The Saluki Welfare Fund

Registered Charity No. 1013212

Health Seminar

26 March 2000

The Playhouse
Playhouse Square
Harlow
Essex

Seminar Notes
of
Dr W Jean Dodds, DVM

CANINE THYROID AND AUTOIMMUNE DISEASE

(Genetics, nutrition, vaccine-related issue)

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Seminar Notes
From
The Saluki Welfare Fund
Health Seminar 26th March 2000

Hypothyroidism is the most common endocrine disorder of canines. A recent survey of breed clubs conducted by the American Kennel Club Delegates committee on health matters indicated that hypothyroidism was the most common health concern of the majority of purebred dog fanciers. An estimated 80% of the cases of canine hypothyroidism result from autoimmune (lymphocytic) thyroiditis. The heritable nature of this disorder poses significant genetic implications for breeding stock.

Accurate diagnosis of the early compensatory stages of canine autoimmune thyroiditis leading upto hypothyroidism affords important genetic and clinical options for prompt intervention and case management.

Although thyroid dysfunction is the most frequently recognised 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, (table 1). (next page).

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. Doctor David Panciera (1977) succinctly captured this situation in a recent editorial – " a healthy dose of sceptism should accompany interpretation of any thyroid function test, with evaluation of the history and physical examination findings being paramount to an accurate diagnosis".

Table 1. Clinical Signs of Canine Hypothyroidism

Alterations in Cellular Metabolism	
Lethargy Mental Dullness Exercise intolerance Neurologic signs – polyneuropathy - seizures	Weight gain Cold intolerance Mood Swings Hyperexcitablity Stunted growth Chronic infections
Neuromuscular Problems	
Weakness Stiffness Laryngeal paralysis Facial paralysis "Tragic" expression Incontinence	Knuckling or dragging feet Muscle wasting Megaesophagus Head tilt Drooping eyelids Ruptured cruciate ligament
Dermatologic Diseases	
Dry, scaly skin and dandruff Coarse, dull coat "Rat tail"; puppy coat Hyperpigmentation Pyderma or skin infections	Chronic offensive skin odour Bilaterally symmetrical hair loss Seborrhoea with greasy skin Seborrhoea with dry skin Myxedema
Reproductive Disorders	
Infertility Lack of libido Testicular Atrophy Hypospermia	Prolonged Interestrus interval Absence of heat cycles Silent heats Pseudo pregnancy
Cardiac Abnormalities	
Slow heart rate (bradycardia) Cardiac arythmias Cardiomyopathy	
Gastrointestinal Disorders	
Constipation Diarrhoea	Vomiting
Hematologic Disorders	
Bleeding Bone Marrow failure	Low red blood cells Low white blood cells Low platelets
Ocular Diseases	
Corneal lipid deposits Uvetitis Infections of eyelid glands (Meibomian gland0	Corneal ulceration Keratoconjunctivitis sicca or 'dry – eye' Vogt-Koyanagi-Harada syndrome
Other Associated Disorders	
IgA deficiency. Glycosuria Loss of taste / Loss of smell (dysosmia)	Other endocrinopathies – adrenal, pancreatic, parathyroid. Chronic active hepatitis

TESTS USED FOR DIAGNOSING THYROID DISEASE (TABLE 2)

Confusion remains over which diagnostic tests are the most specific and sensitive for identifying thyroid dysfunction especially in its early stages. The tests described below can also be used in other animal species, except where noted.

OLDER TESTS FOR THYROID DISEASE

1/ Total T4

Measuring serum T4 (or T3) is not a reliable means for diagnosis of thyroid disease in any species, because it can

- Over diagnose hypothyroidism
- Under diagnose hypothyroidism
- Fail to detect early stages of the compensatory disease and thyroiditis.

This test is greatly influenced (lowered) by the presence of nonthyroidal illness (NTI) and specific drug therapy (e.g. corticosteroids, anti-convulsants, sulfonamides, nonsteroidal anti-inflammatory agents). For these reasons, measuring serum T4 or T3 alone or as the only thyroid analyte of a health profile is not recommended.

2/ TSH response test

This dynamic test of thyroid function was considered the most reliable means of diagnosing clinical hypothyroidism, despite the fact that it only measure thyroid reserve and therefore fails to detect the early stages of thyroid disease. Today, the thyroid-stimulating hormone (TSH) response test is rarely performed because the bovine source of TSH used in the test is no longer marketed. An alternative dynamic test using TRH has recently been evaluated (see below).

