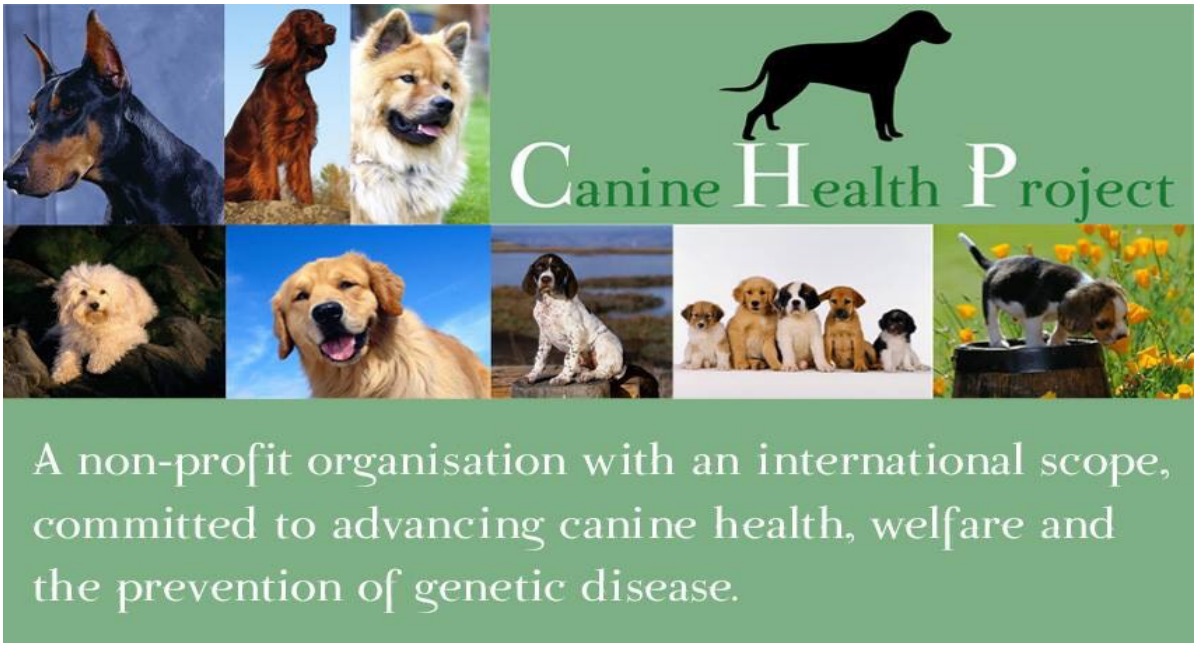

PRESERVING AND IMPROVING CANINE HEALTH AND LONGEVITY

W. Jean Dodds, DVM *
Trustee, Canine Health Project (CHP) Board of Directors †

Glossary of Terms

Phenotype, sum of an individual's traits we can see or measure, as well as the presence or absence of disease.
Genotype, an individual's unique genetic characteristics.

Genome, complete set of genes or genetic material (DNA) present in a cell or organism.

Gene, portion of DNA that is the basic unit of heredity.

MHC, major histocompatibility complex, set of cell surface proteins essential for the acquired immune system to recognize foreign molecules.

DLA/CLA, dog/canine leukocyte antigen part of the MHC.

GWAS, genome wide associations of gene expression.

This review outlines general and specific approaches to preserve and improve the overall health and lifespan of companion animals, and specifically the dog – although the same principles could apply to other companion species like cats and horses, even birds and pocket pets (1-4).

---

* Hemopet, 938 Stanford Street, Santa Monica, CA 90403;310-828-4804. FAX 310-453-5420;
E-mail: jeandodds@hemopet.org
† The Canine Health Project is a US registered 501(c) (3) charity. Federal ID # 81-1206300.

A. General Approaches

Promoting wholesome nutrition and exercise, while minimizing the need for pharmaceuticals, vaccines, and environmental exposures to herbicides, pesticides, air and water pollution is a large part of an overall preventive health care plan for pet animals (1-3).

Optimal nutrition includes feeding functional whole foods and supplements that act as so-called nutraceuticals, by applying the principals of nutrigenomics. Functional foods are nutritional ingredients, such as certain botanicals, amino acids, vitamins and phytonutrients (beneficial plant chemicals) that send signals to the body to trigger healthy expression of our genes (3).

