

# **Subclinical Endocrine and Renal Disorders in Dogs and Cats: More Common Than You Think**

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In the past, the primary focus of preventative medicine in dogs and cats has been vaccination programs, parasite treatment, and proper nutrition. Routine laboratory testing such as a CBC, biochemical profile, urinalysis and TT4 determination was uncommonly performed in apparently healthy animals and was usually reserved for middle-aged or older animals undergoing elective procedures or the seriously ill animal. Little attention was paid to the possibility of pets having subclinical disease.

Recently, however, it has become increasingly clear that subclinical disease is relatively common in the dog and cat. In a clinical study performed at the West Los Angeles Veterinary Group in 1998-1999, routine laboratory tests were performed in 90 dogs and 100 cats. All the dogs and cats were over 7 years of age, in apparent good health according to the owner, and had no underlying medical treatment or condition known to alter laboratory values. The results of the study showed that clinically significant disease such as renal insufficiency, pyelonephritis, canine Cushing's syndrome and hypothyroidism, and feline hyperthyroidism was found in 23% of the canine population and 17% of the feline population and validated the importance of routine veterinary visits and diagnostic laboratory testing, especially in the aging pet.

As a result of increased awareness of subclinical disease in the senior pet population, there has been an increased role of laboratory testing in the overall evaluation of animal patients. This has led to many questions from veterinarians concerning the diagnostic approach to abnormal lab work in healthy animals. For example, "do I do more tests? If so, which ones?" Or "should I follow the lab abnormality by repeating the blood work at a later date, perform a diagnostic procedure, or completely ignore the abnormality?" Below are several of the most common questions that are asked regarding abnormal lab work in apparently normal animals.

## **The ALP is elevated. What now?**

One of the most common group of laboratory abnormalities encountered in small animal practice are abnormal liver enzymes, (ALP and ALT). The majority of animals are asymptomatic and the abnormalities are detected after performing a routine health screen. What should the clinician do? Ignore them, perform additional diagnostic tests, or consider a liver biopsy?

Four of the most common causes of an elevated ALP concentration in the apparently healthy, asymptomatic dog are subclinical Cushing's syndrome, reactive hepatopathy, hepatic nodular hyperplasia, and idiopathic vacuolar hepatopathy. Because these disorders are either in early stages (subclinical Cushing's syndrome) or the clinical course is unremarkable (nodular hyperplasia and idiopathic vacuolar hepatopathy) further

diagnostic testing (other than monitoring hepatic enzymes) or therapeutic intervention is often not warranted. Some clinicians, however, suggest bile acid determinations in any animal with increased liver enzymes, and if bile acids are elevated, a liver biopsy is recommended.

### **Vacuolar Hepatopathy: A Common Cause of ALP Elevations**

Many older dogs with ALP elevations often have what is referred to as a vacuolar hepatopathy. A vacuolar hepatopathy is basically hepatocytes with vacuoles in their cytosolic compartment that may contain glycogen, fat, intracellular water, or other metabolic wastes. The typical liver histology report usually reads, "Diffuse hepatic vacuolar change suggestive of steroid hepatopathy - check for Cushing's syndrome." A number of clinical conditions can cause these changes. If a secondary non-hepatic disease can be identified that could explain the hepatic changes then it is referred to as a reactive hepatopathy. These vacuolar changes can occur secondary to Cushing's syndrome, hypothyroidism, chronic stress, IBD, pancreatitis, non-hepatic neoplasia, and nutritional imbalances. In some dogs the cause of the vacuolar changes cannot be identified. This group of dogs looks like typical steroid hepatopathies based on histology and abnormal serum ALP concentrations. However, in most cases further investigation finds no clinical or laboratory evidence of Cushing's syndrome. Often the only abnormality that initiates liver investigation is the increase in serum ALP. Most cases have no clinical signs. Adrenal function testing is normal. If measured, the glucocorticoid isoenzyme of ALP is elevated. Ultrasound imaging of the liver shows diffuse echogenicity and frequently, but not always, the adrenal glands appear normal. The clinical course of these dogs is often unremarkable, however a small subset of these dogs develop Cushing's syndrome at a later date.

