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This is to certify that the

thesis entitled

CANINE PROGRESSIVE LYMPHOCYTIC THYROIDITIS
PATHOGENETIC AND GENETIC IMPLICATIONS

presented by

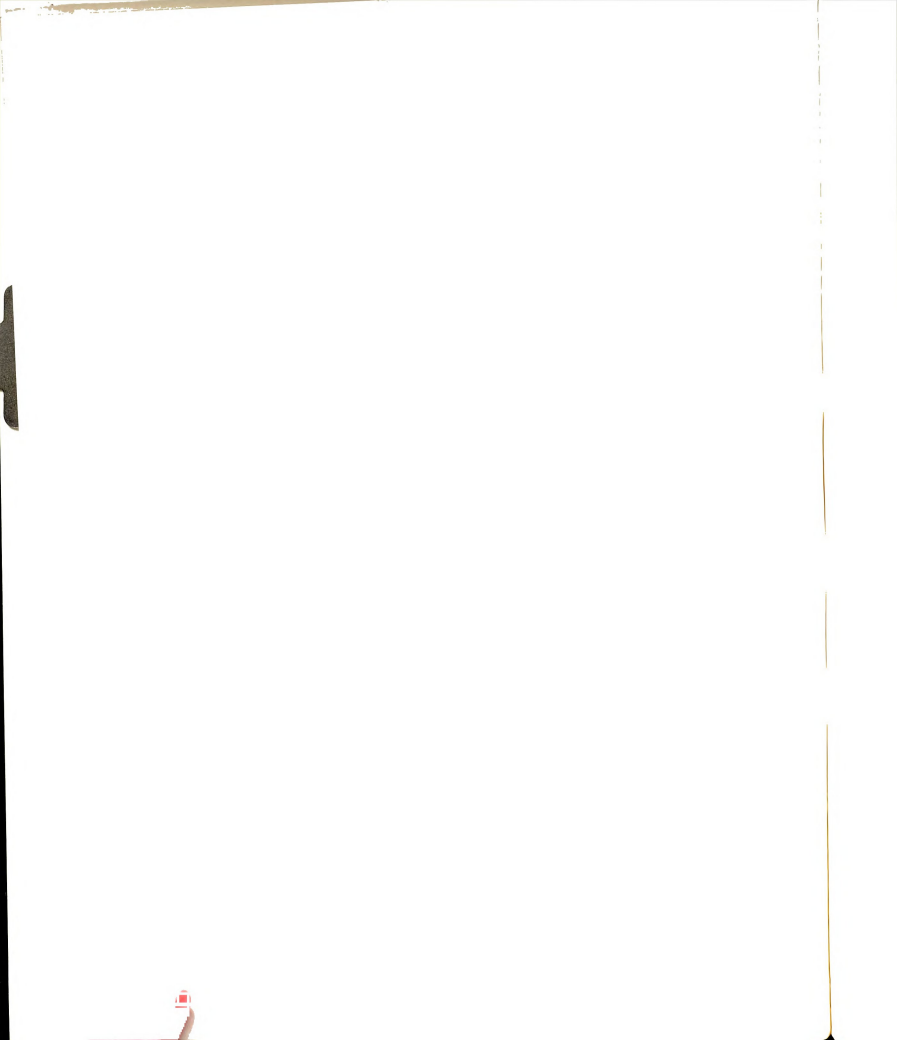
Dale H. Conaway

has been accepted towards fulfillment
of the requirements for

Masters degree in Pathology

George A Padgett
Major professor

Date Oct 22, 84



CANINE PROGRESSIVE LYMPHOCYTIC THYROIDITIS

PATHOGENETIC AND GENETIC IMPLICATIONS

By

Dale H. Conaway

A THESIS

Submitted to

Michigan State University
in partial fulfillment of the requirements
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MASTER OF SCIENCE

Department of Pathology

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ABSTRACT

CANINE PROGRESSIVE LYMPHOCYTIC THYROIDITIS
PATHOGENETIC AND GENETIC IMPLICATIONS

By

Dale H. Conaway

A six year study examining clinico-pathologic changes and genetic data has documented the progressive histomorphologic thyroid gland changes and a possible mode of inheritance involved in lymphocytic thyroiditis (LT) in a colony of related Borzoi dogs. This study encompasses three successive generations of this colony of dogs and uniquely documents the histopathologic progression from the initial thyroid gland degenerative lesions to end stage parenchymal atrophy.

The purpose of this study was to: (1) identify two LT positive animals from this colony of animals which were clinically hypothyroid, successfully reproduce the disorder and determine the frequency in their offspring and; (2) characterize the disease progression utilizing histopathologic, clinical and electron microscopic findings.

Preliminary evidence suggests that canine progressive familial LT eventually terminates in an entity commonly referred to as idiopathic follicular atrophy and that this disease in Borzoi dogs is inherited as an autosomal recessive trait.

TO CARLA JOY and HATTIE

two jewels of inspiration and encouragement

ACKNOWLEDGEMENTS

Special thanks to my major advisor and chairman of my graduate committee, Dr. George A. Padgett, for allowing me the opportunity to pursue a research career, a goal I have long endeavored to attain.

I greatfully acknowledge the "A-19" crew for moral support and help. To Dr. Tracie Bunton, I am deeply indebted for her excellent academic input and electron microscopic work.

To my wife, Carla Joy, who supplied the necessary spiritual, emotional and inspirational strength through some of the most critical and trying times of this thesis.

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LT

HD

T_3

T_4

TSH

CCH

ANA

Ig

LIST OF ABBREVIATIONS

LT	Lymphocytic Thyroiditis
HD	Hashimoto's Disease
T_3	Triiodothyronine
T_4	Thyroxine
TSH	Thyroid Stimulating Hormone
CCH	Chromic Chloride Hemaglutination
ANA	Antinuclear Antibody Assay
Ig	Immunoglobulin

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INTRODUCTION

A six year study examining clinico-pathologic changes and genetic data has documented the histomorphologic changes involved in lymphocytic thyroiditis (LT) and a possible mode of disease inheritance in a colony of related Borzoi dogs. The lesions observed included initial degenerative thyroid parenchymal changes which progressed to subacute inflammation with subsequent fibrosis and end stage thyroid gland disease.

This study encompasses three successive generations of this colony and uniquely documents the histopathologic progression from the initial thyroid gland degenerative lesions to end stage parenchymal atrophy.