CURRENT AND NEW TESTS FOR THYROID DISEASE

1/ Free (unbound) T4

Most veterinary diagnostic laboratories now offer comprehensive diagnostic tests for thyroid disease. The basic panel includes total T4, total T3, Free T4. Free T3, T3 autoantibody (T3AA) and T4 autoantibody (T4AA), which can be augmented with one or more of the newer tests described below. Accurate measurement of Free T4 is the most important component of this analysis because it represents the biologically active (unbound) fraction of the total T4. Appropriate methods include the solid-phase analog and the chemiluminescence assays and equilibrium dialysis (EQD), the latter being considered the "gold standard" against which the other two have been validated with a high degree of correlation (greater than 90%). By contrast liquid-phase analog Free T4 assays used routinely in human medicine are not reliable in animals (usually read too low). Even the EQD method of measuring Free T4 can yield misleading results, because increases to very high levels can occur in non-thyroidal disease, and, if the serum gets too warm, bound T4 can disassociate from its binding proteins thereby raising the unbound or free fraction.

On the plus side, Free T4 assays are less likely to be influenced by NTI and drug therapy. Reliable (validated) methods for measuring this analyte are the most useful for accurate diagnosis of canine hypothyroidism, especially in the early stages or in the presence of NTI.

2/Endogenous canine thyroid stimulating hormone (cTSH)

Validated first generation assays for cTSH are now available and have also been used in cats. In primary hypothyroidism, as serum free T4 levels fall, pituitary output of TSH rises in a regulatory, compensatory response. Elevated serum TSH levels are therefore another indicator of thyroid dysfunction. Recent experience with these tests, however, indicates about 20 – 38% discordancy

between expected and actual results in normal dogs as well as confirmed cases of hypothyroidism, or NTI. Furthermore, a recent study showed that it takes 40 separate measurements to accurately determine the basal TSH level of healthy dogs. With respect to NTI humans with chronic Renal disease (CRD) have a much higher incidence of true hypothyroidism than age-matched control people, although TSH levels using 3rd generation tests are also increased in other CRD patients that are euthyroid. Until these 1st generation TSH assays for animals are refined to improve their predictive capacity, they should not be relied upon as the sole or major basis for interpreting thyroid function status.

3/ Canine thyroglobulin autoanitbodies (TgAA)

An estimated 80% of cases of canine hypothyroidism result from heritable autoimmune (lymphositic) thyroiditis. In most of these cases, TgAA are present in the serum, whereas only about 20% of cases of thyroiditis have elevated circulating T3 and/or T4AA. Thus, the presence of elevated T3 and /or T4AA 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 generic counselling, as affected dogs should not be bred. A commercial TgAA test is available and has been validated with a representative number of field cases from the various breeds affected with autoimmune thyroid disease. It can give false negative results if the dog has received thyroid supplement within the previous 90 days, thereby allowing unscrupulous owners to test dogs whilst on treatment to obtain certification with health registries such as the orthopaedic foundation of America (OFA), thryroid registry [to be certified, the OFA requires normal values for Free T4 by EQD, cTSH, and TgAA, with retesting every 2 years]. Furthermore, false positive results may be obtained if the dog has been vaccinated within the previous 30 – 45 days, or in some cases of NTI.

4/ TRH response test

A new dynamic test of thyroid function, the thyrotropin-releasing hormone (TRH) response test has been promoted as a useful replacement for the TSH response test. However, inconsistent increases in T4 have been noted following TRH stimulation in normal dogs, and this test failed to distinguish hypothyroid from euthyroid dogs with dermatopathies. On the other hand, measuring the serum endogenous TSH level after TRH administration has recently been shown to help evaluate thyroroph function. It may be particularly useful in dogs with concurrent clinical signs of pituitary or hypothalamic disease (e.g. central vision impairement, circling, head pressing) to confirm secondary or tertiary hypothyroidism.

5/ Baseline thyroid profiles

The normal reference ranges for thyroid analytes of healthy adult animals tends to be similar for most breeds of companion animals. Exceptions are the sight hound 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 mid point 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 mid range or even slightly lower. As stated above, a complete baseline thyroid profile typically has total T4, total T3, Free T4, Free T3, T3AA and T4AA, and also can include cTSH and/or TgAA. The TgAA assay is especially important in screening breeding stock for heritable autoimmune thyroid disease (see below).

