PRACTICAL UNDERSTANDING OF THYROID DISEASE

W. Jean Dodds, DVM

INTRODUCTION

Hypothyroidism is the most common endocrine disorder of canines, and up to 80% of cases result from autoimmune (lymphocytic) thyroiditis. The heritable nature of this disorder poses significant genetic implications for breeding stock. Thus, accurate diagnosis of the early compensatory stages of canine autoimmune thyroiditis leading up to hypothyroidism affords important genetic and clinical options for prompt intervention and case management.

Although 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. Many clinical signs mimic those of other causes and so recognition of the condition and interpretation of thyroid function tests can be problematic (Table 1).

Baseline Thyroid Profiles

A complete baseline thyroid profile is measured and typically includes total T4, total T3, free T4, free T3, T3AA and T4AA, and can include cTSH and/or TgAA. The TgAA assay is 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 references 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.

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. Thus, the presence of elevated T3 and/or T4 AA confirms a diagnosis of autoimmune thyroiditis but underestimates its prevalence, as negative (non-elevated) autoantibody levels do not rule out thyroiditis. Measuring TgAA levels also permits early recognition of the disorder, and facilitates genetic counselling (Table 2). Affected dogs should not be used for breeding.

The commercial TgAA test can give false negative results if the dog has received thyroid supplement within the previous 90 days, thereby allowing unscrupulous owners to test dogs while on treatment to assert there 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, false positive TgAA results may be obtained if the dog has been vaccinated within the previous 30-45 days, or in some cases of non-thyroidal illness. Vaccination of pet and research dogs with polyvalent vaccines containing rabies virus or rabies vaccine alone was recently shown to induce production of

antithyroglobulin autoantibodies, a provocative and important finding with implications for the subsequent development of hypothyroidism.

A population study of 287,948 dogs published by the MSU Animal Health Diagnostic Laboratory showed that: Circulating thyroid hormone autoantibodies (T3AA and/or T4AA)) were found in 18,135 of these dogs (6.3%). The 10 breeds with the highest prevalence of thyroid AA from their study were: Pointer, English Setter, English Pointer, Skye Terrier, German Wirehaired Pointer, Old English Sheepdog, Boxer, Maltese, Kuvasz, and Petit Basset Griffon Vendeen. Prevalence was associated with body weight and was highest in dogs 2-4 years old. Females were significantly more likely to have thyroid AA than males.

A bitch with circulating thyroid AA has the potential to pass these along to the puppies transplacentally as well as via the colostrum. Furthermore, any dog having thyroid AA may eventually develop clinical symptoms of thyroid disease and/or be susceptible to other autoimmune diseases. Thyroid screening is thus very important for selecting potential breeding stock as well as for clinical diagnosis.

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 anestrous 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. In fact, genetic screening of intact females for other disorders such as von Willebrand disease (vWD), hip dysplasia, and wellness or reproductive checkups (vaginal cultures, hormone testing) is best scheduled during 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. Generation of annual test results provides comparisons that permit early recognition of developing thyroid dysfunction. This allows for early treatment to avoid the appearance or advancement of clinical signs associated with hypothyroidism.

Canine autoimuune thyroid disease is very similar to Hashimoto's thyroiditis of humans, which has been shown to be associated with human major histocompatibility complex (MHC) tissue types. A similar association with canine MHC genes in hypothyroid dogs has recently been reported in Doberman Pinschers, English Setters and Rhodesian Ridgebacks, who share a rare dog leukocyte antigen (DLA) class II haplotype which contains a unique DLA-DQA1*00101 genetic determinant. While the presence of this determinant doubles the risk of a dog developing hypothyroidism, it was not found in boxers affected with thyroiditis, nor was it found in the Shih Tzu, Yorkshire Terrier, or Siberian Husky, although more studies are needed in these and other susceptible breeds to establish their true status with respect to this marker DLA antigen. This exciting finding of a common genetic determinant associated with thyroid disease in several breeds hopefully will lead to development of a genetic marker test to identify affected breeding stock and allow for selective breeding to reduce disease incidence in pure-bred dogs.