Two litter mates which had LT were bred and the ten offspring produced have all been diagnosed as LT positive based upon thyroid biopsy. A wide range of thyroid gland pathology was demonstrated in this litter which were all affected by 2.5 years of age.

The purpose of this study was two fold; 1) identify two LT positive animals from this colony of Borzoi dogs which were clinically hypothyroid, successfully reproduce the disorder and determine the frequency in their offspring and, 2) characterize the disease in a time-course fashion, as it

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progressed, utilizing the clinical, thyroid histologic and electron microscopic findings to monitor the disease progression.

Histopathologic changes of six related animals were documented as well. The various stages of thyroid gland pathology, in animals ranging from two and one half to eight years of age, revealed a unique disease progression and provided histologic evidence for the pathogenesis of LT in the canine.

LITERATURE REVIEW

Chronic lymphocytic thyroiditis, or Hashimoto's Disease (H.D.), has been increasing in frequency in the U.S. making it the most frequent thyroid disorder in our population. One survey of 5,000 school children estimated a frequency of 1.3%.[27] Moreover, the disease probably accounts for most instances of idiopathic acquired hypothyroidism.[28]

It has become so prevalent in some areas that colloquialisms have been applied, such as Gulf Coast Thyroiditis.[29] The frequency of H.D. based on histological diagnosis of surgically removed thyroid glands rose steadily in the U.S. from .2% in 1930 to 10% in 1960. Some of this increase may be due to increased recognition, but evidence also supports a real and continuing increase in incidence.[1]

The incidence at autopsy is approximately .8%. It is four times more common in women than in men, and four times more common in whites than in blacks. In white females, a careful epidemiological study in Baltimore revealed a staggering incidence of 9% among thyroid operations and 2% at autopsy.[1]

Hashimoto's disease occurs most frequently between the ages of 30 and 50 years of age, but may occur during any period in life. It has also been identified as the most

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common cause of goiter in children, accounting for 50% of childhood goiters. The original description of this chronic disorder with its distinctive histologic appearance was given by Hashimoto in 1912.[30] Until the demonstration of circulating thyroid autoantibodies, H.D. could only be diagnosed with certainty by biopsy of the thyroid. The demonstration of high titers of circulating autoantibodies in most patients with H.D. has led to the use of the term autoimmune thyroiditis to describe the disorder.

The histopathological changes vary in type and extent, but in general, consist of a combination of a diffuse lymphocytic infiltration, followed by obliteration and degeneration of thyroid follicles with fibrosis. In most cases, there is destruction of epithelial cells and fragmentation of the follicular basement membrane. The remaining epithelial cells may be larger and show oxyphilic changes in the cytoplasm; these so called Askanazy cells are virtually pathognomonic of H.D. The interstitial tissue is infiltrated with lymphocytes which may form typical lymphoid follicles with germinal centers.[29,1]

The definative diagnosis of H.D. is based on histopathological findings, but several other features can lead to a clinical diagnosis. Symptoms commonly encountered include dysphagia, tenderness in the thyroid region and difficulty in breathing.

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The results of the common tests of thyroid function may be variable depending upon the stage of the disease. At first, the tests indicate the presence of thyroid hyperfunction without overproduction of metabolically active hormone. The thyroid I^{131} uptake is often increased and the Protein Bound Iodine (PBI) slightly elevated, but serum T_4 concentration is normal, and hence PBI-T_4 iodine difference is abnormally large.[29] At this stage, the patient is eumetabolic, as indicated by a normal basal metabolic rate. The glandular hyperfunction is reflected by hypersecretion of thyroid stimulating hormone (TSH) since it is suppressed by exogenous hormone.

With the passage of time, evidence of hyperfunction diminishes, and the Thyroid I^{131} uptake, PBI and serum T_4 concentration progressively approach subnormal levels. During this period, serum TSH may be increased, and the response to exogenous TSH may be subnormal, indicating diminished thyroid reserve. Ultimately, laboratory indices and the clinical state of the patient will reflect inadequate secretion of the hormone.[29,31] The diagnosis of H.D. can be confirmed by the finding of high titers of thyroid autoantibodies in the serum. In H.D., autoantibodies can be detected against four components of the thyroid: thyroglobulin, nonthyroblobulin colloid, microsomal antibodies and nuclear component.[11]

H.D. is now widely believed to be autoimmunologically mediated.[6,32,33,31] Involvement of the immune system in the

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pathophysiology appears evident even with simple clinical observation. Hypergammaglobulinemia will often be a common feature, along with lymphocytic infiltration of the thyroid gland.[14] In 1956, the first clear evidence demonstrating immunologic abnormalities in H.D. was reported. In that year Roitt et al discovered antibodies against thyroglobulin in the serum of patients with H.D.[34] At about the same time, Rose and Witebsky induced experimental autoimmune thyroiditis for the first time by injecting thyroid self-antigen mixed with Freund's adjuvant into rabbits.[35]

Part of the evidence favoring an autoimmune etiology of the disease has also been derived from the reports of familial aggregations of disease, or autoantibodies, or both, and the concurrence of thyroiditis with other putative autoimmune disorders.[32] Siblings of patients with H.D. have an increased frequency and higher titers of thyroid autoantibodies than do controls, as well as an increased frequency of thyroid disease.[32]

Other autoimmune diseases, Sjogrens syndrome, Addison's disease, acquired hemolytic anemia, and systemic lupus erythematosus, have all been reported to be more frequent in patients with H.D. than in other individuals.[36,37] Many experienced endocrinologists have noted in their patients an increased concordance of H.D. with such disorders as hypogonadism, diabetes mellitus, pernicious anemia, and idiopathic hypoparathyroidism.[1]

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The use of animal models in the study of H.D. has been well-documented. Since Witebsky and Rose[38] reported the experimental induction of thyroiditis in rabbits by active immunization, allergic inflammatory lesions have been produced in various organs of several lab animals by similar procedures. Experimental autoimmune thyroiditis has been produced in guinea pigs, dogs, chickens, rats, monkeys and mice. Spontaneous autoimmune thyroiditis has been reported in chickens,[39] rats,[40] and the dog.[2,24,19] These animal models have aided in the understanding of human organ-specific autoimmune diseases. The obese strain (OS) of chickens was developed about 18 years ago by selective breeding for the phenotypic trait of hypothyroidism.[41] The fact that the clinical symptoms were attributable to a spontaneous arising thyroiditis which was autoimmune in nature was recognized 5 years later.[39,42] In subsequent years the avian model was established as the closest counterpart to human H.D.