Exercise, even if modest, is important to improve all aspects of physical and mental health, including memory for ourselves and pets, as is giving people of all ages and pets challenges to learn more and tasks to perform. Equally important are feeding omega-3 fatty acids to help improve brain health and function and slow the loss of cognitive function with aging (3).

1. Feeding Wholesome Foods and Supplements

Wholesome nutrition is key to maintaining healthy immune function and resistance to disease. The principles focus on the basic ingredients and trace vitamins, minerals, and immune-balancing nutrients that promote healthy endocrine and immune function as they apply to health and disease. Commercial foods ingested by animals on a regular basis may not be balanced in terms of major nutrients, minerals and vitamins, and some companies continue to add chemicals to the final product to enhance its stability and shelf-life. Nutritional deficiencies or imbalances as well as exposures to various chemicals, drugs and toxins present a continual immunological challenge which can suppress immune function, especially in those animals genetically susceptible to immune dysfunction (immune deficiency, autoimmunity, allergies) (3).

Genetic differences between individuals lead to quantitative variations in dietary requirements for energy and nutrient needs, and to maintain health. Also, genetic defects may result in inborn errors of metabolism that affect one or more pathways involving nutrients or their metabolites. While minimal and maximal nutrient requirements may have been established for most vitamins and trace mineral elements, optimal amounts for every individual cannot be assumed. Examples of important vitamin and mineral requirements in this regard include vitamin C, vitamin E and selenium, vitamin A, copper and vitamin B_{12}. Similarly, a wide variation occurs in the energy needs of dogs depending on their breed, age, sex, and size.

Nutritional factors that play an important role in immune function include zinc, selenium and vitamin E, vitamin B_6 (pyridoxine), and linoleic acid. Deficiency of these compounds impairs both humoral (circulating) as well as cell-mediated immunity. The requirement for essential nutrients increases during periods of rapid growth or reproduction and also may increase in geriatric individuals, because immune function and the bioavailability of these nutrients generally wanes with aging. As with any nutrient, however, excessive supplementation can lead to significant clinical problems, many of which are similar to the respective deficiency states of these ingredients. Supplementation with vitamins and minerals should not be viewed as a substitute for feeding premium quality fresh and/or commercial pet foods.

The exciting new field of nutrigenomics is an emerging science that studies the molecular relationships between nutrition and the response of genes in promoting health. Different diets elicit varying patterns of gene and protein expression as well as metabolite production; these are termed molecular dietary signatures (3).

Three Key Elements of Ideal Diets

- Variety: To obtain nutritional balance, all necessary food groups *must* be included, such as red meat, poultry (including fat), fish, eggs, organ meats (e.g., liver from beef, chicken, lamb, pork or bison), dairy (sheep and goat), fruits and vegetables. Jean – I'm not sure I'd put dairy in the essential foods category? Like that you don't include cow's milk, though.
- Nutrient-dense: Select fresh, wholesome foods packed with antioxidants, phytonutrients essential fatty acids and high quality amino acids.
- Whole foods: This means *real* food, including fresh meats, fish, eggs, dairy, fruits and vegetables—*not* rendered by-products and synthetic chemicals.

Functional Canine Superfoods

- Berries (e.g., blueberries, cranberries, but *not* strawberries)
- Coconut oil
- Curcumin (turmeric)
- Honeybee products, *raw* (not suitable for puppies)
- Medicinal mushrooms
- Milk thistle
- Omega-3 fatty acids
- Pomegranates
- Probiotics
- Spirulina (a prebiotic, mineral and vitamin supplement and phytonutrient)

A second subject of major concern revolves around the issues of pet over-vaccination and the widespread use of preventives for heartworm disease, fleas and ticks, with little regard to the true potential exposure risk nor the hazards of applying or giving these products to pets with chronic illnesses, aging or genetic predisposition to react adversely (1-4).

Biologics (vaccines and their adjuvants) and drugs have been associated with aggravating immune-mediated disorders, especially of the blood cells, liver and kidneys include the potentiated sulfonamides (trimethoprim-sulfa and ormetoprim-sulfa antibiotics), anticonvulsants, and the newer combination monthly heartworm, flea and tick preventives, although any vaccine or drug has the potential to cause side-effects in susceptible or genetically predisposed individuals (5-7).