Table 2. Diagnosis of Thyroid Disease

Complete Basic Profile
T4, T3, FT4, FT3, T4AA, T3AA

Additional Tests
TSH, TgAA

Older Test (T4, T4 + T3)
Serum T4 and/or T3 alone are not reliable for diagnosis because –

- Over diagnose hypothyroidism
- Under diagnose hypothyroidism
- Fail to detect 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 serum free T4 levels fall, pituitary output of TSH rises

- Elevated TSH usually indicates primary thyroid disease
- 20 – 38% discordancy observed between expected and actual findings
- Published normal ranges may need revising upwards
- Affected by concomitant chronic renal disease
-

Canine TgAA
Thyroglobulin autoantibodies are present in serum of cases with lymphocytic thyroiditis

- Positive results confirm diagnosis
- 20% of cases have circulating T3 and/or T4AA
- Allows for early diagnosis and genetic counselling
- Needs validation in many breeds under field conditions

GENETIC SCREENING FOR THYROID DISEASE

The majority of canine thyroid disease is due to autoimmune thyroiditis, which is a familial disorder of inherited predisposition similar to that of human Hashimoto's disease. Therefore the baseline thyroid profile used for thyroid testing must include assays for thyroid AA (T4AA, T3AA and/or TgAA). This profile can be applied not only to clinical patients suspected of having thyroid disease, but also can be used for generic screening of apparently healthy relatives to evaluate their fitness for breeding. 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 generic 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 anestrous, any influence of sex hormones on baseline thyroid function will be minimised. 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 anestrous. In fact, genetic screening of intact females for other disorders such as Von Willebrand Disease (vWD), hip dysplasia, and wellness or reproductive check ups (vaginal cultures, hormone testing) is best scheduled during anestrous. 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, where indicated, to avoid the appearance or advancement of clinical signs associated with hypothyroidism. For optimal health, puppies and adolescents dogs under 15 – 18 months of age should have baseline thyroid levels in the middle to upper half of adult normal ranges. This pertains to young dogs because they are still growing and maturing, and so require higher levels of thyroid hormones to complete development. Similarly in older animals above 8 –10 years of age, body functions start to slow down and so baseline thyroid levels may be in the lower half of the range in the euthyroid individual. For healthy young adults used for performance or breeding, optimum thyroid function should be at least at the mid point of the established normal ranges for the particular laboratory used. Lower levels even in the absence of clinical signs compatible with thyroid disease, may be indicative of the early stages of thyroiditis, especially if they are found in relatives of dogs from families previously documented to have thyroid disease.

DIAGNOSING DIFFICULT OR EQUIVOCAL CASES

The difficulty in accurately diagnosing some cases of thyroid disease is compounded by the fact that certain patients with typical clinical signs of hypothyroidism have circulating levels of thyroid hormones within the normal range. Many will improve clinically when given thyroid medication, because blood levels of thyroid hormones may not reflect their cellular and tissue levels. A 6 – 8 week clinical trial of thyroid supplement given BID is safe and appropriate for such patients, and is followed by re-checking the complete thyroid profile 4 – 6 hours after the morning pill. Response to thyroid therapy is considered an appropriate justification to continue thyroid therapy along with annual check ups to adjust dosages as appropriate.

If an animal is receiving thyroid supplement and the basis for the original diagnosis is unclear, the clinician may elect to discontinue therapy and retest. In such cases, or when thyroid therapy is discontinued for any other reason, retesting is performed after another 6 weeks. (It takes this long for the pituitary-thyroid axis to be restored to full productive capacity after cessation of thyroid therapy.) To perform thyroid retesting before this period has elapsed would yield relatively low blood levels of thyroid hormones thereby biasing the interpretation in favour of hypothyroidism. Once the appropriate dose of thyroid supplement is established annual retesting is recommended.

CANINE AUTOIMMUNE THYROIDITIS

In recent years the prevalence of autoimmune (immune-mediated) disease has been increasingly rapidly in humans and animals. Scientists and clinicians have attributed this increase to such factors as generic and sex predisposition, nutritional influences, exposure to toxins and drugs, recent viral infections or use of polyvalent vaccines, and pituitary-thyroid axis imbalance. Today, an estimated 80% of cases of canine hypothyroidism result from anti-immune (lymphositic) thyroiditis. The heritable basis of this disorder poses significant generic implications for breeding stock, and affected animals should not be used for breeding.

This author has compiled and analysed 1060 canine cases of autoimmune thyroiditis between Jan 1995 and Jan 1999 (Table 3). Purebreds made up 96% of this group and both sexes were equally represented. The mean age at diagnosis was 4.4 years (range 2.6 – 12.0); mean levels of T3AA and T4AA were 6.0 (range 1.2 – 22.2) and 1.6 (range 0.6 – 8.8), respectively, with normal levels being below 2. The most prevalent circulating thyroid AA was against T3 (996/1060 cases; 94%) and 254/1060 (24%) had combined T3 and T4 AA. In a few instances (51/723; 7%), the dogs demonstrated only T4AA. The 12 breeds most affected were the Golden Retriever (209 cases), Shetland Sheepdog (124 cases), American Cocker Spaniel (68 cases), Boxer (51 cases), Doberman Pincher (42 cases), Labrador Retriever (40 cases), German Shepherd (19 cases), Akita (15 cases), Irish Setter (14 cases), English Setter (13 cases), Old English Sheepdog (12 cases), and Collie (10 cases), although many other breeds and mixed breeds were also represented (Table 3). All of these dogs also would be expected to have elevated levels of TgAA. In fact, all 75 dogs selected for testing at random from this case cohort had high TgAA levels.

