting (18%), vomiting (13%), and shivering or trembling (10%). It is important to remember that even when clinical signs are observed, they are often relatively mild. When observed, signs were present for as long as 2 years. Few abnormalities are detected on physical examination. In 149 of 210 dogs with PHP (71%), the medical record stated that no abnormalities were seen. When noted, abnormalities included muscle wasting, slowness to rise, obesity in some, and thin body condition in others. Each of these problems was seen in <10% of dogs with PHP.

CLINICOPATHOLOGIC ABNORMALITIES IN DOGS WITH PHP

Hypercalcemia (i.e., serum total calcium concentrations >12 mg/dl; reference range of 9.9 to 11.6 mg/dl) was identified in all 210 dogs. This may be misleading since we do not evaluate dogs for hypercalcemia unless this criterion is met. The mean total serum calcium concentration was 14.5 mg/dl with a range of 12.1 to 23.4 mg/dl. About 50% of these dogs had serum total calcium concentrations >12 and <14 mg/dl; about 30% had values >14 and <16 mg/dl; about 10% had values >16 and <18 mg/dl; and slightly more than 5% had values >18 mg/dl. The mean plasma ionized calcium concentration in these 210 dogs with PHP was 1.71 MM/L (range 1.22 to 2.41; reference range 1.12 to 1.41 MM/L). Just under 10% of the dogs with PHP had a serum ionized calcium concentration within the reference range; almost 30% had values between 1.42 and 1.65 MM/L; almost 50% had concentrations between 1.66 and 1.90 MM/L; and the remaining 16% had concentrations >1.91 MM/L.

It may be of interest to point out the most common reason for referral of dogs ultimately diagnosed with PHP: concern on the part of the referring veterinarian that if not treated, these dogs would develop renal failure. However, this is not the case. Of 210 dogs with PHP, their mean BUN concentration (<17 mg/dl) was less than the reference range, their mean serum creatinine concentration (0.8 mg/dl) was well within the reference range and their mean serum phosphate concentration (2.8 mg/dl) was less than the reference range. All these values were significantly less than values from 200 dogs of similar ages that were randomly reviewed from our hospital population. In other words, PHP actually seems to protect these dogs from renal failure rather than predisposing to this condition. Duration of hypercalcemia was also not a factor, since some PHP dogs went as long as 2 to 3 years without treatment. The polyuria and polydipsia was well supported by finding a mean urine specific gravity in 210 dogs with PHP of 1.012. 30% of these dogs had urinary tract infection and about 30% had cystic calculi. While impending renal failure is rare and not a reason for treating a dog that has PHP, infection and calculi are common and certainly would be reason for recommending therapy.

CONFIRMATION OF PRIMARY HYPERPARATHYROIDISM (USE OF SERUM PTH AND PTHrP CONCENTRATIONS)

Are PTH Assay Results Vital? Veterinarians value a logical, practical, and cost effective approach to problem solving. One can rest assured that the differential diagnosis for hypercalcemia is relatively small and veterinarians should be able to rule in or rule out most of the possibilities based on the diagnostic approach recommended at the beginning of this paper. The need for sophisticated and relatively expensive studies, such as assaying serum PTH and PTHrP concentrations take on less importance in this context. We have assayed serum PTH concentrations on every dog with PHP that we have diagnosed since the early 1980's. However, to be fair, a majority of these results are seen days-to-weeks *after* treatment has been completed. In other words, diagnosis was made without evaluating these assay results because we used a logical approach to the potential causes of hypercalcemia. This is not to suggest that the assays have no value, rather, it is to suggest that in many dogs, the assay results are not vital.