A number of dogs with idiopathic vacuolar hepatopathy have been investigated. It is speculated that this syndrome is some type of abnormal steroid hepatopathy. This speculation is supported by the fact that affected dogs given empirical ketoconazole or mitotane therapy have decreases in ALP concentrations and hepatic glycogen accumulation. Because adrenal nodular hyperplasia is a common finding in older dogs it may be possible that some of these dogs have functional hyperplastic nodules producing other adrenal steroids. A number of dogs having a vacuolar hepatopathy have been identified to have abnormal concentrations of one or more adrenal steroids (e.g., 17-hydroxyprogesterone, estradiol, testosterone, progesterone). For example, as a breed, Scottish terriers, commonly have elevated SAP levels and appear to be predisposed to this condition. The big question is should these dogs be treated with ketoconazole, trilostane or mitotane. Until the clinical cause of this syndrome is further investigated and since the majority of dogs with idiopathic vacuolar hepatopathy appear clinically normal, many clinicians recommend no treatment. However, some clinicians have suggested dietary modification with low protein diets and the use of nutraceuticals such as S-adenosylmethionine (SAME) and milk thistle to treat this disorder.

### **Diagnostic approach for the asymptomatic dog with elevated SAP concentrations**

Step 1: Rule out obvious causes of a reactive hepatopathy (e.g., dental or dermatologic disease) or vacuolar hepatopathy (e.g., hyperlipidemia).

Step 2: If step 1 is negative consider an abdominal ultrasound. The objective is to evaluate liver size, architecture and echogenicity, gallbladder, adrenal size (bilateral vs. unilateral enlargement), pancreas, kidneys, bowel thickness and mesenteric lymph nodes and look for any other surprise that may appear.

Step 3: If the abdominal ultrasound is consistent with either a reactive or vacuolar hepatopathy or hepatic nodular hyperplasia (all may appear as diffusely hyperechoic) consider nutraceutical supplementation and monitoring clinical signs and laboratory parameters such as SAP, USG, urine protein (MA or UPC), bile acids and blood pressure measurements.

Step 4: If abdominal ultrasound is not possible consider a screening test for Cushing's disease. However, the interpretation of the test results is critical. A negative test does not entirely rule-out Cushing's disease and a positive test is not necessarily confirmatory of this disorder (false positive tests are not uncommon). The "best test" in this situation is arguably the ACTH response test. This test has the lowest sensitivity of the screening tests for Cushing's disease. It may be best to miss a diagnosis of early disease than to falsely diagnose this disorder. And even if the index of suspicion for Cushing's disease is high, treatment of asymptomatic Cushing's disease (referring to pituitary-dependent hyperadrenocorticism) is not recommended by most endocrinologists.

### **What is the best test to diagnose canine hypothyroidism?**

Hypothyroidism is the most common endocrine disorder of canines, and up to 90% of cases are believed to result from autoimmune (lymphocytic) thyroiditis. It takes destruction of at least 75% of the thyroid gland by targeted T-lymphocytes, before classical clinical signs of hypothyroidism are manifested. Thus, accurate diagnosis of the early compensatory stages of canine autoimmune thyroiditis that lead up to hypothyroidism affords important genetic and clinical options for prompt intervention and case management. The heritable nature of this disorder poses significant genetic implications for breeding stock.

Despite the fact that thyroid dysfunction is the most frequently recognized endocrine disorder of pet animals, it is often difficult to make a definitive diagnosis. As the thyroid gland regulates metabolism of all body cellular functions, reduced thyroid function can produce a wide range of clinical manifestations, sometimes vague, other times classical, and occasionally very unusual. Many of these clinical signs mimic those resulting from other causes and so recognition of the condition and interpretation of thyroid function tests can be problematic. Further, development of thyroid dysfunction is a continuum that begins with normalcy and progresses gradually over months to several years to end-stage disease.

When asked the question which is the best test to diagnose hypothyroidism, the so-called best test depends on the clinical situation. For example, if an animal has classic textbook signs of hypothyroidism (lethargy, weight gain, bilateral symmetrical alopecia) then a total T4 level will often suffice. However if the animal has vague symptomatology or genetic screening for thyroid disease is considered important then a complete baseline thyroid profile should be measured.