More recently, the dog has moved into focus as an even more viable animal model in the study of H.D. Most of the investigations in dogs with thyroiditis have been on colonies of laboratory beagles.[2,25,19] Tucker[25] detected a 16.2% incidence in thyroiditis in their colony of young adult beagles with males and females being equally affected. In this colony, thyroiditis was diagnosed by careful histological examination of the thyroid gland, since there were no clinical signs of hypothyroidism or macroscopic lesions.

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The focal lymphocytic thyroiditis observed in these laboratory beagles was not associated with significant alterations in thyroid function.

Lymphocytic thyroiditis in dogs appears to represent an example of an autoimmune disease with a pattern of inheritance similar to that observed with H.D. in humans.[2,43] Mizejewski et al[19] reported that thyroiditis in laboratory beagles was similar serologically to human thyroiditis. Antibodies were present against thyroglobulin, a second colloid antigen, and a microsomal antigen. They, unfortunately, were unable to find a positive correlation between the occurrence of the thyroglobulin antibody titers and the occurrence or severity of thyroiditis. Gosselin et al[11] demonstrated antibody titers against thyroglobulin in 48% of the pet dogs they examined at Ohio State University with primary hypothyroidism by utilizing the chromic chloride passive hemagglutination test (CCH).

An animal model of autoimmune thyroiditis is particularly attractive for a number of reasons. It could potentially increase our understanding of human forms of chronic thyroiditis and related autoimmune diseases of the thyroid. Much of the genetic and immunopathological data obtained from studies of animals could be translated directly or indirectly back to the human disease. Chronic thyroiditis itself serves as a prototype for the larger group of organ specific autoimmune diseases that represent a significant problem in human medicine. In this group are the several

autoimmune endocrine disorders, such as juvenile onset, insulin-dependent diabetes mellitus and idiopathic failure of the parathyroid and adrenal glands.

The endocrinopathies that affect the thyroid, adrenal, parathyroid, pancreatic islets, as well as gastric mucosa, all seem to be associated not only by a similar pathogenetic mechanism but also by an overlapping familial incidence, suggesting common genetic defects. Other organ-specific autoimmune disorders include the anti-receptor diseases such as myasthenia gravis, the syndrome of extreme insulin resistance and acanthosis nigricans, and forms of thyrotoxicosis due to the production of thyroid-stimulating antibodies. Finally, autoimmune thyroiditis provides a spectrum of animal models for the study of autoimmunity ranging from a spontaneous, genetically determined disease to an induced experimental reaction to a defined protein antigen, thyroglobulin.

PART I

PATHOGENETIC IMPLICATIONS

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MATERIALS and METHODS

Animals

The dogs used in this study consisted of 10 inbred Borzoi which were born July 11, 1981, and 6 closely related-dogs The dogs were vaccinated against distemper, leptospirosis, hepatitis and parvovirus.

Blood Collection

Blood was collected at monthly intervals from birth using 22 gauge, 1 1/2 inch needles and 10cc Klotz vacutainer tubes. The specimens were allowed to clot and placed in a centrifuge at 1000 RPM for 15 minutes. Serum was then drawn off and placed in 3 ml plastic test tubes and frozen at -20°C until analyzed.

Thyroid Hormone Assays and TSH Stimulation Tests

Serum T_3 and T_4 were determined at 30 day intervals by radioimmunoassay using the Becton-Dickinson Solid Phase Kit. The studies examined serum samples over a 24 month period from January 1982 to December 1983.

TSH stimulation tests were performed every 6 months to measure the thyroid's quantitative response. Comparing these results with normal controls we were able to ascertain

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thyroid function. Ten (IU) international units of bovine thyrotropin (bTSH) were administered intravenously. Blood samples were obtained before (pre) and 4 hours after (post) injection of bTSH. Pre and post serum samples were analyzed for T_3 and T_4 concentrations using radioimmunoassay.

Immunologic Studies

Thyroglobulin Autoantibody Assay

The thyroglobulin autoantibodies were evaluated by the chromic chloride hemagglutination (CCH) test. The CCH tests reported in this study were completed in the laboratory of Dr. Charles C. Capen using the procedure of Poston[23] as modified by Gosselin et. al.[11]

Antinuclear Antibody Assay (ANA)

Antinuclear Antibodies (ANA) were assayed using standardized kits purchased from Microbiological Research Corporation, Bountiful, Utah 84010.

Immunoglobulin Studies (Ig)

Canine immunoglobulins for IgA, IgG and IgM were quantitated using standardized kits purchased from Miles Laboratories, Research Product Division, Elkhart, Indiana.

Histologic Studies

Thyroid gland biopsies were performed on each animal in this study between the ages of 2 and 8 years of age. Tissue

sections were fixed in 10% neutral buffered formalin, embedded in paraffin, sectioned and stained with hematoxylin and eosin.

Electron Microscopic Studies

Small sections of tissue were fixed in paraformaldehyde/glutaraldehyde fixative in cacodylate buffer, which was adjusted to 550 mOsm and pH 7.4. They were then post fixed with 1.0% osmium tetroxide, dehydrated with a graded series of ethanol, infiltrated with propylene oxide and embedded in Araldite 502. Ultrathin sections were examined using a Zeiss 2 transmission electron microscope.

Data Analysis

The results were analyzed utilizing the student's t-test two-tailed, (unpaired) differences with a $P<0.05$ were considered to be significant.

RESULTS

Clinical Evaluation

In 1978, a study was launched to determine the cause of hypothyroidism in a colony of Borzoi dogs in Buckley, Michigan. All animals were owned by a Borzoi breeder and were part of the same kennel. The index case was a female who initially had low T_3 levels (0.59 ng/ml) and low T_4 levels (11.7 ng/ml) which over a period of 3 years fell to near zero ng/ml for both T_3 and T_4. Canine T_3 levels less than 0.70 ng/ml and canine T_4 levels less than 15 ng/ml are considered hypothyroid.[21] The index case was bred to an unrelated male from another kennel, and a litter of eight puppies was produced, one of which died perinatally. Of the remaining seven dogs, three exhibited a moderate to severe lympho-plasmacytic thyroiditis. These three dogs all began exhibiting clinical signs of hypothyroidism by two years of age (skin abnormalities, weight gain, low T_3-T_4 levels). The prospective mating of two of these affected littermates produced a litter of ten dogs, four females and six males.