Serum Parathyroid Hormone (PTH) Concentrations. Serum PTH concentrations are commercially available and normal to increased concentrations confirm the diagnosis of PHP in non renal failure hypercalcemic dogs. Dogs with renal failure may also have increased serum PTH concentrations but within the context of the renal parameters, the serum phosphate concentration, ionized serum calcium concentration and other pertinent information, PHP should be able to be distinguished from renal failure. One must remember that as serum calcium concentrations rise in healthy dogs, serum PTH concentrations should become undetectable. Therefore, the term “normal range” can be misleading, since the average dog with PHP has a serum PTH concentration that is “normal.” This seems counter-intuitive. The term “reference range” makes more sense, since increasing serum calcium concentrations should drop the serum PTH concentration below the reference range while values within the reference range are physiologically abnormal. The reference range for serum PTH concentrations is 2 to 13 pmol/L and 135 of 185 (73%) dogs with PHP had serum PTH concentrations within that range; 45% had results of 2.3 to 7.9 pmol/L, 28% had results of 8.0 to 13.0 pmol/L, 11% had results between 13 and 20 pmol/L, and 16% had results >20 pmol/L.

Serum Parathyroid Hormone related Protein (PTHrP) concentrations. Increased serum PTHrP concentrations in hypercalcemic dogs would be most consistent with lymphoma or apocrine gland carcinoma of the anal sac. If a specific explanation for hypercalcemia remains elusive, we recommend "response to treatment" be a *last resort*. Before any medication is given, aspiration or biopsy of lymph nodes, spleen, and/or liver should be considered in an attempt to rule out lymphoma. Lymphoma is emphasized here because in some dogs it can be quite difficult to confirm, even more difficult if glucocorticoids have been administered.

LOCALIZING PARATHYROID TISSUE CAUSING HYPERPARATHYROIDISM

Surgery. Once the diagnosis of PHP has been confirmed, the most cost effective and expedient approach to patient management would be surgical exploration of the neck. Abnormal, autonomously secreting, parathyroid masses may not always be obvious at surgery, although experienced surgeons rarely have difficulty in identifying the parathyroid tissue causing hypercalcemia. The abnormal parathyroid adenoma, carcinoma, or adenomatous hyperplastic tissue is typically larger and a different color than normal parathyroid glands. Surgeons may benefit from knowing which side of the neck or specific location within one side of the neck that a tumor or abnormal parathyroid tissue is likely to be found.

Cervical Ultrasound. Ultrasound examination of the cervical area has recently received attention because it is available, noninvasive and relatively cost efficient. Ultrasonography, as much as any diagnostic tool utilized in veterinary medicine, is "operator dependent." The skill of the individual performing the examination is a major factor in assessing the value of ultrasound. As facilities, use of various transducers, and the experience of radiologists improve, this diagnostic tool holds great potential. Parathyroid tumors are typically round-to-oval hypoechoic masses that measure 4 to 8 mm in greatest diameter; some are as large as 20 mm in greatest diameter. Most masses are 4 - 6 mm in greatest diameter. Cervical ultrasound was performed in 130 of 210 dogs with PHP in our series. In 116 of these 130 dogs, a solitary parathyroid mass was visualized. In 13 dogs, two distinct parathyroid masses were seen. In one dog, no parathyroid mass was visualized. Ultrasonography correctly identified 142 of 143 parathyroid tumors. This level of success is impressive, but it also indicates how much opportunity our radiologists have to develop expertise. Further, in many cases, the first or second (less experienced) radiologist may have missed a mass while a more experienced individual did identify a mass correctly. Our statistics only refer to the correlation between treatment results and the *final* ultrasound report.

Other Tests. Abnormal parathyroid tissue has been localized in humans using Tc99 sestamibi nuclear scintigraphy. Results in dogs with PHP have been inconsistent at best and the procedure is not recommended. Recent attempts to localize abnormal parathyroid tissue utilizing selective venous sampling to measure the serum concentrations of PTH were not satisfactory.