### **Common Thyroid Tests: Pros, Cons and General Comments**

#### ***Total T4 (TT4)***

The search for the best test to diagnose hypothyroidism has evolved from the question “can the measurement of a TT4 be sufficient to diagnose this disorder?” This is a debatable point and it’s hard to argue with the wisdom of confirming the diagnosis with additional tests. Measuring serum TT4 **alone** is considered to be imperfect for diagnosis of thyroid disease, because it can: over diagnose hypothyroidism; under diagnose hyperthyroidism; fail to detect early stages of the compensatory disease; and cannot identify the presence of thyroiditis. This test is greatly influenced (lowered) by the presence of nonthyroidal illness (NTI) and specific drug therapy (e.g. corticosteroids, anticonvulsants, potentiated sulfonamides, some nonsteroidal anti-inflammatory agents). However, in a dog with classic clinical signs that is not obviously ill from another cause and is not being medicated with the above drugs, the finding of a low TT4 value may suffice for the diagnosis. If cost is not a consideration, the FT4ED is preferred over the TT4 because it is a more specific test. When the FT4ED or TT4 is used in combination with cTSH and the cTSH is elevated and the FT4ED or TT4 is low, the specificity is nearly 100%.

Interestingly, a total T4 may be a better test to rule out hypothyroidism than to confirm the diagnosis. In general, a TT4 > 2 mcg/dl or a FT4ED > 20 nmol/L in a suspect dog means that hypothyroidism is unlikely. However, TT4 and FT4ED concentrations above these “cut-off” values for hypothyroidism do not rule out early (subclinical) progressive lymphocytic thyroiditis.

#### ***Free (Unbound) T4***

Serum free T4 represents the small (<0.1%) biologically active fraction of the total T4, and is therefore less likely to be influenced by NTI. As a single test, accurate measurement of free T4 has been shown to have the highest sensitivity, specificity, and accuracy for diagnosing canine hypothyroidism. The techniques used in veterinary medicine for assaying free T4 include: direct radioimmunoassay (RIA) determination after equilibrium dialysis (ED), considered by many to be the "gold standard"; one-step or two-step solid phase or liquid-phase analog RIAs; enzyme-linked immunosorbent assay (ELISA); and chemiluminescence. The advantages and disadvantages of current free T4 assays have been vigorously debated. Methods used routinely at Antech Diagnostics include a one-step RIA method and the dialyzed [ED] RIA method.

### ***Endogenous Canine TSH (cTSH)***

In primary hypothyroidism, as serum free T4 levels fall, pituitary output of thyroid stimulating hormone (TSH) rises in a regulatory, compensatory response. In human medicine, highly sensitive and accurate endogenous TSH assays are available which make diagnostic testing straightforward, as virtually all hypothyroid patients have elevated TSH levels. However, in veterinary medicine, canine endogenous TSH (cTSH) is poorly predictive of primary hypothyroidism in dogs (70%) versus > 95% in humans, and can give 20-40% discordant results [both false positive and false negative]. This finding has been verified by several published studies. The reason is unclear, but it appears that some dogs have a slightly different bioform of TSH that reacts poorly or unpredictably in the assay. Thus, the cTSH assay by itself is not recommended for diagnosing canine hypothyroidism, and spuriously low or high cTSH levels can be seen in some hypothyroid or euthyroid dogs, respectively

### ***Canine Thyroglobulin Autoantibodies (TgAA)***

An estimated 80% of cases of canine hypothyroidism result from heritable autoimmune (lymphocytic) thyroiditis. Many popular breeds are at increased risk for this disorder, with English Setters being the breed exhibiting the highest prevalence of thyroiditis today (> 40% of those tested). The presence of elevated TgAA levels confirms thyroiditis, promotes early recognition of the disorder, and facilitates genetic counseling. Low-grade false positive results can occur if the dog has been vaccinated recently, especially with rabies vaccine. False negative results can occur in up to 8% of T3AA and/or T4AA confirmed positive thyroiditis cases, presumably because not all epitopes of TgAA are recognized by the assay reagent. Dogs on thyroid supplement should be off this medication for at least 90 days to obtain accurate TgAA results. Please note that reporting units for the TgAA normal reference range have changed recently from <200 % to <20%. For cases with equivocal or positive results, the assay is repeated after non-specific binding (NSB) antibodies are removed; the normal reference range for TgAA NSB is < 10%.