Over a 24 month period starting in January of 1982, these ten littermate Borzoi dogs were evaluated for thyroid function, immunological abnormalities, and clinical signs of hypothyroidism. During this period, skin abnormalities in

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two of the littermates, were observed. Initially, these lesions began on the head and facial regions and subsequently spread to the trunk and limbs. The skin changes were grossly characterized by a dry, scaley, nonpuritic bilateral alopecia. Skin lesions were observed in the first dog at 1 year of age and at that time his T_4 levels were low normal (17.8 ng/ml) but his T_3 values were abnormally low (.46 ng/ml). The second animal developed skin abnormalities at 1 1/2 years of age. T_4 and T_3 levels at this time were 13.8 ng/ml and 0.66 ng/ml, respectively. Skin biopsies taken at this time from this animal were characterized by marked infundibular keratin plugging, follicular atrophy with basket weave orthokeratosis and atrophy of the sebaceous glands. No other significant skin lesions developed in the other eight littermates during this 24 month period.

The chromic chloride passive hemagglutination (CCH) test was utilized to detect the presence of thyroglobulin autoantibodies. A 1:40 antibody titer against thyroglobulin was detected in the paternal parent of the ten affected littermates at age two. A 1:20 antibody titer against thyroglobulin was detected in the serum of one of the ten affected littermates. All serum samples tested for antinuclear antibody (ANA) in this colony of ten were negative. Immunoglobulin (IG) levels were assayed with standardized kits (Miles Laboratories, Elkhart, Indiana). In five serum samples taken from each of the ten littermates, between October of 1982 and December of 1983, only one dog, at 2

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years of age, had abnormally high levels of IgG. Serum electrophoresis on this sample confirmed an elevation of the beta two and gamma one region of the gamma globulin peak.

Thyroid hormone levels of T_4 in affected dogs (combined means) showed a steady decrease in the first and second years of this study (Fig. 1a). These levels were compared to nine control Borzoi of the same age in both sexes. The T_4 levels in affected dogs were significantly lower when compared to the control group. Mean control T_4 levels were approximately 24±4.1 ng/ml. In affected dogs in the first twelve months, T_4 levels were 18.3±3.4 ng/ml ($P<0.025$) in the second twelve months they were 15.8±2.3 ng/ml ($P<.001$) (Fig. 1).

The mean T_3 values were significantly different from controls in the second twelve months only. When comparing control mean T_3 values (0.93±0.15 ng/ml) to the mean T_3 values in the experimental group during the second twelve months (1.23±0.15 ng/ml) the T_3 values in our experimental group were significantly higher, $P<0.015$. Thyroid gland output as measured via thyrotropin (TSH) stimulation was not significantly different in the two groups.

Histologic Examination

Histologic alterations were present in three successive generations of related Borzoi dogs. The thyroid gland lesions described present a unique documentation of the progression of the disease state in this family of dogs.

Thyroid gland changes for our purposes will be classified as degenerative-non-inflammatory, inflammatory and end-stage. The inflammatory lesions will be further divided into three catagories: acute, subacute and chronic.

A relatively normal thyroid gland, from a minimally affected dog illustrates (Fig. 2) variable sized follicles. A few follicles are smaller than normal; the follicular separation is artifactual. The degenerative but non-inflamed gland exhibited focal zones of follicular atrophy (Fig. 3).

Acute inflammatory changes were characterized by a subendothelial margination of neutrophils with medial thickening and proliferation (Fig. 4). Subacute inflammatory changes varied in their extent and intensity. Focal infiltration of lymphocytes and plasma cells, with local follicular destruction (Fig. 5) is also apparent. The most severe, subacute inflammatory change is characterized by a diffuse infiltration of lymphocytes, plasma cells and macrophages (Fig. 6). Lymphoid nodules were common with extensive parenchymal destruction and subsequent loss of normal architechture. Thyroid C cells (parafollicular cells) are more prominent in the more normal appearing follicles (Fig. 6-inset). A more chronic progression of this stage of subacute inflammation (Fig. 7) has fewer plasma cells with narrowed follicular lumens containing little or no colloid. Follicles present are lined by columnar follicular cells. This section was taken from the 3 1/2 year old maternal parent of the animals previously discussed.

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Electron microscopic studies paralleled histopathologic findings beginning with occasional individual lymphocytes observed migrating between epithelial cells (Fig. 8). Discreet electron dense deposits were present with the region of the basal lamina (Fig. 9). C cells in this stage of the disease appeared unaffected. The most severe stage of subacute thyroiditis (comparable to Fig. 6) was ultrastructurally characterized by plasma cells and lymphocytes in the interstitium, with occasional neutrophils. Plasma cells were situated perivascularly, or subjacent to the follicular basal lamina (Fig. 10).

Chronic LT was characterized by replacement of the thyroid gland with dense fibrous connective tissue and diffusely scattered lymphocytes. Follicular remnants were distorted, presumably due to subsequent fibrous connective tissue contraction around these structures (Fig. 11). This tissue biopsy was taken from the 3 1/2 year old paternal parent of the animals represented in Figures 2-6.

The apparent end stage of the progression of this disease was characterized by fewer follicles with extensive adipose connective tissue replacement of atrophied parenchymal structures (Fig. 12). There was still evidence of residual inflammatory cell infiltrates present in this tissue as well. The described changes were consistent with idiopathatic-follicular atrophy, as characterized in the canine.[12] This histopath section (Fig. 12) depicts the

changes present in the 8 year old maternal grandparent of the animals represented in Figures 2-6.

Fig 1a. Compares the control T_4 mean values with affected T_4 mean values. T_4 values in the control group were significantly higher ($P<.025$) than affected after 12 months and after 24 months ($P<.001$). Each vertical bar (I) represents one standard deviation from the mean.

T_4 ng/ml

T_3 ng/ml

Fig 1b. Compares the control T_3 mean values with affected T_3 mean values. T_3 values in the control group were significantly lower than T_3 values in the affected group after the 24 month period only ($P<.015$). Each vertical bar (I) represents one standard deviation from the mean.