POLYGLANDULAR AUTOIMMUNITY

Individuals genetically susceptible to autoimmune thyroid disease may also become more susceptible to immune-mediated diseases affecting other target tissues and organs, especially the bone marrow, liver, adrenal gland, pancreas, skin, kidney, joints, bowel, and central nervous system. The resulting "polyglandular autoimmune syndrome" of humans is

becoming more commonly recognized in the dog, and probably occurs in other species as well. The syndrome tends to run in families and is believed to have an inherited basis. Multiple endocrine glands and nonendocrine systems become involved in a systemic immune-mediated process. This multiple endocrinopathy often occurs in patients with underlying autoimmune thyroid disease (hypo- or hyperthyroidism) and concurrent Addison's disease, diabetes, reproductive gonadal failure, skin disease and alopecia, and malabsorption syndrome. The most common nonendocrinologic autoimmune disorders associated with this syndrome are autoimmune hemolytic anemia (AIHA), idiopathic thrombocytopenic purpura (ITP), chronic active hepatitis, and immune-complex glomerulonephritis (systemic lupus erythematosus; SLE).

The most commonly recognized polyglandular endocrinopathy of dogs is Schmidt's syndrome (thyroiditis and Addison's disease). Examples of breeds genetically predisposed to this disorder include the Standard Poodle, Old English Sheepdog, Bearded Collie, Portuguese Water Dog, Nova Scotia Duck Tolling Retriever, and Leonberger, although any breed or mixed breed can be affected. Our study cohort of 162 cases of autoimmune blood and endocrine disorders in Old English Sheepdogs (1980-1989) included 115 AIHA and/or ITP, 99 thyroid disease, 23 Addison's disease, 7 vaccine reactions, 3 SLE, 2 diabetes, 1 rheumatoid arthritis and 1 hypoparathyroidism. The group comprised 110 females (15 spayed) and 52 males (3 neutered). Seven of the most recent 103 cases had two or more endocrine disorders, and 101 of the 108 cases where pedigrees were available showed a familial relationship going back several generations. Data from surveying the Bearded Collie breed reported 55 hypothyroid, 17 Addison's disease, and 31 polyglandular autoimmunity (5 were hypothyroid).

ABERRANT BEHAVIOR AND THYROID DYSFUNCTION

The principal reason for pet euthanasia stems not from disease, but undesirable behavior. While this abnormal behavior can have a variety of medical causes, it also can reflect underlying problems of a psychological nature.

An association between behavioral and psychologic changes and thyroid dysfunction has been recognized in humans since the 19th century. In a recent study, 66% of people with attention deficit-hyperactivity disorder were found to be hypothyroid, and supplementing their thyroid levels was largely curative. Furthermore, an association has recently been established between aberrant behavior and thyroid dysfunction in the dog, and has been noticed in cats with hyperthyroidism. Typical clinical signs include unprovoked aggression towards other animals and/or people, sudden onset of seizure disorder in adulthood, disorientation, moodiness, erratic temperament, periods of hyperactivity, hypoattentiveness, depression, fearfulness and phobias, anxiety, submissiveness, passivity, compulsiveness, and irritability. After episodes, most of the animals appeared to come out of a trance like state, and were unaware of their bizarre behavior.

The mechanism whereby diminished thyroid function affects behavior is unclear. Hypothyroid patients have reduced cortisol clearance, as well as suppressed TSH output and lowered production of thyroid hormones. Constantly elevated levels of circulating cortisol mimic the condition of an animal in a constant state of stress. In people and seemingly in dogs, mental function is impaired and the animal is likely to respond to stress in a stereotypical rather than reasoned fashion. Chronic stress in humans has been implicated in the pathogenesis of affective disorders such as depression. Major depression has been shown in imaging studies to produce changes in neural activity or volume in areas of the brain which regulate aggressive and other behaviors. Dopamine and serotonin receptors have been clearly demonstrated to be involved in aggressive pathways in the CNS. Hypothyroid rats have increased turnover of serotonin and dopamine receptors, and increased sensitivity to ambient neurotransmitter levels.

Investigators in recent years have noted the sudden onset of behavioral changes in dogs around the time of puberty or as young adults. Most of the dogs have been purebreds or crossbreeds, with an apparent predilection for certain breeds. For a significant proportion of these animals, neutering does not alter the symptoms and in some cases the behaviors intensify. The seasonal effects of allergies to inhalants and ectoparasites such as fleas and ticks, followed by the onset of skin and coat disorders including pyoderma, allergic dermatitis, alopecia, and intense itching, have also been linked to changes in behavior.