### ***T3 and/or T4 Autoantibodies (T3AA/T4AA)***

Whereas most cases of autoimmune thyroiditis (~92%) have elevated TgAA in their serum, only about 20% have elevated serum T3 and/or T4 AA. Thus, the presence of elevated T3 and/or T4 AA supports a diagnosis of autoimmune thyroiditis but underestimates its prevalence, as negative (non-elevated) serum T3 and/or T4 AA levels do not rule out thyroiditis. On the other hand, positive results support the presence of thyroiditis, even if the TgAA level is normal. Most circulating antibodies are against T3 (~70%), some affect both T3 and T4 (~25%), and only a few affect T4 alone (~5%). When these autoantibodies are present, measurement T4 and T3 levels will be spuriously high.

### ***OFA Thyroid Registry Profile***

The OFA Thyroid Registry Profile is offered by Antech Diagnostics (New York branch); and the required OFA forms and instructions for testing must be used. The profile includes: freeT4 ED, cTSH, and TgAA. This profile may fail to identify the small % of dogs with autoimmune thyroid disease that are T3AA and/or T4AA positive but TgAA negative. Accordingly, an extended OFA Plus profile is offered which includes the three OFA analytes and the remainder of the thyroid antibody profile [T4, T3, freeT3, T3AA, T4AA], so that the client receives not only the OFA Thyroid Registry report, but also has more complete analysis for archival reference. This availability is especially important for evaluating the thyroid status of breeding stock and family background.

### ***Post-Thyroxine Therapeutic Monitoring***

Follow up testing is beneficial to ensure adequacy of the prescribed dosage as well as client compliance. For dogs receiving thyroid supplementation, measuring the total T4 and free T4 is recommended at the peak sampling time of 4-6 hours post-BID or SID therapy. Alternatively, a trough level or both peak and trough levels also can be run. Both tests are sometimes needed because measuring T4 alone could lead to an inappropriate dose increase if a sub-optimal T4 result is due to concomitant NTI or use of certain drugs listed above.

Monitoring patients on thyroxine is recommended at least once a year and ideally twice a year. The pharmacokinetics, metabolism and excretion of the drug can vary from individual-to-individual or over time in the same individual, resulting in an absorption rate that ranges from 12-55% (mean 37%). Further, on the day of testing, the medication should be given directly by mouth and *not* with a meal, as calcium binds to thyroxine and can retard absorption of the drug.

Note that the reported reference ranges for these tests reflect basal and not peak therapeutic levels, and that peak levels for dogs receiving levothyroxine should be in the upper 1/3 to 1/3 above the upper limits of the basal ranges for good metabolic control.

### **Baseline Thyroid Profiles: General Comments**

A complete baseline thyroid profile typically includes total T4, total T3, free T4, free T3, thyroid autoantibodies, and may also include cTSH. The autoantibody (AA) assays (T3AA, T4AA, TgAA) are especially important in screening breeding stock for heritable autoimmune thyroid disease.

The normal reference ranges for thyroid analytes of healthy adult animals tend to be similar for most breeds of companion animals. Exceptions are the sighthound and giant breeds of dogs which have lower basal levels. Typical thyroid levels for healthy sighthounds, such as retired racing greyhounds, are at or just below the established laboratory reference ranges, whereas healthy giant breeds have optimal levels around the midpoint of these ranges.

Similarly, because young animals are still growing and adolescents are maturing, optimal thyroid levels are expected to be in the upper half of the reference ranges. For

geriatric animals, basal metabolism is usually slowing down, and so optimal thyroid levels are likely to be closer to midrange or even slightly lower.