Table 3. Summary of Cases with Autoimmune Thyroiditis January 1995 – January 1999

Total # Of Dogs	Breed	Sex			Mean Age	Mean T3AA	Mean T4AA	Rank Popularity			
209	Golden Retriever	102	96	11	4.2	5.7	1.8	4	4	4	2
124	Shetland Sheepdog	64	57	3	4.6	6.6	1.8	13	14	15	15
68	Cocker Spaniel (American)	28	40	0	5.0	6.4	1.4	7	8	8	13
51	Boxer	26	25	0	3.8	8.2	1.6	15	13	13	12
42	Doberman Pinscher	17	25	0	3.4	5.3	1.7	18	20	22	22
40	Labrador Retriever	17	22	1	5.2	5.2	1.4	1	1	1	1
19	German Shepherd	5	13	1	5.0	5.4	1.9	3	3	3	3
15	Akita	7	4	4	2.8	7.9	1.7	35	35	34	36
14	Irish Setter	5	9	0	3.0	7.5	1.9	56	57	59	60
13	English Setter	3	8	2	4.6	4.7	1.2	83	87	86	91
12	Old English Sheepdog	4	5	3	4.1	9.8	1.9	55	56	60	65
10	Collie	4	6	0	2.8	3.3	1.3	29	29	30	31
9	Poodle	6	3	0	6.7	3.4	1.3	6	6	5	7
7	Skye Terrier	3	4	0	4.9	2.7	1.1	133	135	130	130
7	Bull Mastiff	1	4	2	3.2	6.7	1.0	53	52	53	52
6	Scottish Terrier	4	0	1	1.7	9.8	1.6	41	41	43	42
6	Siberian Husky	1	5	0	7.0	7.6	1.6	17	17	16	18
43	Mixed Breeds	18	25	0	5.2	5.8	2.2				
269	Purebreds (<5 dogs)	109	150	10	4.7	4.7	1.5				
96	Unknown Breed	58	38	0	3.8	7.5	1.6				
1060	Total Number of Cases				4.4	6.0	1.6				

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 recognised in the canine, 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 non-endocrine systems become involved in a systemic immune-mediated process. This multiple endocrinopathy often occurs in patients with underlying autoimmune thyroid disease (hypo- or hypothyroidism) 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 haemolytic anaemia (AIHA), idiopathic thrombocytopenic purpura (ITP), chronic active hepatitis, and immune-complex glomerulonephritis (systemic lupus erythematosus; SLE). The most commonly recognised polyglandular endocrinopathy of dogs is Schmidt’s syndrome (thyroiditis and Addison’s Disease). Dog 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). 7 of the most recent 103 cases had 2 or more endocrine disorders, and 101 of the 108 cases where pedigrees were available a familiale 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 BEHAVIOUR AND THYROID DYSFUNCTION

An additional note worthy clinical finding in dogs affected with thyroid or polyglandular autoimmune disease has been the sudden or progressive onset of aberrant behaviour including aggression, submissiveness, shyness, fearfulness, passivity, seizure disorder, excitability, sensitivity to noise, anxiety, irritability, compulsiveness, chewing, moodiness, lethargy, depression, and unstable temperament. A similar association between behavioural and psychological changes and thyroid dysfunction has been recognised in humans since the 19th Century, and more recently has been noticed in cats with hypothyroidism. In a recent human study, 66% of patients with attention deficit/ hyperactivity disorder were found to be hypothyroid, and supplementing their thyroid levels was largely curative. Tables 4-5 summarize results of complete thyroid diagnostic profiling on 634 canine cases of aberrant behaviour, compiled by this author in collaboration with Dr's Nicholas Dodman, Linda Aronson, and Jean Denapoli of Tufts University School of Veterinary Medicine, North Grafton MA. 90% (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. 63% 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 behaviour were aggression (40% of cases), Seizures (30% of cases), fearfulness (9% of cases), and hyperactivity (7% of cases); some dogs exhibited more than one of these behaviours (Table 5). Within these 4 categories, thyroid dysfunction was found in 62% of the aggressive dogs, 77% of seizuring dogs, 47% of fearful dogs, 31% of hyperactive dogs. Outcomes of treatment intervention with standard twice-daily doses of thyroid replacement were evaluated in 95 cases. Of these, 58 dogs had greater than 50% improvement in their behaviour as judged by a pre defined 6 point subjective scale (34 were improved by greater than 75%) and another 23 dogs had greater than 25 but less than 50% improvement. Only 10 dogs experienced no appreciable change, and 2 dogs had a worsening of their behaviour. When compared to 20 cases of dominance aggression treated with conventional behaviour 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 euthanised 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 behaviour.