TREATMENT OF PRIMARY HYPERPARATHYROIDISM

Pre-Treatment Considerations - Candidates for Percutaneous Treatment. There are several situations that must be considered prior to treatment recommendations. First, if a dog has cystic calculi, especially a male dog, surgery is recommended to remove the calculi and surgery on the neck to remove the parathyroid tumor is performed under the same anesthesia. Second, percutaneous treatment candidates must have a tumor large enough to have a needle placed percutaneously and the mass cannot be too close to the carotid artery. If a dog has two parathyroid masses and one is located on each side of the neck, surgery is recommended or the percutaneous treatment should be “staged” at least 30 days apart to avoid iatrogenic laryngeal paralysis, an uncommon but possible problem.

Pre-Treatment Considerations - Serum Calcium Concentrations. If the pre surgery serum calcium concentration is $\geq$12 but $\leq$14.0 mg/dl, we simply monitor serum calcium or ionized calcium concentrations twice daily for 5 to 7 days after surgery. Typically, dogs are not at risk for developing hypocalcemia in the first 24 to 48 hours after treatment. Vitamin D therapy is only instituted if the serum calcium concentration decreases below 8.0 mg/dl, the ionized calcium decreases below 0.85

mmol/L, or clinical signs of tetany are observed. This level of decrease usually takes 3 to 7 days. If the serum calcium concentration prior to surgery is ≥15 mg/dl, the incidence of post surgical hypocalcemia is greater and we initiate vitamin D therapy (calcitriol: 10 to 20 ng/kg BID) and then tapered to ever decreasing dosages over a 2 to 6 month time period) the morning before surgery or immediately after surgery. Monitoring of serum calcium is carried forth as described and parenteral calcium is only administered if tetany occurs or is thought to be imminent.

Percutaneous Ultrasound-Guided Heat Ablation. This procedure has become the recommended treatment of dogs with PHP at our hospital if the previously mentioned criteria are met. Dogs are placed under anesthesia and, with ultrasound guidance, a needle is placed into the parathyroid mass. The needle is attached to a radio-frequency unit (radio frequency waves are naturally converted to heat at the needle tip). The wattage is started at a low level and increased based on observation of a "bubbling" appearance to the tissue. The needle is moved several times to assure that the entire parathyroid mass has been ablated. Percutaneous ultrasound guided heat ablation requires 15 to 30 minutes of anesthesia and is usually about one-half the cost of surgery. Of the first 48 dogs so-treated, 44 (92%) had resolution of their PHP, 43 with one treatment and one dog required a second procedure.

Surgery. Complete exploratory surgery of the thyroid area is recommended for dogs with PHP that do not meet the criteria for percutaneous ultrasound guided heat ablation. An effort should be made to evaluate both sides of the neck and to evaluate both the ventral and dorsal surfaces of the thyroid lobes. In most dogs with PHP, the abnormal parathyroid tissue is solitary, off-color, and larger than normal parathyroid tissue, easily recognized and easily extirpated. Only the abnormal parathyroid tissue is removed if possible, although when a parathyroid tumor lies within a thyroid lobe, both are usually removed. If no parathyroid mass is observed and the diagnosis is thought to be correct, one thyroid/parathyroid complex should be removed and examined histologically. If two abnormal parathyroids are observed, both should be removed. Since we began performing percutaneous treatment, 52 dogs have been treated at our hospital with surgery. Fifty of these 52 dogs (96%) had complete resolution of their PHP, again with one dog requiring a second procedure. Thus, percutaneous and surgical treatments were both efficacious.

Post-Treatment Care. Dogs are kept in-hospital for 5 to 7 days after treatment. This is not primarily to monitor serum calcium concentrations but to keep each dog quiet. Since most dogs are quiet in-hospital, it can be appreciated that the quiet hypocalcemic dog is less prone to clinical tetany than would be the case if the dog was active. Dogs that are unusually active in-hospital, are sent home for this reason. We usually monitor serum total calcium concentrations twice daily until release from the hospital.

Histology. Parathyroid tumors have been histologically classified as adenoma, hyperplastic or carcinoma. These classifications have not had use clinically, since all parathyroid masses are biologically similar. We have not experienced a dog with local tumor invasion nor with distant metastasis. Recurrence rate is about 10% regardless of the histology.