All animals are not the same

- Puppies have higher basal thyroid levels than adults
- Geriatrics have lower basal thyroid levels than adults
- Large / giant breeds have lower basal thyroid levels
- Sighthounds have much lower basal thyroid levels

***Genetic Screening for Thyroid Disease***

Most cases of thyroiditis have elevated serum TgAA levels, whereas only about 20-40% of cases have elevated circulating T3 and/or T4 AA. The presence of elevated T3 and/or T4 AA confirms a diagnosis of autoimmune thyroiditis but underestimates its prevalence, as the diagnosis in some cases is revealed only by finding lymphocytic infiltrates within thyroid biopsies. Measuring AA levels also permits early recognition of the disorder, and facilitates genetic counseling. It is recommended that affected dogs not be used as breeding stock

The commercial TgAA test can give false negative results if the dog has received thyroid supplement within the previous 90 days, thereby allowing unscrupulous individuals to test dogs while on treatment to assert their normalcy, or to obtain certification with health registries such as the OFA Thyroid Registry. False negative TgAA results also can occur in about 8% of dogs verified to have high T3AA and/or T4AA. Furthermore, low-grade false positive TgAA results may be obtained if the dog has been vaccinated within the previous 40-90 days, or occasionally in cases of non-thyroidal illness. Published studies indicate that prevalence of thyroiditis is directly associated with body weight, is highest in dogs 2-4 years old, and more likely to occur in females than males.

Thyroid testing for genetic screening purposes is less likely to be meaningful before puberty. Screening is initiated, therefore, once healthy dogs and bitches have reached sexual maturity (between 10-14 months in males and during the first anestrus period for females following their maiden heat). As the female sexual cycle is quiescent during anestrus, any influence of sex hormones on baseline thyroid function will be minimized. This period generally begins 12 weeks from the onset of the previous heat and lasts one month or longer. The interpretation of results from baseline thyroid profiles in intact females will be more reliable when they are tested in anestrus. Once the initial thyroid profile is obtained, dogs and bitches should be rechecked on an annual basis to assess their thyroid function and overall health. Obtaining annual test results provides comparisons that permit early recognition of developing thyroid dysfunction. This allows for prompt treatment, where indicated, to avoid the appearance or advancement of clinical signs associated with hypothyroidism.

In a current report from the MSU Endocrine Diagnostic Laboratory, a one year follow-up of 173 TgAA positive dogs (all apparently healthy with normal cTSH and FT4ED concentrations) indicated that 20% had progressed to subclinical or end-stage hypothyroidism. Presumably, many of the remaining dogs will eventually become hypothyroid. The question remains over whether to begin thyroid supplementation to

reverse the production of thyroid autoantibody and the destruction of thyroid tissue or wait until signs develop. Given that there is a statistically significant relationship in dogs between thyroid dysfunction and seizure disorders and dog-to-human aggression plus the fact that dogs with one autoimmune condition are at risk for developing other autoimmune problems, some clinicians are proponents of beginning thyroid replacement once the diagnosis has been established.

#### Screening for Canine Autoimmune Thyroiditis

- Complete thyroid antibody profile required
- Test intact bitches during anestrus
- Need T3AA, T4AA, TgAA; not just freeT4, TSH, TgAA
- OFA Thyroid Registry is limited panel
- Some cases (~8%) are T3AA and/or T4AA +, but TgAA –
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#### Do not breed dogs with autoimmune thyroiditis

- Heritable trait, regardless of clinical status
- Screen relatives annually from puberty
- Consider for breeding, if negative, after age three

### **Relationship Between Canine Thyroid Dysfunction and Aberrant Behavior**

The principal reason for pet euthanasia stems not from disease, but undesirable behaviour. While this abnormal behaviour can have a variety of medical causes, it also can reflect underlying problems of a psychological nature. An association has recently been established between aberrant behaviour and thyroid dysfunction in the dog. Typical clinical signs include unprovoked aggression towards other animals and/or people, sudden onset of a seizure disorder in adulthood, disorientation, moodiness, erratic temperament, periods of hyperactivity, hypoattentiveness, depression, fearfulness and phobias, anxiety, submissiveness, passivity, compulsiveness, and irritability. After the episodes, most of the animals appeared to be coming out of a trance like state, and were unaware of their previous behaviour.

An ongoing study at Tufts University involves over 1500 cases of dogs presented to veterinary clinics for aberrant behavior. The first 499 cases have been analyzed independently by a neural network correlative statistical program. Results showed a significant relationship between thyroid dysfunction and seizure disorder, and thyroid dysfunction and dog-to-human aggression. Treatment outcomes in 95 cases showed a significant behavioral improvement in 61% of the dogs. Collectively, these findings confirm the importance of including a complete thyroid antibody profile as part of the laboratory and clinical work up of any behavioral case.