Many of these dogs belong to a certain group of breeds or dog families susceptible to a variety of immune problems and allergies (e.g. Golden Retriever, Akita, Rottweiler, Doberman Pinscher, English Springer Spaniel, Shetland Sheepdog, and German Shepherd Dog). The clinical signs in these animals, before they show the sudden onset of behavioral aggression, can include minor problems such as inattentiveness, fearfulness, seasonal allergies, skin and coat disorders, and intense itching. These may be early subtle signs of thyroid dysfunction, with no other typical signs of thyroid disease being manifested.

The typical history starts out with a quite, well-mannered and sweet-natured puppy or young adult dog. The animal was outgoing, attended training classes for obedience, working, or dog show events, and came from a reputable breeder whose kennel has had no prior history of producing animals with behavioral problems. At the onset of puberty or thereafter, however, sudden changes in personality are observed. Typical signs can be incessant whining, nervousness, schizoid behavior, fear in the presence of strangers, hyperventilating and undue sweating, disorientation, and failure to be attentive. This can progress to sudden unprovoked aggressiveness in unfamiliar situations with animals, people and especially with children.

Another group of dogs show seizure or seizure-like disorders of sudden onset that can occur at any time from puberty to mid-life. These dogs appear perfectly healthy outwardly, have normal hair coats and energy, but suddenly seizure for no apparent reason. The seizures are often spaced several weeks to months apart, may coincide with the full moon, and can appear in brief clusters. In some cases the animals become aggressive and attack those around them shortly before or after having one of the seizures. Two recent cases involved young dogs referred for sudden onset seizure disorder shortly after puberty. Both dogs were found to have early onset autoimmune thyroiditis, which was clinically responsive to thyroid supplementation, to the extent that anticonvulsant medications could be gradually withdrawn. The numbers of animals showing various types of aberrant behavior are increasing in frequency over the last decade.

In dogs with aberrant aggression, a large collaborative study between our group and Dr. Dodman and colleagues at Tufts University School of Veterinary Medicine has shown a favorable response to thyroid replacement therapy within the first week of treatment, whereas it took about three weeks to correct their metabolic deficit. Dramatic reversal of behavior with resumption of previous problems has occurred in some cases if only a single dose is missed. A similar pattern of aggression responsive to thyroid replacement has been reported in a horse.

Results of complete thyroid diagnostic profiling were analyzed on the first 634 canine cases of aberrant behavior, compiled by this author in collaboration with Drs. Nicholas Dodman, Linda Aronson, and Jean DeNapoli of Tufts University School of Veterinary Medicine, North Grafton, MA. Ninety percent (568 dogs) were purebreds and 10% were mixed breeds. There was no sex predilection found in this case cohort, whether or not the animals were intact or neutered. Sixty-three percent of the dogs had thyroid dysfunction as judged by finding 3 or more

abnormal results on the comprehensive thyroid profile. The major categories of aberrant behavior were aggression (40% of cases), seizures (30%), fearfulness (9%), and hyperactivity (7%); some dogs exhibited more than one of these behaviors. Within these 4 categories, thyroid dysfunction was found in 62% of the aggressive dogs, 77% of seizuring dogs, 47% of fearful dogs, and 31% of hyperactive dogs.

Outcomes of treatment intervention with standard twice daily doses of thyroid replacement were evaluated in 95 cases, and showed a significant behavioral improvement in 61% of the dogs. Of these, 58 dogs had greater than 50% improvement in their behavior as judged by a predefined 6-point subjective scale (34 were improved > 75%), and another 23 dogs had >25 but <50% improvement. Only 10 dogs experienced no appreciable change, and 2 dogs had a worsening of their behavior. When compared to 20 cases of dominance aggression treated with conventional behavior or other habit modification over the same time period, only 11 dogs improved more than 25%, and of the remaining 9 cases, 3 failed to improve and 3 were euthanized or placed in another home. These initial results are so promising that complete thyroid diagnostic profiling and treatment with thyroid supplement, where indicated, is warranted for all cases presenting with aberrant behavior.

Our ongoing study now includes 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.**

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.

REFERENCES

● Aronson LP, Dodds WJ. The effect of hypothyroid function on canine behavior. Proc Int Vet Beh Med 2005.

● Aronson LP and Dodman NH Thyroid function as a cause of aggression in dogs and cats. Proc Deutch Vet Gesellshaft 1997, p. 228.

● Beaver BV and Haug LI . Canine behaviors associated with hypothyroidism. J Am An Hosp Assoc 39: 431-434, 2003.