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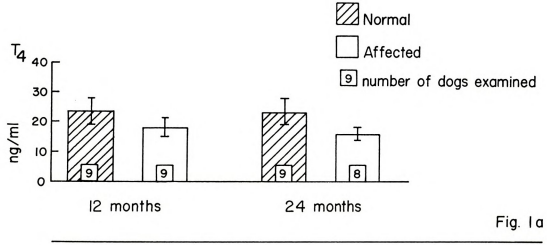

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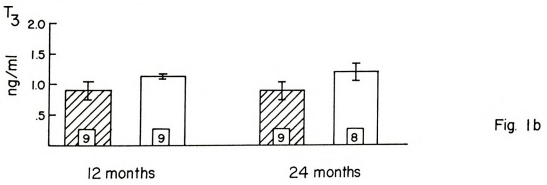

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Fig 2. Thyroid gland from 2.5 year old Borzoi dog with moderate decrease in the size of follicles.

Fig 3. Severely degenerated thyroid gland follicles (arrows) with follicular atrophy and narrowing of lumens (non-inflammatory). From 2.5 year old Borzoi dog.

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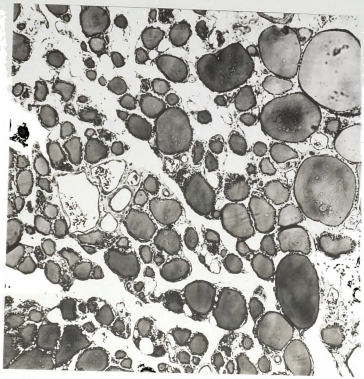

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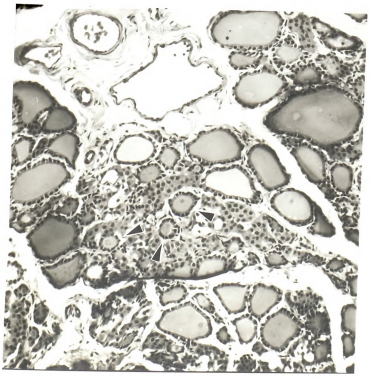

Fig. 3

Fig 4. Thyroid gland with acute vascular changes present. Neutrophils (arrows) are seen infiltrating endothelial walls (inset) with subsequent endothelial proliferation and thickening. From 2.5 year old Borzoi dog.

Fig 5. Focal infiltrates of lymphocytes and plasma cells in close proximity to a large blood vessel (V) causing local thyroid parenchymal destruction. From 2.5 year old Borzoi dog.

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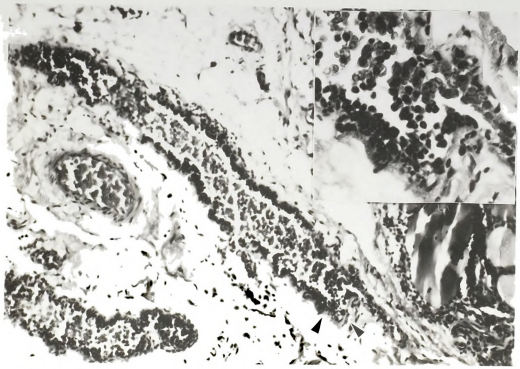

Fig. 4

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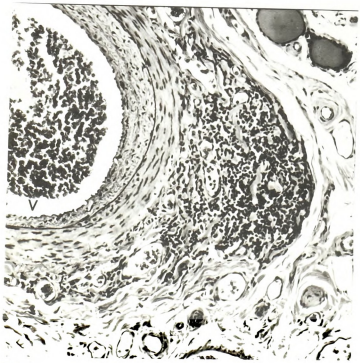

Fig. 5

Fig 6. Severe lymphocytic thyroiditis with diffuse infiltration of interstitium and parenchyma with lymphocytes, plasma cells, and macrophages. C cells (arrow) were more prominent (inset) in this stage of the disease. From 2.5 year old Borzoi dog.

Fig 7. Thyroid gland from 3.5 year old Borzoi dog with foci of inflammatory cells. Severe loss of thyroidal architecture. Decrease in follicular lumens (L) with absence of colloid.

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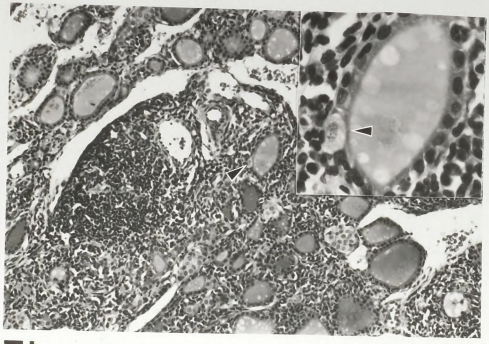

Fig. 6

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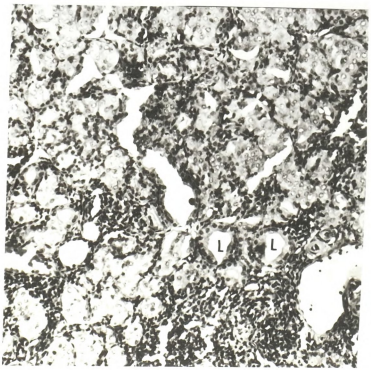

Fig. 7

Fig 8. Transmission electron micrograph. Lymphocyte (Ly) between follicular cells (Ep). Note also electron dense deposits (arrows). Follicular lumen (L), parafollicular cell (C).

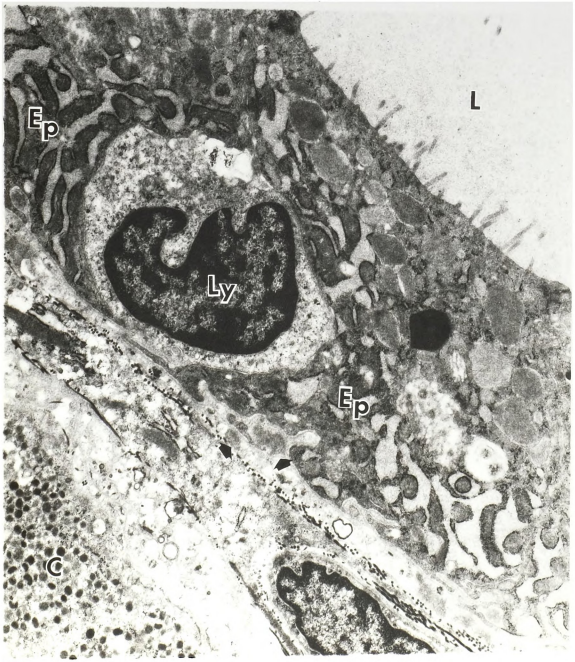

Fig. 8

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Fig 9. Transmission electron micrograph. Note electron dense deposit (arrows) in region of basal lamina. Follicular cell nucleus (Nu).