Idiopathic Hypercalcemia in Cats - When to Intervene?

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Within the past 10 years, idiopathic hypercalcemia (IHC) in cats has been recognized.[1,2] Its frequency of diagnosis continues to increase, and it now appears to be the most common cause of ionized hypercalcemia in cats in the USA. Although it was originally suggested that idiopathic hypercalcemia was a local geographic phenomenon,[3] it is now widespread across the United States. Reports of idiopathic hypercalcemia in cats are emerging from several other parts of the world (England, Scandinavia, Switzerland) in recent years.

Differential Diagnosis

Increased serum total calcium (tCa) is the initial pivotal finding on a serum biochemistry panel. Hypercalcemia is often fortuitously discovered during review of the results from routine serum biochemistry submitted from cats that are undergoing wellness examinations, pre-anesthesia screening, evaluation of urolithiasis, and vague gastrointestinal signs that include weight loss, constipation, and vomiting.

The initial finding of a mild increase in serum tCa should be repeated to see if the hypercalcemia is persistent. A transient increase in serum tCa is documented in some cats with minor increases in serum tCa; further workup is not indicated in these instances in which the serum tCa concentration is normal on subsequent analysis.

Measurement of serum iCa is the next step in the diagnostic evaluation of those with persistent or more substantial increases of serum tCa. Prediction of iCa status from tCa measurement is not accurate, and iCa needs to be specifically measured. Increased iCa concentration is documented in all cats with IHC, but may be normal or low in other conditions associated with increased serum tCa, especially chronic renal failure (CRF). Serum iCa can be measured alone, or preferably at the same time that parathyroid hormone (PTH) concentration is measured.

There are many potential causes of hypercalcemia, and an exhaustive list is presented in Table 1. Though cancer-associated hypercalcemia has traditionally been noted to be the primary cause of elevated serum tCa in cats reported from referral centers, IHC appears to be the most prominent cause, followed by renal failure, and then malignancy in primary care practice. In some cats with persistent hypercalcemia, the diagnosis of the cause of the hypercalcemia will be obvious after analysis of history (vitamin D exposure, drugs, ingestion of houseplants), and findings from physical examination (masses, organomegaly, cancer or granulomatous disease). In other cases, the cause will not be obvious and information from hematology, serum biochemistry, body cavity imaging, cytology, and histopathology will be necessary.

Table 1. Hypercalcemia Differential Diagnosis
HARDIONS Eponym

H = Hyperparathyroidism (1°,3°, hyperplasia), Humoral Hypercalcemia of Malignancy, Houseplants, Hyperthyroid
A = Addison's Disease, Aluminum Toxicity, Vitamin A, Milk-Alkali
R = Renal Disease, Raisins(Grapes)- dogs
D = Vitamin D Toxicosis (Granulomatous Dz), Drugs, Dovonex, Dehydration, DMSO (calcinosis cutis), Diet
I = Idiopathic (Cats), Infectious, Inflammatory, Immobilization
O = Osteolytic (osteomyelitis, immobilization, Local Osteolytic Hypercalcemia, bone infarct)
N = Neoplasia (HHM and LOH), Nutritional
S = Spurious, Schistosomiasis , Salts of Calcium, Supplements

Increased serum iCa, low or normal range PTH (parathyroid-independent hypercalcemia), normal range 25-hydroxyvitamin D, normal to low range 1,25-dihydroxyvitamin D (calcitriol), and negative parathyroid hormone related polypeptide (PTHrP) are expected findings in cats with IHC.[4] Serum phosphorus is usually in the normal range in cats with IHC unless it is increased due to the presence of concurrent CRF. Urinary specific gravity from one study revealed a mean of 1.036 ± 0.013, and it appears that many cats with hypercalcemia can still maximally concentrate their urine if they do not have concurrent excretory renal failure.[2]