Table 5.
Most Commonly Represented Breeds with Thyroid Dysfunction and Aberrant Behaviour*

Table 4.
Canine Aberrant Behaviour*

Total No. Cases	Purebreds	Mixed Breeds	Thyroid Dysfunction	Euthyroid
634	568	66	401	233

* Mean Age = 3.7 years (Range 0.5 – 12 years). Median Age = 2.5 years

Breed	Thyroid Dysfunction 401/634 (63%)	Aggression 251/634 (40%)	Seizures 189/634 (30%)	Fearful 55/634 (9%)	Hyperactive 42/634 (7%)
Golden Retriever	50/73	12/16	22/30	4/6	1/6
German Shepherd	34/53	10/22	14/16	3/7	2/2
Akita	27/38	24/33	0/1	0	0/2
Labrador Retriever	8/30	6/11	12/16	2/15	0/3
Shetland Sheepdog	14/25	3/6	2/3	2/4	3/3
Collie	8/9	0	7/7	0	0
English Setter	4/6	1/1	0	1/3	½
Other purebreds	217/334	89/135	72/93	10/15	5/16
Mixed Breeds	39/66	11/27	16/23	4/5	1/8
Totals	401/634 (63%)	156/251 (62%)	145/189 (77%)	26/55 (47%)	13/42 (31%)

*Some dogs had more than 1 abnormal behaviour. Numerator = Thyroid dysfunction Denominator = Aberrant behaviour. Total = 634 cases; 72 dog breeds represented.

VON WILLEBRAND'S DISEASE AND THYROID METABOLISM

An acquired form of Vwd associated with hypothyroidism has been recognised in humans and several dog breeds, particularly the Doberman Pincher but also the Shetland Sheepdog, Rottweiler, and Golden Retriever. The relationship is complex and has yet to be fully elucidated at the molecular level. Clearly, not all humans or dogs with hypothyroidism have low levels of Von Willebrand factor (vWF), and not all those with low vWF have hypothyroidism. Asymptomatic vWF carriers often express a bleeding tendency in midlife when they become hypothyroid. Development of hypothyroidism apparently exacerbates their original trait and compromises haemostasis. In our own studies, the average age of onset of bleeding signs in Doberman Pinchers was over 4 years. The question appears to relate to the metabolic regulation of vWF biosynthesis and secretion rather than plasma levels or even platelet adhesiveness as measured by the mucosal bleeding time. In other breeds there are insufficient data at present to casually link vWD with hypothyroidism, despite the fact that most (45 or more) of the 59 or more breeds recognised to have vWD also suffer from familiale hypothyroidism. Therefore, the casual relationship established for several breeds does not necessarily apply to all affected breeds. In the Irish Wolfhound, more than half of the several hundred dogs screened to date at their annual national speciality shows have had low vWF levels and about one quarter have had low thyroid parameters. However, when these data were analysed there was a poor correlation between the two findings. Perhaps only those dogs that develop a particular type of thyroid disease (e.g. an autoimmune thyroiditis with elevated TgAA, or T3/T4 AA) are the ones most likely to express an acquired form of vWD as adults. The more definitive way to study this relationship has been in thyroidectomised individuals, and those with congenital hypothyroidism or clinically expressed vWD and hypothyroidism. Results of these studies support the fact that haemostatic function is altered when thyroid metabolism is impaired, although the mechanism is not understood. This defect in haemostatic function is rapidly corrected (within 12 – 24 hours) by giving standard doses of thyroid supplement. Regardless the debate about the nature and extent of this physiologic and pathologic relationship is likely to continue because of its underlying clinical significance.

OTHER FACTORS INFLUENCING THYROID METABOLISM 1/ NUTRITIONAL FACTORS

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. Iron and Zinc are also important minerals in regulating thyroid metabolism. Another important 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. While commercial pet food manufacturers compensate for variations in basal ingredients by adding vitamin and mineral supplements, it is difficult to determine optimum levels for so many different breeds of animals having varying genetic backgrounds and metabolic needs. 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 anti-oxidants used in 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. Because animals with autoimmune thyroid disease have generalised metabolic imbalance and often have associated immunological dysfunction, it is advisable to minimise their exposures to unnecessary drugs, chemicals and toxins, and to optimise their nutritional status with healthy balanced diets. Families of dogs susceptible to thyroid and other autoimmune diseases show generalised improvement in health when fed premium cereal-based diets preserved naturally with vitamins E and C rather than with the synthetic chemical antioxidants such as ethoxyquin, BHA, and BHT. Fresh vegetables cooked with Italian herbs and garlic, dairy products such as yoghurt or low fat cottage cheese, or meats such as lamb, rabbit, venison, chicken and turkey can be added as supplements.