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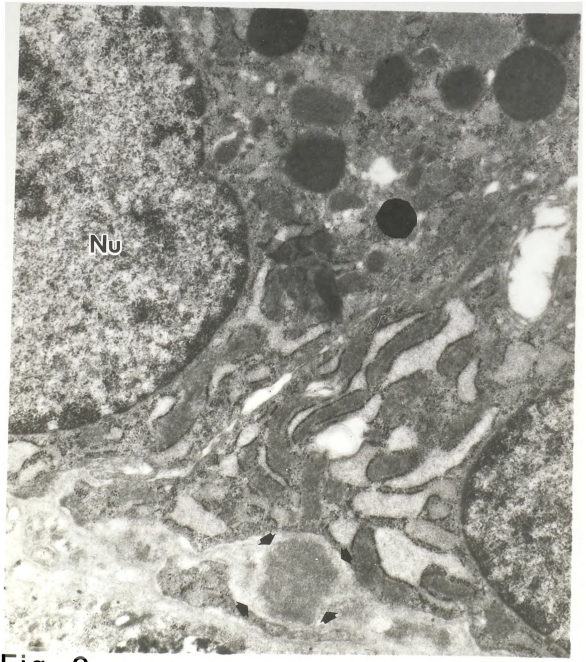

Fig. 9

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Fig 10. Transmission electron micrograph. Note plasma cells (Pl) adjacent to the follicular epithelial cell (Ep) basal lamina. vessel (v). Bar = 1 µm.

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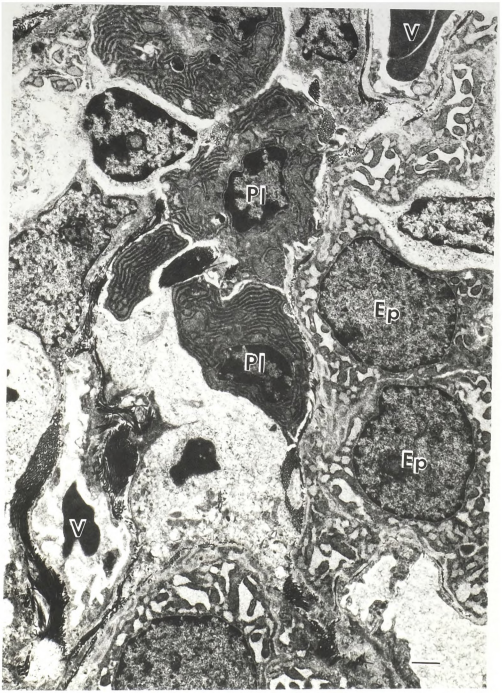


Fig. 10

Fig 11. Dense fibrous connective tissue replacement of thyroid gland parenchyma. Bizarre shaped lumens (L). No colloid present. Note scattered foci of chronic inflammatory cells. From four year old Borzoi dog. Paternal parent.

Fig 12. End stage thyroid gland disease. Adipose connective tissue (A) replacement of thyroid parenchyma. A few small follicles (arrows) remain. From eight year old Borzoi dog. Maternal grandparent.

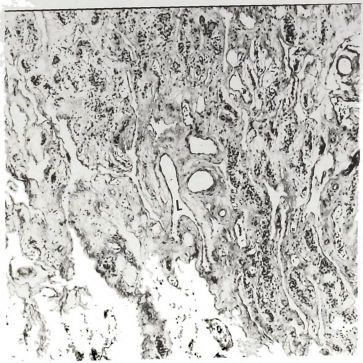
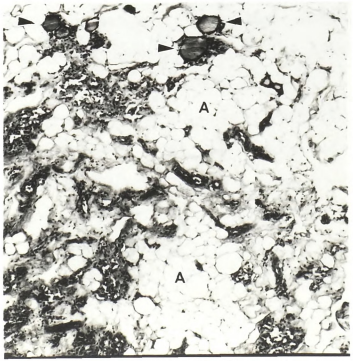


Fig. 11



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DISCUSSION

Clinical hypothyroidism in dogs associated with lymphocytic thyroiditis has been reported.[11,12,13,18] Our 6 year study documents progressive thyroid gland disease in a family of Borzoi dogs.

Similarities noted in our canine study and in human patients, with LT, were the presence of abnormally high gammaglobulin levels present in the most severely affected animal in the third generation pedigree. Elevated IgG levels are associated with antibodies being produced against more than one specific antigen.[14,15] Skin abnormalities were compatible with dermatopathology seen in patients with primary hypothyroidism in both man and dogs.[3,4,9]

Although the thyroid stimulating hormone tests were not significantly altered in the affected dogs when compared to age and breed matched controls, differences in T_3 and T_4 levels were significant. During the first 12 months a significant decrease in thyroxine (T_4) levels were seen in the affected dogs when compared to age-breed matched controls ($P<.025$). Decreases in T_4 levels during the second 12 months were even more significant ($P<.001$). These decreases were presumably due to progressive, primary thyroid gland disease.