In a recent review of 427 cats with IHC, cats with IHC ranged in age from 0.5 to 20 years old (mean 9.8 ± 4.6 yr), and long-haired cats were over represented, accounting for 27% of the cases (compared to an overall submission rate of 14% from long-haired cats). Males and females were equally represented. No obvious clinical signs were noted in nearly half of these cases. Of all cats, 46% had no clinical signs, 18% had mild weight loss with no other clinical signs, 6% had inflammatory bowel disease, 5% were

chronically constipated, 4% were vomiting and 1% were anorectic. Uroliths or renoliths were observed in 15%, and calcium oxalate stones were specifically noted in 10% of cases.[5] Unlike dogs, cats with IHC do not commonly exhibit polyuria and polydipsia. No IHC cats of one study had owner reported polyuria or polydipsia.[2]

Should All Cats with IHC Be Treated?

Excessive calcium ions are toxic to cells. Although all tissues may be subject to the dangerous effects of hypercalcemia, effects on the central nervous system, gastrointestinal tract, heart, and kidneys are of most importance clinically. Mineralization of soft tissues (especially the heart and kidneys) is an important complication of hypercalcemia. The serum phosphorus concentration at the time hypercalcemia develops is important in determining the extent of soft tissue mineralization. Soft tissue mineralization is most severe when the calcium (mg/dL) times phosphorus (mg/dL) product is greater than 60. Soft tissue mineralization occurs regardless of the serum phosphorus concentration in severe hypercalcemia.

The impetus to prescribe therapeutic intervention for cats with IHC becomes more pressing when the magnitude of ionized hypercalcemia continues to increase or clinical signs become more obvious. Aggressive treatment to decrease iCa concentration is warranted in cats with chronic kidney disease, chronic kidney failure, and or those with calcium-containing urinary stones. Continued ionized hypercalcemia poses a risk for further development of renal lesions and for development of new stones and enlargement of existing stones.

Treatment of IHC

Acute rescue from hypercalcemia related to IHC is rarely indicated, as hypercalcemia has been gradual in development and relatively longstanding, and dramatic clinical signs are usually absent. Most cats with IHC will be treated as outpatients with either dietary change alone or in combination with drug therapy. Unfortunately, in IHC the causative mechanism(s) that generate hypercalcemia are unknown. Consequently most of our treatments have been empirical to date.

Diet. Changing to a different diet sometimes restores normocalcemia. The specific difference between the new and former diet that is providing the benefit is not often obvious. The feeding of increased dietary fiber was noted by investigators at the Minnesota Urolith Center to restore normocalcemia in some cats with IHC and calcium-oxalate urolithiasis.[6] The effects of fiber on intestinal absorption are complex, and depend on the types of fiber in the diet, amount of fiber, and other nutrients present in the diet. High fiber diets may decrease intestinal absorption of calcium by decreasing gastrointestinal transit time. It should be noted that most pet food manufacturers increase the quantity of calcium in diets containing an increased fiber content to offset the potential for decreased absorption. The beneficial effect of dietary change to restore normocalcemia was not seen in any cat with IHC of another study.[2]

Feeding diets designed for cats in renal failure may result in normocalcemia in some cats with IHC, possibly due to the reduced calcium content of these diets. Veterinary renal diets are considered alkalinizing, or at least less acidifying than maintenance diets, and are generally low in calcium and phosphorus. The restriction of dietary calcium is generally more severe in canned versus dry renal diets. Beneficial effects from feeding a renal diet for treatment of idiopathic hypercalcemia could result from decreased dietary calcium intake with subsequently decreased intestinal calcium absorption, or possibly from the effects of alkalinization that can decrease the release of calcium from bone.

Diets specifically formulated for prevention of calcium-oxalate urolithiasis could have a role in the treatment of IHC cats with or without urolithiasis. These diets may exert benefits through dietary calcium restriction and less urinary acidification (neutral pH urine production); some are also restricted in oxalic acid and sodium, and contain increased moisture in the canned formulation.

Some cats that do have an initial decline in serum iCa concentration following dietary change will have a recrudescence of hypercalcemia after variable periods of feeding. In these cats, change to another diet or medical therapy should be considered.