2. Addressing Issues with Pet Vaccinations (5-7)

While routine use of pet vaccines has no doubt saved countless lives**, t**he challenge to produce effective and safe vaccines for the prevalent infectious diseases of humans and animals has become increasingly difficult. In veterinary medicine, evidence implicating vaccines in triggering immune-mediated and other chronic disorders (vaccinosis) is compelling. While some of these problems have been traced to contaminated or poorly attenuated batches of vaccine that revert to virulence, others apparently reflect the host's genetic predisposition to react adversely

upon receiving the single (monovalent) or multiple antigen "combo" (polyvalent) products given routinely to animals. Animals of certain susceptible breeds or families appear to be at increased risk for severe and lingering adverse reactions to vaccines.

Except where vaccination is required by law, all animals, but especially those dogs or close relatives that previously experienced an adverse reaction to vaccination can have serum antibody titers measured annually instead of revaccination. If adequate titers are found, the animal should not need revaccination until some future date. Rechecking antibody titers can be performed annually, thereafter, or can be offered as an alternative to pet owners who prefer not to follow the conventional practice of annual boosters. Reliable serologic vaccine titering is available from several university and commercial laboratories and the cost is reasonable. An in-house test for use in veterinary practices is also now available. Interpreting titers correctly depends upon the disease in question. Some titers must reach a certain level to indicate immunity, but with other agents like those that produce sterile immunity, the presence of any measurable antibody shows protection (5-7).

Alternatives to Current Vaccine Practices (5-7)

- avoid unnecessary vaccines or over-vaccinating.
- check vaccine titers instead.
- caution in vaccinating sick or febrile animals or those on pharmaceuticals, especially immunologically active drugs e.g. cyclosporine or corticosteroids.
- tailor specific minimal vaccine protocol for dogs/cats at risk for adverse reactions.
- start vaccination series later (9-10 wks, dog; 8 wks cat
- alert caregiver to watch puppy/kitten behavior and health after boosters.
- avoid revaccination of those with prior adverse event.

Finally, what does nearly two decades of experience with vaccine titer testing reveal? Published studies in refereed journals show that 90-98% of dogs and cats that have been properly vaccinated develop good measurable antibody titers to the infectious agent measured. In general, serum antibody titers to the "core" vaccines along with any natural exposures last a minimum of 7-9 years, and likely are present for life. This corresponds with what we see clinically as the number of cases and deaths due to these diseases has decreased in the vaccinated population. So, despite concerns of some colleagues, using vaccine titer testing to assess vaccine-induced protection will likely result in the animal avoiding needless and unwise booster vaccinations (5, 6). In fact, boosting immune animals has zero impact on improving immunity and could possibly be classed as unnecessary intervention.

3. Addressing Common Canine Disorders (1-4, 8-10)

Conditions such as **obesity** (a disorder stemming from chronic tissue inflammation and excess soluble carbs and excess poor quality calories) and its increased risk of diabetes, cancer, weight-related joint, bowel and other organ and tissue dysfunctions, **endocrine disorders (**especially thyroid and adrenal dysfunction), **immune dysfunction**, and **disorders of other organs** such as heart (cardiomyopathy), liver and kidneys (3, 4, 8-10).

a. Obesity (3)

Obesity is the leading health threat to companion dogs (and cats) and the number one preventable medical condition treated by veterinarians. No matter what else is done for the

companion animal, optimum health cannot be achieved if the animal is overweight or obese. Unfortunately, the obesity rate among companion animals is rising dramatically. In the 2012 National Pet Obesity Awareness Day Survey, the Association for Pet Obesity Prevention revealed that 52.5% of dogs and 58.3% of cats are overweight or obese, according to the veterinarians who treat them. This means that approximately 36.7 million dogs and 43.2 million cats in the USA alone are at increased risk of suffering from weight-related disorders, including diabetes, osteoarthritis, hypertension and many cancers.

Overweight dogs are at increased risk for many diseases, including:

- Cardiorespiratory diseases, including airway obstruction syndrome (e.g. brachycephalic breeds) and laryngeal paralysis.
- Endocrine disorders, including hyperadrenocorticism (Cushing's disease) and hypothyroidism.
- Functional alterations, such as decreased respiratory capacity, exercise intolerance, heat intolerance/stroke and decreased immune functions.
- Metabolic abnormalities, such as hyperlipidemia/dyslipidemia (high or abnormal blood lipid levels).
- Neoplasia, including transitional cell carcinoma of the bladder.
- Orthopedic disorders, such as osteoarthritis, anterior cruciate ligament rupture and intervertebral disk disease.
- Urogenital system conditions, including transitional cell carcinoma bladder.