● Cameron DL, Crocker AD. The hypothyroid rat as a model of increased sensitivity to dopamine receptor agonists. Pharm Biochem Behav 37:627-632, 1990.

● Denicoff KD, Joffe RT, Lakschmanan MC, Robbins J, Rubinow DR. Neuropsychiatric manifestations of altered thyroid state. Am J Psych 147:94-99, 1990.

● Dewey CW, Shelton GD, Bailey, CS. Neuromuscular dysfunction in five dogs with acquired myasthenia gravis and presumptive hypothyroidism. Prog Vet Neurol 6: 117-123, 1995.

● Diaz Espineira MM, J.A. Mol JA, Peeters ME, Pollak YWEA, Iversen L,van Dijk JE, Rijnberk A, Kooistra HS. Assessment of thyroid function in dogs with low plasma thyroxine concentration. J Vet Intern Med 21:25–32, 2007.

● Dixon RM, Graham PA, Mooney CT. Serum thyrotropin concentrations: a new diagnostic test for canine hypothyroidism. Vet Rec 138: 594-595, 1996.

● Dodds, WJ. Thyroid can alter behavior. Dog World 1992, 77(10); 40-42.

● Dodds WJ. Estimating disease prevalence with health surveys and genetic screening. Adv Vet Sci Comp Med, 39: 29-96, 1995.

● Dodds WJ. Autoimmune thyroiditis and polyglandular autoimmunity of purebred dogs. Can Pract 22 (1): 18-19, 1997.

● Dodds WJ. What's new in thyroid disease ? Proc Am Hol Vet Med Assoc 1997; pp 82-95.

● Dodds WJ. Behavioral changes associated with thyroid dysfunction in dogs. Proc Am Hol Vet Med Assoc, 80-82, 1999.
● Dodman NH, Mertens PA, Aronson, LP. Aggression in two hypothyroid dogs, behavior case of the month. J Am Vet Med Assoc 207:1168-1171, 1995.
● Feldman EC, Nelson RW. Canine and Feline Endocrinology and Reproduction. Second Edition. Philadelphia: WB Saunders Co, 1996.
● Frank LA. Comparison of thyrotropin-releasing hormone (TRH) to thyrotropin (TSH) stimulation for evaluating thyroid function in dogs. J Am An Hosp Assoc 32: 481- 487, 1996.
● Hall IA, Campbell KC, Chambers MD, et al. Effect of trimethoprim-sulfamethoxazole on thyroid function in dogs with pyoderma. J Am Vet Med Assoc 202:1959-1962, 1993.
● Happ GM. Thyroiditis - A model canine autoimmune disease. Adv Vet Sci Comp Med 39: 97-139, 1995.
● Happ GM, Ollier W, Kennedy LJ. Genetic determinants of susceptibility to hypothyroid disease in dogs. AKC Research Foundation Report, Sept 2005.
● Hauser P, Zametkin AJ, Martinez, P et al. Attention deficit-hyperactivity disorder in people with generalized resistence to thyroid hormone. N Eng J Med 328:997-1001, 1993.
● Henley WN, Chen X, Klettner C. Bellush LL, Notestine MA. Hypothyroidism increases serotonin turnover and sympathetic activity in the adult rat. Can J Physiol Pharmacol 69:205-210, 1991.
● International Symposium on Canine Hypothyroidism, University of California, Davis. Can Pract 22 (1) : 4-62, 1997.
● Iverson L, Jensen AL, Høier R, et al. Biological variation of canine serum thyrotropin (TSH) concentration. Vet Clin Pathol 28:16-19, 1999.
● Jensen AL, Iversen L, Høier R, et al. Evaluation of an immunoradiometric assay for thyrotropin in serum and plasma samples of dogs with primary hypothyroidism. J Comp Pathol 114: 339-346, 1996.
● Kaptein EM. Thyroid hormone metabolism and thyroid diseases in chronic renal failure. End Rev 17:45-63, 1996.
● Kennedy LJ, Quarmby S, Happ GM, Barnes A et al. Association of canine hypothyroid disease with a common major histocompatibility complex DLA class II allele. Tissue Antigens 68:82-86, 2006.
● Kennedy LJ, Hudson HJ, Leonard J, Angles JM, et al. Association of hypothyroid disease in Doberman pinscher dogs with a rare major histocompatibility complex DLA class II haplotype. Tissue Antigens 67:53-56, 2005.
● McGregor AM. Autoimmunity in the thyroid - Can the molecular revolution contribute to our understanding? Quart J Med 82 (297): 1-13, 1992.
● Nachreiner RF, Refsal KR. Radioimmunoassay monitoring of thyroid hormone concentrations in dogs on thyroid replacement therapy: 2,674 cases (1985-1987). J Am Vet Med Assoc 201: 623-629, 1992.
● Nachreiner RF, Refsal KR, Davis WR, et al. Pharmacokinetics of L-thyroxine after its oral administration in dogs. Am J Vet Res 54: 2091-2098, 1993.
● Nachreiner RF, Refsal KR, Graham PA, et al. Prevalence of autoantibodies to thyroglobulin in dogs with nonthyroidal illness. Am J Vet Res 59:951-955, 1998.
● Nachreiner RF, Refsal KR, Graham PA, Bowman MM. Prevalence of serum thyroid hormone autoantibodies in dogs with clinical signs of hypothyroidism. J Am Vet Med Assoc 220:466-471, 2002.
● Overall KL. Clinical Behavioral Medicine for the Small Animal. St. Louis, Mosby, 1998
● Panciera DL, Johnson GS. Hypothyroidism and von Willebrand factor. J Am Vet Med Assoc 206: 595-596, 1995.
● Panciera DL. Clinical manifestations of canine hypothyroidism. Vet Med 92: 44-49, 1997.
● Panciera DL. Thyroid-function testing: Is the future here? Vet Med 92: 50-57, 1997.
● Panciera DL. Treating hypothyroidism. Vet Med 92: 58-68, 1997.
● Panciera DL. Hypothyroidism in dogs: 66 cases (1987-1992). J Am Vet Med Assoc204: 761-767, 1994.
● Paradis M, Pagé N, Larivière N, et al. Serum-free thyroxine concentrations, measured by chemiluminescence assay before and after thyrotropin administration in healthy dogs, hypothyroid dogs, and euthyroid dogs with dermatopathies. Can Vet J 37: 289-294, 1996.
● Peterson ME, Melian C, Nichols R. Measurement of serum total thyroxine, triiodothyronine, free thyroxine, and thyrotropin concentrations for diagnosis of hypothyroidism in dogs. J Am Vet Med Assoc 211:1396-1402, 1997.
● Schmidt MA, Bland JS. Thyroid gland as sentinel: Interface between internal and external environment. Altern Ther 3: 78-81, 1997.