#### Screening for Canine Thyroid Dysfunction

- Complete thyroid antibody profile preferred
- cTSH poorly predictive as compared to humans.
- Basal T4 levels affected by certain drugs (steroids, Pb, sulfonamides)

- Basal T4 levels lowered by estrogen; raised by progesterone [sex hormonal cycle effects]

## Summary of Testing Recommendations

As previously mentioned the best test to diagnose hypothyroidism is based on the clinical situation. Common clinical situations are the following

**Low or low normal T4 as part of a wellness screen in a clinically normal dog.** The odds are that the dog is probably euthyroid and the T4 concentration happens to be low or low-normal that day. Best to follow the dog clinically over 6 to 12 months. Alternatively a thyroid profile could be performed.

**Low or low normal T4 in a dog with vague clinical symptoms.** This is a “could be or might be” hypothyroid dog. Consider a therapeutic trial or a thyroid profile

**Aberrant behavior or genetic counseling.** A thyroid profile is recommended

**A dog with classic signs of hypothyroidism.** A T4 or FT4ED will usually suffice.

## The Free T4 by equilibrium dialysis is elevated. Is the cat hyperthyroid?

Confusion over the diagnostic utility of FT4ED has led to misdiagnosis of hyperthyroidism in the cat. By using the FT4ED alone as a diagnostic aid (without evaluating a concurrent TT4) more cats are being diagnosed with hyperthyroidism than actually have the disorder.

FT4 is the unprotein bound physiology active form of T4 and, theoretically, is the best marker of thyroid status in the dog and the cat. And indeed, in cats with overt hyperthyroidism (clinical signs consistent with the disease, palpable thyroid nodule(s) and elevated TT4 concentrations (TT4 > 4 µg/dl), FT4 concentrations are elevated. In addition, in cats with early or mild hyperthyroidism (these cats generally have more mild signs of disease, palpable thyroid nodule(s) and TT4 concentrations in the upper half of the normal reference range) the FT4 when measured using a direct dialysis technique (FT4ED) is usually elevated.

However, in cats with nonthyroidal (e.g., chronic renal failure, IBD, neoplasia) the FT4ED can also be elevated for reasons that are unclear. These cats may have signs consistent with hyperthyroidism. (e.g., weight loss, vomiting) but there is no palpable thyroid nodule(s), and the TT4 concentrations are usually less than 2 µg/dl. Measured alone, a FT4ED concentration can be misleading without evaluating the TT4 concentration concurrently as well as the results of the history, physical exam, and routine bloodwork.

**Case example:** A 15-year-old cat castrated male cat is presented for polyuria and polydipsia and mild weight loss. The serum biochemical profile abnormalities include an

elevated BUN and creatinine (40 mg/dl and 2.5 mg/dl respectively). The USG is 1.010. The FT4ED is 70 nmol/L normal range 10-50 nmol/L), the TT4 is 1 µg/dl (normal range 1-4 µg/dl).

**Assessment:** Chronic renal failure in the cat with spurious elevation of FT4ED. This cat is not hyperthyroid. The diagnostic key is the TT4, which is the lower half of the normal reference range.

## **The urine specific gravity is low. Is this clinically significant?**

A random low urine specific gravity may be a normal variation or may be a marker for an underlying polyuric disorder. If a history of polyuria and polydipsia exists, a workup is recommended. If there is no history of polyuria and polydipsia, consider repeating the urine specific gravity along with a complete urinalysis at a later date or have the owner quantify water intake at home.

The urinalysis is a major key in determining the presence of a water balance problem and which disorder is causing the polyuria and polydipsia. The most important features of the urinalysis are the specific gravity, the presence or absence of glucose, protein, or bacteria, and the cellularity of the sample. A urine specific gravity less than 1.035 in dogs and 1.040 in cats suggests a concentrating defect and hence supports the complaint of polyuria. Persistent glycosuria is diagnostic of primary renal glycosuria or, more commonly diabetes mellitus. Significant proteinuria in the presence of an inactive urinary sediment and dilute urine can be associated with hyperadrenocorticism or pyelonephritis. An active urine sediment (pyuria, hematuria, or bacteriuria) in a sample obtained by catheterization or cystocentesis supports urinary tract infection and possible pyelonephritis.