Studies also show that overweight and obese dogs live an average of *two years less* than their ideal-weight counterparts.

b. <u>Thyroid Disorders</u> (1, 2, 4, 8-18)

Hypothyroidism is the most common endocrine disorder of dogs, and up to 90% of cases result from an autoimmune disease that progressively destroys the thyroid gland (autoimmune thyroiditis). Once more than 70% of the gland is destroyed by this process, classical clinical signs of hypothyroidism appear. Because the condition is heritable, it has significant genetic implications for breeding stock. Accurate diagnosis of the early stages of autoimmune thyroiditis offers important genetic and clinical options for prompt intervention (2).

Nutritional influences can have a profound effect on thyroid metabolism. The classical example is the iodine deficiency that occurs in individuals eating cereal grain crops grown on iodine-deficient soil. This will impair thyroid metabolism because iodine is essential for formation of thyroid hormones. However, too much iodine can be as harmful to thyroid function as too little. Commercial kibbles contain plenty of iodine, so caution is advised when adding extra supplements that include kelp and seaweed (16, 18). Moderation is the general rule with supplements (2, 3).

Another link has recently been shown between selenium deficiency and hypothyroidism. Cereal grain crops grown on selenium-deficient soil will contain relatively low levels of selenium. The selenium-thyroid connection has significant clinical relevance, because blood, but not tissue, levels of thyroid hormones rise in selenium deficiency. Thus, selenium-deficient individuals showing clinical signs of hypothyroidism could be overlooked on the basis that blood levels of thyroid hormones appear normal. The selenium issue is further complicated because the synthetic antioxidants still used in some foods to protect fats from rancidity can impair the

bioavailability of vitamin A, vitamin E and selenium, and alter cellular membrane function, metabolism and detoxification.

Iron and zinc also are important minerals in regulating thyroid metabolism. Vitamin D (as vitamin D3) is now called a co-hormone of thyroid function as it needs to be present at sufficient levels in all cells in order for the thyroid hormone to function at the cellular level. Be cautious about supplements as over- supplementation with vitamin D3 can lead to hypercalcemia.

Copper plays an important role in thyroid metabolism, especially in hormone production and absorption. Copper stimulates the production of thyroxine (T4), and helps control the body's calcium levels. Like any supplement, however, excessive supplementation with copper can lead to copper storage disease and eventually to liver failure.

Autoimmune thyroid disease can be triggered in genetically susceptible people and pets by eating glutens. Gluten-based grains (wheat, barley, rye, couscous, spelt, and kamut) contain a protein called gliadin, which mimics the thyroid hormone molecule leading to production of autoantibodies against the food, gut lining, and the thyroid gland (2, 3, 8).

c. Adrenal Dysfunction (8, 9)

Cushing's disease, or hyperadrenocorticism (19-21), is much more commonly seen in middle-aged dogs, especially females. One of the causes is a tumor of the pituitary gland, or, in 85% percent of cases, enlargement of the pituitary gland. The other 15 percent of cases are due to a cortisol-secreting adrenocortical cancer which frequently metastasizes. Another cause is the frequent administration of cortisone–containing drugs and topicals, a condition known as iatrogenic (induced) hyperadrenocorticism.

Addison's disease, or hypoadrenocorticism (22-26), has been reported in many individual dogs, although some breeds exhibit a greater incidence than the population as a whole. Addison's is an autoimmune hereditary defect although the mode of inheritance varies somewhat between affected breeds. The heritability and mode of inheritance of Addison's disease has been studied in the standard poodle, Nova Scotia duck tolling retriever and Leonberger. Addison's disease in the Portuguese water dog was recently shown to be inherited under the control of a single, autosomal recessive locus, and most closely resembles the condition in standard poodles.

d. Immune Dysfunction [Genetically Based Immune Disorders] (4, 8)

Autoimmune Diseases. Distinguishing between self- and non-self antigens is a vital function of the immune system and serves as a specific defense against invading microorganisms. Failure of this self-tolerance leads to "autoimmunity", which literally means immunity against self and is caused by an immune-mediated reaction to self-antigens. Susceptibility of the host to pathological autoimmune states has a genetic basis in humans and animals, although numerous viruses, bacteria, chemicals, toxins and drugs have been implicated as the triggering environmental agents. This mechanism operates by a process of molecular mimicry and/or non-specific inflammation, and is most often mediated by T-cells or their dysfunction. The resultant autoimmune diseases reflect the sum of the genetic and environmental factors involved. As stated in a landmark review "perhaps the biggest challenge in the future will be the search for the environmental events that trigger self-reactivity" (4).