2/ INFECTIOUS AGENTS AND VACCINES

Challenging the immune system of animals affected by thyroid disorders with infectious diseases or polyvalent modified-live vaccines has been associated with adverse effects in some cases. General recommendations are: to reduce exposure to contagious diseases and allergens; avoid booster vaccinations of geriatric patients, and during times of illness, recovery or relapses; use killed vaccine products, when these are available and space vaccines at least 10 –14 days apart to avoid excessive antigenic challenge; or perform serum antibody titration (vaccine titers) as an alternative to booster vaccination to assess the adequacy of existing immune memory. In some affected dog families, use of polyvalent combination modified-live vaccines has apparently induced seizure disorders AIHA and/or ITP, bone marrow failure, acute fevers, and renal failure leading to amyloidosis, lameness, stiffness and arthritic pain to the extent that many of these dogs cannot stand up or move. This is just one example of the general principle to avoid unduly challenging susceptible animals during periods of rapid growth, hormonal change or stress events.

3/ DRUGS

Many drugs are known to affect thyroid function. They produce their effects by various mechanisms including

- Decreasing TSH secretions (e.g. steroids, dopamine)
- Decreasing thyroid hormone secretion (e.g. sulfonamides, lithium, iodide, amidarone)
- Decreasing T4 absorption (e.g. sucralfate, ferrous sulphate, aluminium hydroxide)
- Decreasing T3 and T4 transport in serum (e.g. oestrogens, mitotame, androgens, steroids, furosemide, salicylates)
- Increasing T3 and T4 metablosim (e.g. phenobarbitol, rifampin, phenytoin, steroids, amidarone)

4/ CHEMICAL (XENOBIOTIC) EXPOSURES

The ability of the body to handle chemical exposures to such compounds as polybrominated biphenyls, phenolics, including bioflavinoids, chlorinated compounds, goitrogens, and the detoxification of drugs and chemicals via cytochrome P_{450} pathways all depend upon adequate and sustained thyroid function.

THYROID THERAPY

The mean residence time of thyroid hormone in companion animal species varies from 12 – 16 hours. The rationale for supplementing hypothyroid animals twice rather than once daily, is partly based on this fact, but also is supported by the improved clinical response observed when the daily metabolic requirement is split into two equal doses. Most clinicians use synthetic L- thyroxine, preferably of brand name, rather than generic source. The standard dose is 0.1 mg per 10 lbs or 4.5 Kg BID for dogs, other than giant breeds or sighthounds, in which case the dosage is reduced to 0.1mg per 15 – 20 lbs or 6.5-9 kg BID. For geriatric dogs, the lower dosage is recommended because of their less active metabolism. Generally, even giant breed dogs are started at no more than 0.8 mg BID and then increased from there, if needed. Post pill thyroid monitoring should be performed after a 6 – 8 week therapeutic trial, taking the sample 4 – 6 hours after the morning dosage, and then repeated annually.

Typically the need for thyroid replacement is life long, although an occasional human or canine case can go into complete remission. Holistic practitioners may opt to treat thyroid disorders with natural glandular products and/or to boost thyroid function with nutritional and herbal support. In this authors experience thyroid or pituitary-thyroid combination glandulars have given uneven clinical responses, especially in larger dogs. For this reason, we prefer to use synthetic L-thyroxine BID to regulate thyroid function, and then use complementary approaches to control related or concurrent clinical problems. These include minimising and detoxifying environmental exposures; balancing dietary trace mineral, vitamin and fatty acid need; and feeding hypoallergenic diets along with digestive support.