### **What if the blood work is normal?**

The direction of the diagnostic work-up, especially in those cases with a normal physical examination and a normal serum biochemical profile and electrolytes, can often be based on urine specific gravity. For example, animals with a specific gravity > 1.035 (dogs) or 1.040 (cats) without glycosuria are probably not polyuric and, therefore, need no further workup, at least for polyuria and polydipsia. A urine specific gravity consistently less than 1.008 in a middle-aged to older dog is usually associated with central DI, psychogenic polydipsia, or an uncommon form of hyperadrenocorticism whereby the serum alkaline phosphatase levels are normal or only mildly elevated. In general, when considering this group of disorders, hyperadrenocorticism should be ruled out first before testing for central DI and psychogenic polydipsia. There are several reasons for making this recommendation. These disorders are less common than hyperadrenocorticism. The diagnostic tests of choice to differentiate these disorders, the modified water deprivation test or therapeutic trial with ADH, are time consuming and expensive. And lastly, dogs with hyperadrenocorticism may respond to these tests similarly to dogs with central DI causing a misdiagnosis. A urine specific gravity 1.008 to 1.012 or greater (but less than 1.035) is also associated with atypical hyperadrenocorticism and psychogenic polydipsia, as well as early renal insufficiency, and pyelonephritis. With this group of disorders, pyelonephritis and early renal

insufficiency should be initially ruled out prior to evaluating the animal for psychogenic polydipsia with a water deprivation test. Performing a water deprivation test as a diagnostic tool in the face of unsuspected renal insufficiency or pyelonephritis could induce overt renal failure or urosepsis. To avoid this complication, a sensible approach is to first evaluate renal size and architecture with abdominal radiography or preferably renal ultrasonography. The sonographic appearance of renal parenchymal disease (chronic renal failure) includes increased cortical echogenicity and loss of a distinct corticomedullary junction. The kidneys may appear smaller than normal and have an ill-defined or irregular border. Similar sonographic findings, in addition to a dilated renal pelvis, are characteristic of pyelonephritis. If radiographic or ultrasonographic findings are equivocal, a creatinine or iothexol clearance test, renal biopsy or a therapeutic trial with antibiotics for suspected pyelonephritis may be indicated.

### **Microalbuminuria: What is it and is it clinically significant?**

Proteinuria has received renewed attention as a factor impacting the progression of cases of canine and feline chronic renal failure (CRF) and as a marker of early renal disease. Primary renal disease, as well as various infectious, inflammatory, metabolic and neoplastic disorders can damage glomerular vasculature and cause leakage of albumin into the glomerular filtrate, even in subclinical stages. Microalbuminuria (MA), the persistence of small amounts of albumin in the urine, is an early indicator of primary renal disease, lower urinary tract disease, or the presence of some other underlying disease causing early renal damage. Detection of MA during a routine health examination provides veterinarians with a new tool to help identify these situations.

#### **Background**

Protein traffic across the glomerular barrier primarily involves albumin, and is influenced by many factors, including: damage to glomerular basement membrane, glomerular capillary hemodynamics, and endothelial cell dysfunction. The appearance of protein in urine is also influenced by proximal tubular cell function, as these cells normally reabsorb and degrade any filtered protein, thereby reducing the amount appearing in urine.

Common causes of MA can be classified as glomerular and post-glomerular. Glomerular causes of MA arise from altered glomerular membrane permeability, occurring either from glomerular injury or glomerular capillary hypertension. The ensuing leakage of albumin into the glomerular filtrate exceeds tubular capacity to reabsorb or degrade the excess albumin. Post-glomerular causes of MA include: failure of renal tubules to degrade or reabsorb filtered albumin (e.g., acute or chronic tubulointerstitial disease), or hemorrhage and/or inflammation of the lower urinary tract.

#### **Measuring MA**

The trace amounts of albumin in urine detected by MA testing (1 to 30 mg/dL) are below the limits of protein detected by conventional urine dipsticks. Urine albumin concentrations above this limit are classified as overt proteinuria and can often be detected by measuring the protein: creatinine ratio. Antech's newly introduced reference

MA test is a species-specific immunoassay, which correlates very closely to results obtained with the Heska ERD Healthscreen™ Urine test in clinical studies.