The four main causative factors of autoimmune disease have been stated to be:

- Genetic predisposition
- Hormonal influences, especially of sex hormones
- Infections, especially of viruses
- Stress

The more commonly recognized autoimmune disorders in animals include those affecting: endocrine glands (1, 8), namely the thyroid (thyroiditis), adrenals (Addison's disease), pancreas (diabetes), and parathyroid; bone marrow and hematologic cells, marrow stem cells, erythrocytes, platelets, and leukocytes; muscle, myasthenia gravis, masticatory muscle myositis, polymyositis, and dermatomyositis; the eyes, keratoconjunctivitis sicca (dry eye), uveitis, pannus, and uveodermatologic syndrome (VKH); skin, pemphigus disorders, systemic lupus erythematosus, and vitiligo; neurologic tissue, immune-complex meningoencephalitis; the kidneys, immune-complex glomerulonephritis, and systemic lupus erythematosus; the joints, rheumatoid arthritis.

B. Specific Approaches [Applying Diagnostics to Identify Diseases & Disease Predispositions]

More specific approaches include applying the principles of general health profiling for both preventive and diagnostic assessments (1, 4, 8). Specific testing needs to be applied when selecting certain health disorders for review and analysis. For the more common heritable conditions, a comprehensive approach requires not only a review of the current status of phenotypic diagnostic testing but also implementation of genotypic testing at the molecular level. Genetic molecular testing involves genome wide associations (GWAS), specific major histocompatibility complex (MHC), dog leukocyte antigen (DLA) studies, and specific gene identification and sequencing of the gene loci and targeted genes involved in predisposing certain dog breeds to these diseases (8, 10-12).

1. General Health Profiling (1-4, 9)

Laboratory diagnostic tests play an important role along with a thorough physical examination and patient history in the overall evaluation of both human and animal patients.

Until recently, veterinary medicine focused on the diagnosis and treatment of disease once symptoms were manifested, when an owner brings the pet in for diagnosis and treatment. Fortunately this paradigm has changed significantly to the extent that more dogs and cats are diagnosed with conditions such as chronic renal failure today. Further, recent studies have shown the value of early intervention in greatly improving pet patient survival and life span.

2. Specific Testing for Health Disorders [See accompanying Research Proposal]

a. Thyroid Disorders (1-4, 8, 9-18)

The importance of breed type, age, health, and activity status should not be overlooked in assessing the thyroid function parameters of pet animals.

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
- Sight hounds have much lower basal thyroid levels

Screening for Canine Thyroid Dysfunction (1, 2, 4, 8, 27-31)

- Complete thyroid antibody profile preferred
- cTSH poorly predictive (~ 70%) compared to humans
- Age-and breed-specific norms essential for accurate diagnosis; reference lab ranges *not* based on age and breed type
- Basal levels affected by certain drugs (steroids, phenobarbital, sulfonamides, iodine)
- Basal levels lowered by estrogen; raised by progesterone [sex hormonal cycle effects]

b. Adrenal Disorders (8, 9, 19-26)

Steroid hormone profiles are indicated when other routine tests of adrenal function are negative (ACTH stimulation, low-dose dexamethasone suppression) and the dog still exhibits signs of Cushing's syndrome, indicating that the atypical form of the disease is present. Atypical Cushing's disease is diagnosed by measuring 17-hydroxyprogesterone level on the pre- and post-ACTH stimulation serum sample.

REFERENCES

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

2. Dodds WJ and Laverdure DR. "*The Canine Thyroid Epidemic*", Dog Wise Publ, Wenatchee, WA, 2011.

3. Dodds WJ, Laverdure, DR. "Canine Nutrigenomics: The New Science of Feeding your Dog for Optimal Health. Dog Wise Publ, Wenatchee, WA, 2015.

4. Dodds WJ. Complementary and alternative veterinary medicine: the immune system. Clin Tech Sm Anim Pract 17(1): 58·63, 2002.