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Triiodothyronine levels, during the second 12 month period, were significantly higher in our affected animals when compared to age-breed matched controls ($P<.015$). This increase in T_3 levels may be attributed to an abnormal conversion of free-T_4 (fT_4) to T_3. In one study, a significant inverse correlation was observed between serum T_4 levels and the conversion rate of T_4 to T_3, while a positive correlation existed between the conversion rate and T_3 production rates.[5] The latter findings are consistent with our T_3 observations. Increases in T_4 to T_3 conversion rates observed in hypothyroidism may reflect decreased T_4 disposal by nondeiodative pathways.[17] Alternatively, there may be an increased synthesis and secretion of T_3 by the thyroid gland. Manifestations of hyperthyroidism have been reported in the early phases of lymphocytic thyroiditis in about 50% of the human patients.[26] Transient hyperthyroidism in some human patients with lymphocytic thyroiditis appears to be compatible with the transient, unregulated discharge of thyroid follicle contents.[9,10] This transient phase of hyperthyroidism, could explain the increase in T_3 production rate in our colony, as reported in a human study.[8] Acute thyroiditis is one of the known thyroid disease states that does give rise to increased plasma T_3 levels, which rise before plasma T_4 levels.[16] The increase in T_4 to T_3 conversion rates, secretion and synthesis of T_3 in subacute thyroiditis has not been fully explained. These phenomena may represent compensatory mechanisms, seen in degenerative

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thyroid gland diseases, that facilitate the production of the most biologically active of the thyroid hormones (T_3). It is generally accepted that the effects of the thyroid gland are expressed primarily through the hormonal actions of T_3 which is derived principally from peripheral deiodination of T_4.[20] In humans, the thyroid gland in LT may be hyperfunctional, normal or hypofunctional depending on the stage of the disease.[1,10] Because of significant T_3 data observed in this study, the question relative to the diagnostic value of T_3 is raised. Our data appears to indicate that T_3 has diagnostic value in potential cases of primary hypothyroidism. In individual dogs, T_3 values fluctuated, as did T_4 values, until a significant amount of parenchymal destruction was evident. The data indicates that T_3 levels should be viewed relative to stage of the disease, T_4 levels, and T_4 to T_3 conversion rates.

The unique documentation of the histopathological changes observed in this family of dogs has provided evidence of the progressive steps involved in the pathogenesis of LT. Three successive generations, animals ranging from 2 years to 8 years of age, were biopsied and examined.

Our observations indicate that the first thyroidal alterations are subtle follicular changes (Fig. 2 and 3). At this stage there is follicular degeneration characterized by decrease in size and numbers of glandular elements, with collapse of the follicular lumens. These initial changes are degenerative, but noninflammatory.

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Inflammatory changes are observed in the next phase. Acute inflammatory changes are apparent in this manifest vasculitis (Fig. 4). Ultrastructural findings of basal laminal deposits (Fig. 10), along with acute vascular changes suggests immune complex involvement in this phase of the disease. When significant quantities of immune complexes accumulate, they tend to be deposited in blood vessels.[24] The formation of immune complexes via the combination of antigen with antibody has been determined to be the initiating step in a number of biological processes, one of which leads to neutrophil accumulation and the development of acute vasculitis (Fig. 4).[7,24]

Subacute inflammatory changes (Fig. 5,6,7) with subsequent parenchymal destruction appears as the disease progresses. Chronic inflammatory changes with fibrous connective tissue replacement of the thyroid parenchyma appears next (Fig. 11). Histologically, the end stage of this disease state manifest itself as idiopathathic follicular atrophy.[12] Idiopathic follicular atrophy appears much later on in the disease process seen here in an animal eight years old (Fig. 12).

The presence of lymphocytes migrating between follicular cells (Fig. 8) suggest the involvement of a cell-mediated hypersensitivity in this disease as well. Antigenic stimulation of T cells lead to the formation of effector cells with a variety of different specific functions.[6] Some T cells may differentiate into specific

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cytotoxic cells capable of destroying target cells bearing the sensitizing antigens.[24,17]

The thyroid gland changes depicted in figures 2-6 are from dogs of the same litter. These littermates were housed and maintained in the same environment. These histologic data then clearly illustrate the diversity in rates of progression of the disease in individual dogs. This phenomenon may be attributed to biological variations of the immune response in individual animals.

The results of this study indicated that familial canine LT progresses spontaneously from the initial lesions of follicular degeneration to inflammatory destruction of the thyroid gland. The end stage of this thyroid gland disease was characterized by an entity commonly referred to as idiopathic follicular atrophy.

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PART II

GENETIC IMPLICATIONS

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MATERIALS AND METHODS

Animals

Initially, a mating of 2 unrelated borzoi dogs (1 and 2, Fig. 1) produced 7 offspring (3-9, Fig. 1). Of these 7 dogs, one female (9, Fig. 1) was bred to an unrelated male (10, Fig. 1) and produced 8 puppies (11-18, Fig. 1). Dog 9 later developed LT and became the propositus for this study. The mating of 2 of the affected offsping (11 and 12) of the propositus resulted in a litter of 10 puppies. All dogs in this study were vaccinated for distemper, leptospirosis, hepatitis, rabies and parvo virus.

Thyroid Biopsy

Thyroid biopsies were performed on 18 animals (1-2, 9-14, 19-28, Fig. 1) between 2 and 8 years of age at the time of biopsy. Tissue sections were fixed in 10% buffered formalin, embedded in paraffin, sectioned and stained with hematoxylin and eosin.

Thyroid Hormone Assays

Serum T_3 and T_4 levels were determined at 30 day intervals by radioimmunoassay using the Becton-Dickinson solid Phase Kit. The studies examined the fourth generation serum

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RESULTS

A familial pattern of thyroid gland disease was documented in this group of Borzoi dogs. In order to characterize this pattern, we would like to briefly describe the matings and the resultant thyroid gland pathology. In 1978 a study was undertaken to determine the cause of hypothyroidism which developed in one dog (9) in a colony of Borzoi dogs in Buckley, Michigan. All animals were owned by a Borzoi breeder and were part of the same kennel. Dogs 1 and 2 were clinically normal with T_3-T_4 levels within the normal range. These dogs were both biopsied at 8 years of age and had severe thyroid gland alterations. These changes were characterized by follicular atrophy with connective tissue replacement of normal parenchymal structures and marked decrease or absence of normal colloid. Although degenerative changes were present in these glands, no inflammatory cells were present. The degenerative changes seen in dogs 1 and 2 are not like the inflammatory lesions present in the affected dogs and these changes may well be age related.

Of the seven dogs (3-9, Fig. 1) produced from the mating of dogs 1 and 2, only animal number 9 was available to us for evaluation as the other littermates had been sold and distributed across the country. Thyroid hormone levels

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in dog 9 fell to near zero ng/ml by age 6. Dog 9 was biopsied at 8 years of age and there was a moderate infiltration of inflammatory cells consisting of lymphocytes and plasma cells. There was prominent connective tissue replacement of glandular structures causing subsequent degenerative changes within the gland. These changes were consistent with idiopathic follicular atrophy, an entity described in dogs (Gosselin et al., 1981) and this change appears to be the end stage of LT in this colony of dogs (Conaway et al. in preparation for publication). Dog 10, an animal originating in an unrelated kennel, was clinically normal with no observed thyroid gland pathology. Three dogs, (11-13, Fig. 1) from the group of eight offspring produced by dogs 9 and 10, were LT positive with clinical signs of hypothyroidism. Animals 15-17 (Fig. 1) have remained clinically normal with no signs of thyroid gland disease. The status of dog 18 was not determined due to infant death (ID). Dogs 11 and 12, both had a moderate to severe lymphoplasmacytic infiltration of their biopsied thyroid glands.