● Scott-Moncrieff JCR, Nelson RW. Change in serum thyroid stimulating hormone concentration in response to administration of thyrotropin-releasing hormone to healthy dogs, hypothyroid dogs, and euthyroid dogs with concurrent disease. J Am Vet Med Assoc 213:1435-1438, 1998.
● Scott-Moncrieff JCR, Nelson RW, Bruner JM, et al. Comparison of thyroid-stimulating hormone in healthy dogs, hypothyroid dogs, and euthyroid dogs with concurrent disease. J Am Vet Med Assoc 212:387-391, 1998.
● Scott-Moncrieff JC, Azcona-Olivera J, Glickman NW, Glickman LT, HogenEsch H. Evaluation of antithyroglobulin antibodies after routine vaccination in pet and research dogs. J Am Vet Med Assoc 221: 515-521, 2002.
● Surks MI, Sievert R. Drugs and thyroid function. N Eng J Med 333: 1688-1694, 1995.
● Thacker EL, Refsal KR, Bull RW. Prevalence of autoantibodies to thyroglobulin, thyroxine, or triiodothronine and relationship of autoantibodies and serum concentration of iodothyronines in dogs. Am J Vet Res 53: 449-453, 1992.
● Thacker EL, Davis JM, Refsal KR, et al. Isolation of thyroid peroxidase and lack of antibodies to the enzyme in dogs with autoimmune thyroid disease. Am J Vet Res 56: 34-38, 1995.
● Tomer Y, Davies TF. Infection, thyroid disease, and autoimmunity. End Rev 14: 107-120, 1993.
● Uchida Y, Dodman NH, DeNapoli J, Aronson LP. Characterization and treatment of 20 canine dominance aggression cases. J Vet Med Sci 59:397-399. 1997.
● Vajner L. Lymphocytic thyroiditis in beagle dogs in a breeding colony: findings of serum autoantibodies. Vet Med Czech 11:333-338, 1997.
● Williams DA, Scott-Moncrieff C, Bruner J, et al. Validation of an immunoassay for canine thyroid-stimulating hormone and changes in serum concentration following induction of hypothyroidism in dogs. J Am Vet Med Assoc 209: 1730-1732, 1996.