5. Twark L, Dodds WJ. Clinical application of serum parvovirus and distemper virus antibody titers for determining revaccination strategies in healthy dogs. J Am Vet. Med Assoc 217: 1021-1024, 2000.

6. Dodds WJ. Vaccination protocols for dogs predisposed to vaccine reactions. J Am Anim Hosp Assoc 38: 1-4, 2001.

7. Dodds WJ. Efficacy of a half-dose canine parvovirus and distemper vaccine in small adult dogs: a pilot study. J Am Hol Vet Med Assoc 41: 12-21, Winter 2015.

8. Dodds WJ. Guest Editor's Introduction to Endocrinology. J Am Hol Vet Med Assoc 40; 8-21, Fall 2015.

9. Oliver JW. Steroid profiles in the diagnosis of canine adrenal disorders. Proc 25th ACVIM Forum, Seattle, WA, 471-473, 2007.

10. Happ GM. Thyroiditis - A model canine autoimmune disease. Adv Vet Sci Comp Med 39: 97-139, 1995.

11. 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.

12. Bianchi M, Dahlgren S, Massey J et al (17 authors). A multi-breed genome-wide association analysis for canine hypothyroidism identifies a shared major risk locus on CFA-12. PLoS ONE 10 (8): 1-16, 2015. doi:10.1371/journal.pone.0134720.

13. Dodds WJ. Behavioral changes associated with thyroid dysfunction in dogs. Proc Am Hol Vet Med Assoc 80-82, 1999.

14. Dodman NH, Aronson A., Cottam N., Dodds WJ. The effect of thyroid replacement in dogs with suboptimal thyroid function on owner-directed aggression: A randomized, double-blind, placebo-controlled clinical trial. J Vet Behav 8: 225–230, 2013.

15. 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.

16. Köhler BC, Stengel C, Neiger R. Dietary hyperthyroidism in dogs. J Sm Anim Pract 53:182-184, 2012.

17. 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.

18. Hasan-Sontas B, Schwendenwein I, Schäfer-Somi S. Primary anestrus due to dietary hyperthyroidism in a miniature pinscher bitch. Can Vet J 55:781-785, 2014.

19. Ruckstuhl NS, Nett CS, Reusch CE. Results of clinical examinations, laboratory tests, and ultrasonography in dogs with pituitary-dependent hyperadrenocorticism treated with trilostane. Am J Vet Res 63: 506-512, 2002.

20. Ristic JME, Ramsey IK, Heath FM, et al. The use of 17-hydroxyprogesterone in the diagnosis of canine hyperadrenocorticism. J Vet Int Med, 16: 433-439, 2002.

21. Frank LA, Davis JA, Oliver JW. Serum concentrations of cortisol, sex hormones of adrenal origin, and adrenocortical steroid intermediates in healthy dogs following stimulation with two doses of cosyntropin. Am J Vet Res 65:1631–1633, 2004.

22. Smallwood LJ, Barsanti JA. Hypoadrenocorticism in a family of Leonbergers. J Am Anim Hosp Assoc 31:301–305,1995.

23. Burton S, DeLay J, Holmes A, et al. Hypoadrenocorticism in young related Nova Scotia duck tolling retrievers. Can Vet J 38:231–234, 1997.

24. Oberbauer AM, Benemann KS, Belanger JM, et al. Inheritance of hypoadrenocorticism in bearded collies. Am J Vet Res 63: 643–647,2002.

25. Famula TR, Belanger JM, Oberbauer AM. Heritability and complex segregation analysis of hypoadrenocorticism in the standard poodle. J Small Anim Pract 44: 8–12, 2003

26. Oberbauer AM, Bell JS, Belanger JM, et al. Genetic evaluation of Addison's disease in the Portuguese water dog. BMC Vet Res 2:15, 2006.

27. 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.

28. 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.

29. 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.

30. Scott-Moncrieff JC, Azcona-Olivera J, Glickman NW, Glickman LT, et al. Evaluation of antithyroglobulin antibodies after routine vaccination in pet and research dogs. J Am Vet Med Assoc 221: 515-521, 2002.

31. Diaz-Espineira MM, Mol JA, Peeters ME, Pollak YWEA, et al. Assessment of thyroid function in dogs with low plasma thyroxine concentration. J Vet Intern Med 21:25–32, 2007.