The T_3 level in dog 11 during this time was 0.37 ng/ml and her T_4 level was 7.4 ng/ml. The T_3 level in dog 12 was 0.67 ng/ml and his T_4 level was 5.3 ng/ml during this period. Canine T_3 levels less than 0.70 ng/ml and canine T_4 levels less than 15 ng/ml are considered hypothyroid (Nesbitt et. al., 1980). Dog 13, a full sister, also had a severe, diffuse lymphoplasmatic inflammatory infiltrate,

with severe follicular atrophy and degeneration. Her T_3-T_4 levels were 0.57 and 7.3 ng/ml respectively, both levels being abnormally low.

The mating of 11 and 12 produced a litter of ten Borzoi pups, (19-28, Fig. 1) all of which eventually exhibited a broad range of thyroid gland pathology with varying degrees of lymphocyte and plasma cell infiltration and thyroid gland destruction by 2 1/2 years of age. These lesions ranged from a mild infiltration of lymphocytes, to a severe, diffuse lymphoplasmacytic inflamation with subsequent destruction of the thyroidal parenchyma (Fig. 2 and 3). Variations in T_3 and T_4 levels in these 10 dogs appear to correspond with the degree of inflammatory involvement and destruction of the thyroid parenchyma. A more detailed description of the thyroid gland pathology, biochemical, immunological and clinical abnormalities in this colony of dogs, is in preparation for publication.

Fig 13. Borzoi Pedigree through four generations.

Figure 13

Borzoi Pedigree Chart

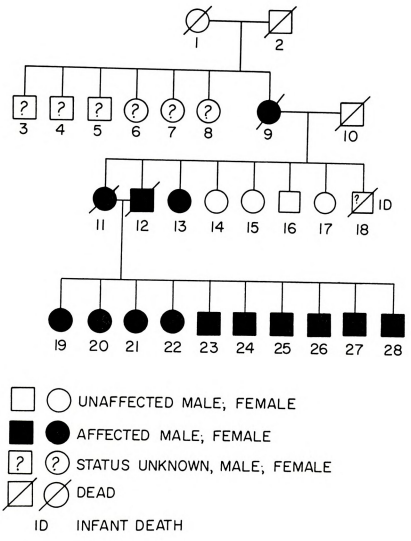

Fig 14. Severe lymphocytic thyroiditis with diffuse infiltration of interstitium by lymphocytes, plasma cells, and macrophages. Lymphoid nodules (arrows) were common.

Fig 15. Higher magnification depicts local destruction of thyroid parenchyma. Lymphocytes infiltrating follicular lumen (L) that have little colloid remaining.

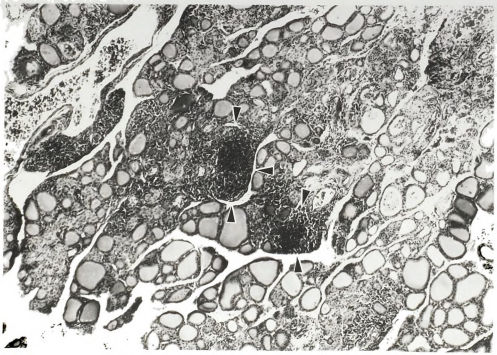

Fig. 14

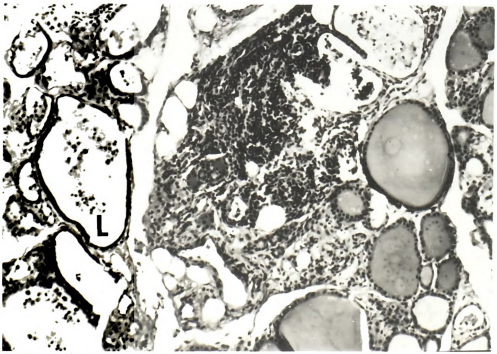

Fig. 15

DISCUSSION

Lymphocytic thyroiditis has been defined as an organ specific autoimmune disorder [Jansson, 1983]. Synonyms include struma lymphomatosa, Hashimoto's disease (HD), autoimmune thyroiditis and chronic lymphocytic thyroiditis [Beal and Solomon, 1978]. The aggregation of LT in the same family has been well documented [Goldsmith et al., 1973]. The genetic influence in human thyroid autoimmunity was evidenced by identical twins, both of whom were reported to develop HD [Irvine et al., 1961]. Thyroid antibodies were found in over 50 percent of the siblings of LT patients [Hall et al., 1960]. In humans, the genetic transmission of LT has been thought to be polygenic [Hall et al., 1972]. Spontaneous autoimmune thyroiditis in the Obese strain (OS) chicken has been shown to be a polygenic trait with some degree of dominance [Cole, 1966]. With all ten offspring of the fourth generation (see pedigree chart) having affected thyroid glands, a different mode of inheritance will be suggested for the dog.

The mating of dogs 1 and 2 produced at least one affected offspring, dog 9. Because dogs 1 and 2 were clinically and biochemically normal; we conclude that they were

both heterozygous for the mutant gene. An autosomal recessive disease is generally manifested clinically only in the homozygote. In the usual mating situation as seen in people, both parents are free of the disease but are heterozygous for the mutant gene [Nora and Fraser, 1974]. The prospective mating of dog 9, an affected dog, to 10, a clinically normal animal produced three known affected dogs (11-13, Fig. 1) and three normal dogs (15-17, Fig. 2) with the status of one animal, 18, unknown due to infant death. This suggests that dog 10 was a heterozygous carrier of the trait. The prospective mating of two known affected animals, 11 and 12, gave the expected results when two homozygous recessive animals are mated, 100% affected offspring, which is what we have in the ten offspring in the fourth generation.

We conclude from this data that this trait in Borzoi dogs is inherited as an autosomal recessive trait.

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