TREATING REFRACTORY CASES OR CIRCULATING THYROID AUTOANTIBODIES

1/ USE OF T3 SUPPLEMENT

When clinical signs of thyroid disease are only partially or poorly ameliorated by supplementation with L-thyroxine at the standard dosages listed above, combination therapy is often successful. In these cases, the T4 supplement may be poorly converted to T3 by the liver and the other tissues, so that addition of a T3 supplement or a thyroid glandular product containing both T3 and T4 is indicated. The typical treatment regimen includes the full dosage of T4 supplement given BID plus 1Ugm per llb or 2.2 Ugm per kg of T3 supplement (Cytomel r) given BID or TID. This combination has been particularly beneficial for patients with concomitant liver disease or dysfunction, because the liver is the primary site of conversion of T4 to T3 and so conversion may be impaired in the presence of the hepatocellular disease. The other situation applies to patients on anticonvulsant therapy for seizure disorders. Providing a low dosage of T3 supplement helps maintain adequate levels of T3 in the central nervous system and may assist in raising the seizure threshold. Experience with this approach indicates that the addition of T3 supplement may allow the dosage of anticonvulsant required for seizure control to be lowered or even discontinued. A second advantage could be to offset any adverse effects of anticonvulsants on liver metabolism, which could impair hepatocellular conversion of T4 to T3.

2/ REVERSAL OF THYROID AUTOANTIBODIES

For patients with circulating T4 and/or T3 AA, even in the absence of typical clinical signs of thyroid disease, the rationale for thyroid supplementation is to interrupt the progression of thyroiditis and reverse the stimulus for production of thyroid AA. Expreince with over 100 cases followed periodically for up to 6 years indicates that it takes between 5 – 7 months of thyroid replacement to cause levels of circulating thyroid AA to wane progressively and then disappear. Occasional cases never completely reverse AA production. We do not recommend using these animals in a breeding program, because of the heritable nature of thyroiditis. Supplementation with L-thyroxine is believed to reverse the production of circulating thyroid AA by either inducing immune tolerance and/or by negative feedback inhibition of TSH and its effects on the TSH receptor. In a typical case, the standard therapeutic dose of L-thyroxine is given BID for 8 – 12 weeks. At that point the complete baseline thyroid profile is measured again to determine whether thyroid levels are waning. Patients rarely need retesting prior to this time because the presence of thyroid AA interferes with the accurate measurements of T3 and/or T4, and so little is gained from the additional cost to the client of rechecking at an earlier time point. Other clinical problems, such as pruritic skin disease, are treated with conventional or alternative approaches.

VACCINE-RELATED ISSUES

1/ CHANGING VACCINE PROTOCOLS

The 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 monovalent or polyvalent products given routinely to animals. Animals of certain susceptible breeds or families appear to be at increased risk for severe and lingering vaccine reactions. Recent studies also implicate vaccines in triggering autoimmune thyroiditis. The onset of adverse reactions to conventional vaccinations (or other inciting drugs, chemicals, or infectious agents) can be an immediate hypersensitivity or anaphylactic reaction, or can occur acutely (24 – 48 hours afterwards), or later on (10 – 30 days) in a delayed type immune response usually caused by immune-complex formation. Typical signs of adverse immune reactions include fever, stiffness, sore joints and abdominal tenderness, susceptibility to infections, central and peripheral nervous system disorders or inflammation, collapse with autoagglutinated red blood cells and jaundice, or generalised pinpoint haemorrhages or bruises. Liver enzymes may be markedly elevated and liver or kidney failure may accompany bone marrow suppression. Furthermore, recent vaccination of genetically susceptible breeds has been associated with transient seizures in puppies and adult dogs, as well as a variety of autoimmune diseases including those affecting the blood, endocrine organs, joints, skin and mucosa, eyes, muscles, liver, kidneys and bowel. The underlying genetic basis of these conditions places other littermates and close relatives at increased risk. Vaccination also can overwhelm the immunocompromised or even healthy host that is repeatedly bombarded with other environmental stimuli and is genetically predisposed to react adversely upon viral challenge. The recently weaned young puppy or kitten entering a new environment is at greater risk here, as its immature immune system can be temporarily or more permanently harmed. Consequences in later life may be the increased susceptibility to chronic debilitating diseases. As combination (polyvalent) vaccines contain antigens other than the clinically important infectious disease agents, some may be unnecessary, and their use may increase the risk of adverse reactions. Today's licensed leptospirosis bacterins afford little, if any, protection against the clinically important

fields strains and the antibodies they elicit last only a few months. Other vaccines, such as for Lyme disease, may not be needed, because the disease is limited to certain geographical area. Annual revaccination for rabies is required by some states even though USDA licensed rabies vaccine has a 3-year duration. Thus, the overall risk-benefit ratio of using certain vaccines or multiple antigen vaccines given simultaneously and repeatedly should be re-examined. It must be recognised, however, that the luxury of asking such questions today is presented only because the risk of disease has been effectively reduced by the widespread use of vaccination programs. Given this troublesome situation, what are the experts saying about these issues? In 1995, a landmark review commentary focused the attention of the veterinary profession on the advisability of current vaccine practices. Are we over vaccinating companion animals, and if so, what is the appropriate periodicity of booster vaccines? Discussion of this provocative topic generally leads to other questions about the duration of immunity conferred by the currently licensed vaccine components. In response to questions posed above, veterinary vaccinologists have recommended new protocols for dogs and cats. These include –

- Giving the puppy or kitten vaccine series followed by a booster at one year of age
- Administering further boosters in a combination vaccine every three years or as split components alternating every other year until …….
- The pet reaches geriatric age, at which time booster vaccination is likely to be unnecessary and may be unadvisable for those with aging or immunologic disorders.