Additional dietary sodium chloride could be useful in the treatment of IHC cats if the added salt enhances calcium excretion into urine without increasing the risk for calcium oxalate urolithiasis, hypertension, or renal disease. Enhanced urinary excretion of calcium occurs in humans, dogs, and some studies of cats in which dietary sodium chloride has been increased.[7,8] There are no studies of cats with IHC that determine the benefits or detriments following the chronic feeding of diets with increased sodium chloride content.

IHC could be a consequence of excessive dietary vitamin D, despite a "normal" serum concentration of 25-hydroxyvitamin D. The minimal requirement for dietary vitamin D intake in cats is debatable, since normal values for circulating 25-hydroxyvitamin D have been established in cats that ingest vitamin D supplemented diets. Cats with IHC rarely have been documented with increased levels of calcitriol or 25-hydroxyvitamin D. It could be that some cats are especially sensitive to the effects of dietary vitamin D despite apparently normal levels of circulating vitamin D metabolites. The amount of vitamin D content in diets is not listed on food labels, so choosing a diet with lower vitamin D supplementation is difficult to determine.

Glucocorticosteroids. Treatment with glucocorticosteroids should be considered for cats with IHC that fail to restore normocalcemia following a 6 to 8 week feeding trial with at least one of the previously mentioned diets. Administration of glucocorticoids can decrease serum calcium concentration through effects that decrease calcium absorption across the intestine, decrease renal tubular calcium reabsorption, and decrease skeletal mobilization of calcium. Prednisone is started at 5 mg/cat/day for one month and the effect on serum iCa is then re-evaluated. If the iCa is normal, the dose is continued for several months. If the serum iCa is still increased, the dose may be increased to 10 mg/cat/day. Some cats require 15 or 20 mg prednisone per day to maintain normocalcemia. The effect of glucocorticosteroid treatment on measurement of calcium-regulatory hormones in normal or IHC cats has not been reported.

Bisphosphonate. If some of the hypercalcemia is generated from increased osteoclastic bone resorption in cats with IHC, treatment with bisphosphonates may be useful in decreasing ionized hypercalcemia. Bisphosphonate treatment may be an alternative to the use of glucocorticosteroids for cats that have failed dietary intervention. The safety and efficacy of pamidronate given IV to two cats with hypercalcemia has been reported; one of these cats had IHC.[9]

Adequate hydration is essential when bisphosphonates are prescribed since administration can result in nephrotoxicity especially at higher doses. We have successfully treated a small number of IHC cats with 10 mg of alendronate orally once weekly for up to one year. Though we do not know the risk for development of esophagitis in cats as occurs in women, we recommend following the weekly pill with 6 mL of tap water given with a dosing syringe and then a small dab of butter to the lips to increase licking and salivation to further promote transit of the pill to the stomach[10]. As with other therapies, escape from the beneficial effects may require an escalation in dose when hypercalcemia returns. The long term safety and efficacy of oral bisphosphonates has not been reported in cats.

Miscellaneous Treatments. Administration of subcutaneous fluids on a daily or every other day basis is a possible treatment that has not been evaluated in cats with IHC. It is possible that the administration of subcutaneous fluids would expand the ECF and promote calciuresis. Furosemide has well known effects that decrease serum iCa during acute rescue protocols for hypercalcemia, usually in combination with IV fluids. Much less is known about the effects of chronic furosemide administration, calcium status, and dehydration. We have concern that cats that undergo diuresis but do not drink enough water will become dehydrated. A new class of drugs called calcimimetics has recently emerged in human medicine. Calcimimetics were designed to interact with the calcium receptor and have been shown to be effective in lowering calcium, phosphorus, and PTH in human patients. The potential use of calcimimetics for the treatment of idiopathic hypercalcemia is intriguing.