### **Prevalence of MA in dogs and cats**

Several studies have evaluated the prevalence of MA. In one study, the prevalence of MA in 86 dogs whose owners were not seeking veterinary care was 19%, whereas it was higher (36%) in 159 dogs whose owners were seeking veterinary care. In another study, the prevalence of MA was 30% in dogs evaluated for health problems at a Veterinary Teaching Hospital. A third study of 3041 staff-owned dogs from over 350 veterinary clinics, found an overall MA prevalence of 24.7%. There was a statistically significant correlation between increasing age and the presence of MA. For example, MA was present in 7.4% of dogs < 3 years old, 8.6% of dogs 3-5 years of age, 20% of dogs 6-8 years of age, 36% of dogs 9-11 years of age, and 49.1% of dogs 12 years of age and older. These findings appear to support previous reports of an increased incidence of glomerular disease in older dogs. Lastly, the overall prevalence of MA of 1243 staff-owned cats from veterinary clinics was 24.5%. Similar to the dog study, there was a statistically significant correlation between increasing age and the presence of MA in geriatric cats. For example, MA was present in 35.5% of cats 12-15 years of age and 72.7% of cats 16-23 years of age.

### **MA in Early Renal Disease and Non-Renal Disease**

Testing for MA has been a good indicator of early renal disease in dogs and cats, especially those with glomerular disease. In one study, 12 dogs were infected with *Dirofilaria immitis* L3 larvae. All of them developed MA 14-23 months post-infection, and the magnitude of MA increased over time and preceded the development of overt proteinuria.

Urine albumin was also studied in 36 male dogs with X-linked hereditary nephropathy, a rapidly progressive glomerular disease, and in 20 Soft-Coated Wheaten Terriers, a breed genetically at risk for the development of protein losing nephropathy. The presence of MA was shown to be a reliable early marker of developing nephropathy and preceded overt proteinuria in both studies.

Non-renal diseases associated with MA fall into the categories of: 1) infectious (e.g., Lyme disease, heartworm disease, FIP, FIV, and FeLV); 2) inflammatory (e.g., periodontal disease, chronic skin disease, pancreatitis, hepatitis, IBD); 3) neoplastic; 4) metabolic (e.g., diabetes mellitus, hyperthyroidism); and 5) cardiovascular disorders. As not all of these diseases are likely to result in permanent renal damage, the presence of MA may be transient and should be interpreted cautiously along with the clinical assessment and other diagnostic testing, as indicated.

### **Identifying Causes of Renal Damage with MA**

In a retrospective study involving 137 dogs with overt proteinuria, (albumin >30 mg/dL) and histopathological diagnosis of glomerulopathy, significant concurrent medical problems were identified in ~ 50% of the dogs. In a recent study of dogs that

were negative for protein on conventional urine protein dipsticks but positive for MA, infectious, inflammatory, or neoplastic diseases were identified in 56% of them.

### **Consensus Statement: Follow-up on Patients with MA or Overt Proteinuria**

The 2004 ACVIM Forum consensus statement with regard to the assessment and management of proteinuria (MA and overt proteinuria) in dogs and cats is as follows. Prospective monitoring sufficient to accomplish time detection of any worsening trends is recommended for

\*Nonazotemic dogs and cats with persistent MA

\*Nonazotemic dogs and cats with UPC values  $> 0.5$ .

Diagnostic investigation that is focused on finding a potentially treatable underlying disease and adequate continued monitoring are recommended for

\*Nonazotemic dogs and cats with rising magnitudes of persistent MA

\*Nonazotemic dogs and cats with persistent proteinuria and UPC values  $> 1.0$

After appropriate investigation and specific treatment of any underlying disease, therapeutic intervention and adequate monitoring is recommended for

\*Dogs with CKD causing azotemia and UPC values  $> 0.5$

\*Cats with CKD causing azotemia and UPC values  $> 0.4$

\*Nonazotemic dogs and cats with persistent proteinuria and UPC values  $> 2$ .

### **Treatment Considerations**

Recent evidence suggests that renal diets, ACE inhibitors (when overt proteinuria is present), the recognition and treatment of hypertension, and low dose calcitriol therapy can slow the progression of renal disease and increase survival time.