Table 1. CLINICAL SIGNS OF CANINE HYPOTHYROIDISM

Alterations in Cellular Metabolism

lethargy	weight gain or weight loss
mental dullness	cold intolerance
exercise intolerance	mood swings
neurologic signs	hyperexcitability
polyneuropathy	stunted growth
seizures	chronic infections

Neuromuscular Problems

weakness	knuckling or dragging feet
stiffness	muscle wasting
laryngeal paralysis	megaesophagus
facial paralysis	head tilt
"tragic" expression	drooping eyelids
incontinence	ruptured cruciate ligament

Dermatologic Diseases

dry, scaly skin and dandruff	chronic offensive skin odor
coarse, dull coat	bilaterally symmetrical hair loss
"rat tail"; "puppy coat"	seborrhea with greasy skin
hyperpigmentation	seborrhea with dry skin
pyoderma or skin infections	myxedema

Reproductive Disorders

infertility	prolonged interestrus interval
lack of libido	absence of heat cycles
testicular atrophy	silent heats
hypospermia	pseudopregnancy
aspermia	weak, dying or stillborn pups

Cardiac Abnormalities

slow heart rate (bradycardia)	cardiac arrhythmias
cardiomyopathy	

Gastrointestinal Disorders

constipation	inappetance or picky eater
diarrhea	vomiting
inflammatory bowel disease	flatulence

Hematologic Disorders

bleeding
bone marrow failure
low red blood cells (anemia), white blood cells, platelets

Ocular Diseases

corneal lipid deposits	corneal ulceration
uveitis	keratoconjunctivitis sicca or "dry eye"
infections of eyelid glands (Meibomian gland)	Vogt-Koyanagi-Harada syndrome

Other Associated Disorders

IgA deficiency	loss of smell (dysosmia)
loss of taste	glycosuria
other endocrinopathies	chronic or reactive hepatitis
adrenal	
pancreatic	
parathyroid	

Table 2. DIAGNOSIS OF THYROID DISEASE

- Complete Basic Thyroid 5 Profile
  -- T4, T3, FT4, FT3, TgAA
- Additional Tests
  -- T3AA, T4AA ,TgAA; TSH (optional)

- **Older Tests (T4, T4 + T3)**

  Serum T4 and/or T3 alone are **not** reliable for diagnosis because:
  -- overdiagnose hypothyroidism
  -- underdiagnose hyperthyroidism
  -- fail to dectect early compensatory disease and thyroiditis
  -- influenced by nonthyroidal illness and certain drugs

- **Newer Tests**

  Free (Unbound) T4

  Less likely to be influenced by nonthyroidal illness or drugs
  Valid -- equilibrium dialysis
  -- solid-phase analog RIA
  -- chemiluminescence solid-phase
  Less reliable -- liquid-phase analog RIA

  Endogenous Canine TSH

  In primary hypothyroidism, as free T4 levels fall, pituitary output of TSH rises
  -- elevated TSH usually indicates primary thyroid disease
  -- reulatory control in dogs also by growth hormone, unlike people
  -- 30% discordancy observed between expected and actual findings
  -- published normal ranges may need revising
  -- affected by concomitant chronic renal disease

  Canine TgAA

  Thyroglobulin autoantibodies are present in serum of
  cases with lymphocytic thyroiditis.
  -- positive results confirm diagnosis ; 8% false negative
  -- 20-40% of cases have circulating T3 and/or T4AA
  -- allows for early diagnosis and genetic counseling

FREQUENTLY ASKED QUESTIONS

Q. When do classical clinical signs of canine hypothyroidism appear ?

A. The classical clinical signs with low thyroid values occur only after 70% or more of thyroid tissue has been destroyed or damaged. Other clinical and behavioral changes can present during the early phase.