Summary

Idiopathic hypercalcemia is the most common cause of ionized hypercalcemia in the cat, yet the cause(s) remains elusive. The role of dietary acidification, dietary magnesium restriction, and/or contribution of any specific dietary constituents (vitamin D, vitamin A, specific carbohydrates, lipids) deserve further consideration. It is conceivable that hypercalcemia develops only in a genetically susceptible population of cats in a provocative environment (diet, toxins, environment, stress, others unknown). A genetic component seems likely given the over-representation of long-haired cats. Idiopathic hypercalcemia may in fact encompass multiple etiologies.

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ROYAL CANIN / OSU
Symposium Speakers

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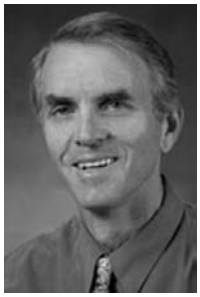
Dr. Dennis Chew is a 1972 graduate of the College of Veterinary Medicine at Michigan State University. He did a 1-year internship at South Weymouth Veterinary Associates (Massachusetts) and a 2-year residency in internal medicine and nephrology at the Animal Medical Center (NY, NY). He became a diplomate of the American College of Veterinary Internal Medicine (Internal Medicine specialty) in 1977. Dr. Chew has been an attending veterinarian at The Ohio State University College of Veterinary Medicine Teaching Hospital since 1975 and has been a Full Professor in the Department of Clinical Sciences since 1989. Most of his work in clinics, research, and publications involves urology/nephrology in small animals. He has special interest in disorders of calcium metabolism (idiopathic hypercalcemia in cats), treatment of renal secondary hyperparathyroidism, acute renal failure, disorders of the feline lower urinary tract (idiopathic/interstitial cystitis and urolithiasis) and urinary endoscopy.



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Dr. Andrew Hillier graduated from Onderstepoort, Faculty of Veterinary Science, University of Pretoria in South Africa in 1982. He spent 8 years in small animal practice in Australia before completing a residency in dermatology at the University of Florida. Dr. Hillier became a diplomate of the American College of Veterinary Dermatology in 1994. He spent two years in his own dermatology referral practice in Australia and then became faculty at The Ohio State University. Dr. Hillier has been an associate professor at The Ohio State University since 2002 and is currently Dermatology Service Chief of the Veterinary Teaching Hospital.

Primary area of research and publications is canine atopic dermatitis with special interest in house dust mite and storage mite allergies. Other research areas and publications include: otitis flea allergy dermatitis, essential fatty acid treatment, yeast dermatitis, deep fungal dermatoses, canine demodicosis, equine allergies. Dr. Hillier is an author of over 35 peer reviewed journal articles and several book chapters as well as an editor of veterinary books.

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Claudia Reusch graduated from the University of Giessen and spent three years in practice before moving to the University of Munich, Germany for eight years. In 1992 she completed her Habilitation on diabetic nephropathies. Thereafter she became Professor for Small Animal Internal Medicine at the University of Munich. Since 1996, she has been the Head of the Clinic for Small Animal Internal Medicine, University of Zurich. She is a founding member of the European Society of Veterinary Endocrinology (ESVE) and served as President from 2001-2003. Since 2003 she has been the President of the ECVIM-CA. Her particular interest is endocrinology.

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Dr. Feldman is a graduate of the UC Davis School of Veterinary Medicine. He completed an internship and residency in small animal medicine, and is a Diplomate of the American College of Veterinary Internal Medicine. He is co-editor with Stephen Ettinger of The Textbook of Veterinary Internal Medicine, which is now in its sixth edition. He is co-author with Richard Nelson of Canine and Feline Endocrinology and Reproduction, now in its third edition. He is also the co-founder and Past President of the Society for Comparative Endocrinology. Currently, Dr. Feldman is a faculty member in small animal internal medicine at UC Davis, where he has been since 1980. He is a reviewer of JAVMA, and is a renowned speaker at national and international meetings on endocrinology.