In the intervening years between booster vaccinations and in the case of geriatric pets, circulating humoral immunity can be evaluated by measuring serum vaccine antibody titers as an indication of the presence of 'immune memory'. This latter phrase is more correct than 'protective immunity', because protection against disease means survival after challenge with the infectious agent and may not correlate with the serum antibody titer. Titers do not distinguish between immunity generated by vaccination is usually lower. Except where vaccination is required by law, animals that previously experienced an adverse reaction to vaccination or are at genetic or physiological risk for such reactions also can have serum antibody titers measured annually instead of revaccination. If adequate titers are found, the animal should not nee revaccination until some future date. Rechecking antibody titers can be performed thereafter, or can be offered as an alternative to pet owners who prefer not to follow the conventional practice of annual or semi-annual vaccination. Reliable serologic vaccine tittering is available from several university and commercial laboratories and the cost is reasonable. Relatively little has been published about the duration of immunity following vaccination, although new data are beginning to appear. In Sweden, an in-depth study found adequate titers against canine distemper virus (CDV) in 83% of a very large group of dogs vaccinated more than 4 years beforehand. Another recent study of dogs vaccinated 9 – 55.5 months previously found 73% of 122 dogs to have protective canine parvovirus (CPV) titers, and 79% of 117 dogs to be adequately protected against CDV. The authors concluded that annual revaccination should be maintained, because less than 90% of those vaccinated reached their criteria for protective titers. However, using similar criteria to assess vaccine antibody titers in a larger group of dogs, we came to a different conclusion (Twark and Dodds, in press, 1999). Our study evaluated 1441 dogs for CPV antibody titer and 1379 dogs for CDV antibody titer. Of these, 95.1% were judged to have adequate CPV titers, and nearly all (97.6%) had adequate CDV titers. Vaccine histories were available for 444 dogs (CPV) and 433 dogs (CDV) (**Table 7**). Only 43 dogs had been vaccinated within the previous year, with the majority of dogs (268 or 60%) having received a booster vaccination 1 – 2 years beforehand.

On the basis of our data, we concluded that annual revaccination is unnecessary. The vaccine histories obtained for this study indicate that the majority of serum samples were submitted at a time when annual booster vaccines typically would be given. When correlated with the high incidence of adequate immune memory found in this population of dogs, this study supports the belief that annual vaccination for CDV and CPV may not be necessary to provide adequate immune memory in the face of exposure to a particular virus. When an adequate immune memory has already been established, there is little reason to introduce unnecessary antigen, adjuvant and preservatives by administering booster vaccines. By tittering annually, one can assess whether a given animal's humoral immune response has fallen below levels of adequate immune memory. In that event, an appropriate vaccine booster can be administered. A multifaceted approach to furthering the recognition of this situation, along with alternative strategies for containing infectious diseases and reducing the environmental impact of conventional vaccines is clearly needed. As a beginning we can increase the interval between adult booster vaccinations from one to three years, except as required by law, and monitor serum antibody levels for assessing immune memory response to the clinically important infectious agents.

Table 6. Age and Titer Results for CPV and CDV				
Age in Years	Inadequate * CPV Titers	Adequate ** CPV Titers	Inadequate* CDV Titers	Adequate** CDV Titers
Unavailable	1	12	1	40
<1	5	33	3	21
1	5	84	5	82
2	7	87	1	88
3	4	123	2	121
4	9	132	2	134
5	7	113	1	112
6	7	111	1	113
7	2	119	2	117
8	11	134	2	136
9	0	86	1	81
10	4	90	5	85
>11	9	216	7	216
Total	71 /1441 (4.9%)	1370/1441 (95.1%)	33/1379 (2.4%)	1346/1379 (97.0%)

*IFA <1.5 **IFA > 1.5 ***oldest dog was 17 years of age (titers were adequate)

Table 7. Time between Last Known Vaccination and Antibody Titers of >1.5		
Interval Between Last Vaccine and Titer (years)	Number of dogs for CPV	Number of dogs for CDV
5	5	5
>3 - <5	44	41
>2 - <3	84	81
>1 - <2	268	263
<1*	43	43
TOTALS	444	433

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