Q. Are basal thyroid levels the same for animals over the age and breed spectrum ?

A. No. 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 as a group have much lower basal thyroid levels

Q. How does one screen effectively for canine thyroid dysfunction ?

A. Accurate assessment requires:

- Complete thyroid antibody profile preferred

Q. What tests should be included in the complete thyroid profile ?

A. At least the majority of the following:

- T4, freeT4, T3, freeT3
- TgAA (important if breeding or for breeds at risk for thyroiditis)
- T3 Autoantibody (T3AA) and T4 Autoantibody (T4AA)
- cTSH poorly predictive (~ 70%) compared to humans

Q. What are some things that can affect basal thyroid activity ?

A. Results may be affected by the following:

- Basal levels affected by certain drugs
- Basal levels lowered by estrogen; raised by progesterone [sex hormonal cycle effects]. Test during anestrus.
- Thyroid levels are suppressed slightly (up to 25%) by corticosteroids, sulfonamides, and Phenobarbital
- Rabies vaccination within previous 45 days can elevate TgAA by ~ 25%

Q. Is T4 alone a sufficient screening test for canine hypothyroidism ?

A. No, T4 alone can give misleading results. It can overdiagnose hypothyroidism in the presence of non-thyroidal illness or use of certain drugs; underdiagnose hyperthyroidism in cats or from thyroxine overdosage; inaccurately assess adequacy of thyroxine therapy; and fail to detect autoimmune thyroiditis.

Q. How is freeT4 measured accurately ?

A. While endocrinologists may favor the equilibrium dialysis (ED) method for measuring free T4, because earlier analog methods were less accurate, newer technology offers other accurate methodology. These new assays are also faster and less costly .

Q. What is the diagnostic importance of measuring canine endogenous TSH ?

A. The cTSH test gives relatively poor predictability for primary hypothyroidism in dogs [~ 70%] vs people [95%], because the dog has another pathway to regulate the pituitary-

thyroid-hypothalamic axis via growth hormone. False negatives and false positives (i.e. discordant results) occur in ~ 30% of cases. New research just published has shown that unlike humans where growth hormone has minimal influence on thyroid regulatory control, the dog uses this additional important regulatory pathway along with endogenous TSH.

Q. When are blood samples drawn for testing dogs on thyroxine therapy ?

A. Blood samples should be drawn 4-6 hrs post-pill for BID Rx.

- Blood samples drawn 8-10 hrs post-pill for SID Rx (horses)
- Minimum testing needed is T4 and freeT4
- Thyroid antibody profile preferred; a must for thyroiditis cases

Q. Should thyroxine be given twice daily or will once daily suffice ?

A. Dividing the daily dose q 12 hrs avoids "peak and valley" effect

- Achieves better steady state over 24 hrs; half life 12-16 hrs
- Dosing once daily results in undesirable cardiovascular stress
- Dosing should be given directly by mouth rather than in food bowl

Q. Should thyroxine be given with or away from food ?

A. Because thyroxine binds to calcium and soy, it should be given at least an hour before or three hours after each meal, to ensure proper absorption.

Q. After discontinuing thyroxine therapy, how long a wait is needed to accurately assess thyroid function ?

A. A minimum of 6 weeks is needed off thyroxine before an accurate assessment of basal thyroid capacity can be made.

Q. Why do some dogs over-supplemented with thyroxine still test hypothyroid ?

A. Because the body can increase thyroxine turnover rate and excrete it faster to avoid thyrotoxicosis.

Q. Screening for canine autoimmune thyroiditis

A. Dogs taking thyroxine must be off this drug for at least 90 days to get accurate TgAA results for thyroiditis. Testing requires:

- Complete thyroid antibody profile
- Test intact females during anestrus
- Need T3AA, T4AA, TgAA; *not* just freeT4, TSH, TgAA
- OFA Thyroid Registry is only a limited panel
- About 8% of TgAA negative cases are T3AA and/or T4AA positive

Q. How is canine autoimmune thyroiditis treated ?

A. Thyroxine therapy will inhibit TSH output from the pituitary gland by negative feedback,which reduces further destruction of thyroid tissue by self-directed targeted lymphocytic attack.

- Treat <u>all</u> cases positive for T3AA and/or T4AA, or TgAA
- Don't wait until dog gets ill or has aberrant behavior
- If *only* low-grade TgAA positive , retest profile in 2-4 mos

- Treat with thyroxine BID; retest profile in 4-6 mos
- Always monitor with the full thyroid antibody profile

Q. Should dogs with autoimmune thyroiditis be used for breeding ?

A. No, regardless of the presence or absence of clinical or behavioral issues.

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

Q. What about testing older cats ?

A. Testing older cats is similar to older dogs.

- Basal thyroid levels in older cats should be lower than adults
- Other illnesses often lower T4, masking hyperthyroidism
- Minimum testing needed is T4 and freeT4
- FT4 by ED method can be high in cases of GI, renal, and liver disease