Mark E. Peterson,
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Dr. Mark E. Peterson was awarded a Doctor of Veterinary Medicine (DVM) degree with High Distinction from the University of Minnesota in 1976. He completed an internship, residency, and post-doctoral fellowship in endocrinology at The Animal Medical Center in New York, and he obtained board certification in the American College of Veterinary Internal Medicine in 1982. Dr. Peterson has served as Head of the Division of Endocrinology in the Department of Medicine at the AMC for over 25 years. Currently, he is also the Chairman of the Center's Institute for Postgraduate Education, and serves as Associate Director of the Caspary Research Institute at the Center.

Over the last 30 years, most of Dr. Peterson's clinical and research efforts have been directed toward advancing our understanding of naturally-occurring endocrine disorders of the dog and cat, especially Cushing's and Addison's disease, hyperthyroidism, hypothyroidism, and diabetes mellitus. He has received several awards in recognition of his clinical research efforts, including the Beecham Award for Research Excellence (1985), the Ralston Purina Small Animal Research Award (1987), the Carnation Award for outstanding contributions to feline medicine (1988), the British Small Animal Veterinary Association (BSAVA), Bougelat Award for outstanding contributions to small animal practice (1993), The Daniels Award for excellence in the advancement of knowledge concerning small animal endocrinology (1991-1997), The Winn Feline Foundation's Excellence in Feline Research Award (1997), Alumni of the Year Award, The Animal Medical Center (1998), and the Bide-A-Wee Association Award for Outstanding Humanitarian Service (2002), presented for more than a quarter century of dedicated research in naturally-occurring endocrine disorders of dogs and cats.

Dr. Peterson has published more than 450 journal articles, book chapters, and research abstracts. With more than 200 lecture presentations to his credit, Dr. Peterson is a frequent speaker at veterinary colleges and scientific seminars both in both the United States and abroad.

ROYAL CANIN / OSU
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Dr. Ray Nachreiner obtained his DVM from Iowa State University in 1966. From there, he served in the United States Air Force until 1968, when he became a research assistant at the University of Wisconsin. He received his PhD from the University of Wisconsin in 1972. From 1972 to 1977, Dr. Nachreiner was an Assistant and Associate Professor at Auburn University before taking his current position as a Professor and Endocrinologist at Michigan State University. For 20 years, he served as the Section Chief of the Endocrinology Section of the MSU Animal Health Diagnostic Lab. He has spent time internationally in Upsala, Sweden at the Swedish University of Agricultural Sciences, and in Vienna, Austria at the Veterinary Medicine University and the International Atomic Energy Agency. Dr. Nachreiner's research interests include: steroid analysis of milk, saliva, serum, and feces to aid diagnosis of reproductive problems of animals in developing countries; developing assays for hormonal assessment in animals; hormonal therapeutic monitoring and pharmacokinetics; and autoimmune thyroiditis, to name a few.

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Dr. Schenck received her Masters in Animal Science and DVM from the University of Illinois. After owning a small animal practice for several years, she completed her PhD in lipid biochemistry at the University of Florida. Before joining the Diagnostic Center for Population and Animal Health at Michigan State University in 2001, she held positions at the USDA, The Ohio State University, and in the pet food industry. She has authored over 70 research papers, book chapters and abstracts. Current research interests include calcium metabolic disorders, feline idiopathic hypercalcemia, and the role of dietary trans fatty acids in endocrine disorders.

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Denise Elliott graduated from the University of Melbourne with a Bachelor in Veterinary Science with Honors in 1991. After completing an internship in Small Animal Medicine and Surgery at the University of Pennsylvania, Denise moved to the University of California-Davis where she completed a residency in Small Animal Medicine, a fellowship in Renal Medicine and Hemodialysis, and a residency in Small Animal Clinical Nutrition. Denise received board certification with the American College of Veterinary Internal Medicine in 1996 and with the American College of Veterinary Nutrition in 2001. The University of California-Davis awarded a PhD in Nutrition in 2001 for her work on Multifrequency Bioelectrical Impedance Analysis in Healthy Cats and Dogs. Denise is currently the Director of Scientific Communications for Royal Canin USA.

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