# THYROID FUNCTION EVALUATION IN CANINE DERMATOSES

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**Thesis submitted in partial fulfilment of the requirement for the degree of**

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## DECLARATION

I hereby declare that this thesis entitled **"THYROID FUNCTION EVALUATION IN CANINE DERMATOSES"** is a bonafide record of research work done by me during the course of research and that the thesis has not previously formed the basis for the award to me of any degree, diploma, associateship, fellowship or other similar title, of any other University or Society.

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# CERTIFICATE

Certified that the thesis entitled **"THYROID FUNCTION EVALUATION IN CANINE DERMATOSES"** is a record of research work done independently by **Renju Alias**, under my guidance and supervision and that it has not previously formed the basis for the award of any degree, diploma, fellowship or associateship to her.

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# CONTENTS

## LIST OF TABLES

## LIST OF FIGURES

# LIST OF PLATES

## LIST OF ABBREVIATIONS

| | |
|---|---|
| g/dl | - gram per decilitre |
| mg/dl | - milligram per decilitre |
| µg/Kg | - microgram per kilogram |
| SD | - standard deviation |
| ng/ml | - nanogram per millilitre |
| mU/L | - milliunit per litre |
| B.U. | - Bodansky Unit |
| U/L | - unit per litre |
| rpm | - rotation per minute |
| $mm^3$ | -Cubic millimetre |
| ® | - Registered trade mark |

# *Introduction*

# 1. INTRODUCTION

Skin disease is common ailment in all species of animals especially in companion animals particularly in dogs and cats. It is the most frequent presenting problem to the small animal practioner. Of this, major part is due to endocrine dermatoses. It is a common multifaceted and frequently confusing problem in veterinary practice.

The skin is the outer covering and largest organ of the body and is the anatomic and physiologic barrier between the animal and its environment. It provides protection from physical, chemical and microbiologic injury and its sensory components perceive heat, cold, pain, touch and pressure. The skin has immunologic, endocrine and antimicrobial properties. The skin is synergistic with internal organ systems thus reflects pathologic processes that are either primary elsewhere or are shared with other tissues (Muller *et al.,* 1989).

Disorders associated with endocrine system malfunction are characterized by changes in the hair coat, giving rise to abnormal character, growth rate, distribution and colour as well as other structural changes in the skin and adnexa. In addition to these changes affecting the hair and skin, clinical signs involving other systems may suggest disease of endocrine origin. The situation of endocrine physiological equilibrium has been likened to an orchestra whose players are, as far as the skin is concerned, the thyroid, adrenal, ovary and testis with the pituitary/hypothalamus the conductor. Once there is disharmony amongst the players (endocrine malfunction) or the conductor (pituitary/hypothalamic disease) then the resulting discord is reflected in abnormalities of the skin and other body systems (Baker and Thomsett, 1990).

Well known clues of endocrine dermatoses include a dull dry coat with bilaterally symmetric alopecia and poor regrowth of hair after it is clipped. Initially patients with endocrine dermatoses are non pruritic. The inadequate protection provided by a thinning coat, as well as various changes in the skin barrier and

immunologic defense mechanisms, predisposes patients with endocrinopathies to the development of secondary pyoderma and seborrhea, which result in pruritus (Shanley, 1990).

Hypothyroidism is frequently a diagnostic consideration in the evaluation of dogs with dermatologic disease. Thyroid hormone plays a dominant role in controlling normal growth and development of skin. It has a pivotal role in differention and maturation of mammalian skin as well as in the maintenance of normal cutaneous function. It is also necessary for the initiation of the anagen phase of the hair follicle cycle. Since thyroid hormones affect numerous metabolic processes and their deficiency may cause variety of clinical signs. It results in epidermal atrophy and abnormal keratinization because of decreased protein synthesis, mitotic activity and oxygen consumption in dogs.

The complex interaction between the hypothalamus, the pituitary and the thyroid gland along with the polysystemic and often vague clinical signs can make it a challenge to establish a diagnosis. Further the various diagnostic tests now available are not adequately reliable. A practioner needs a thorough understanding of hypothyroidism and an awareness of the pitfalls involved in its diagnosis. The diagnosis of hypothyroidism is ideally based on a combination of signalment and history as well as the result of a physical examination and clinicopathological testing.

Thyroid dysfunction manifested by cutaneous disorders, is often neglected by the clinicians, ultimately leading to non- responsive type of dermatosis and gradual progressive deterioration of body conditions. Proper/specific diagnosis especially the thyroid function status is not usually done in early stages. Therefore the present work will help to understand

1. The prevalence of cutaneous disorders in dogs in relation to thyroid dysfunction.
2. To evaluate the functional status of thyroid gland in dogs affected with dermatological disorders.

3. To formulate suitable therapeutic measures based on clinical and laboratory evaluation.

# *Review of Literature*

# 2. REVIEW OF LITERATURE

Hypothyroidism is one of the most commonly diagnosed endocrinopathies in the dog (Kaufman *et al.*, 1985).

It is a clinical syndrome resulted from inadequate circulating thyroid hormone concentration (Dixon, 2001).

## 2.1. ANATOMY AND PHYSIOLOGY

According to Belshaw and Rijnberk (1979), the normal ranges for plasma $T_4$ and $T_3$ in dogs were 1.52 to 3.60 µg/100 ml and 48 to 154 ng/100 ml respectively.

Chastain (1982) stated that only 10 to 15 per cent of the cellular effects of the thyroid hormones were directly due to $T_4$ and a failing thyroid preferentially produce $T_3$ than $T_4$ because of the economy of synthesizing $T_3$ and its intracellular importance.

Thyroxine ($T_4$ ), the main product of thyroid gland, bound to thyroxin binding globulin in the serum and the unbound free $T_4$ that reaches peripheral cells, acted upon by an enzyme that removes one iodine from the molecule ,thus producing $T_3$ (Peterson and Ferguson, 1989).

Free thyroxine ($fT_4$) is the biologically active form of $T_4$ that regulates pituitary thyrotropin secretion (Nelson *et al.*, 1991).

The thyroid gland consists of paired lobes located on the ventrolateral surface of the proximal trachea and microscopically composed of spherical follicles that are lined by epithelial cells which produce colloid containing thyroglobulin within thyroid follicles (Forrester and Monroe, 1997).

The thyroid gland is a bilobed structure that overlays the trachea at a point just below the larynx which is approximately about 0.2 percent of bodyweight (Kaneko, 1997).

## 2.2. ETIOLOGY

### 2.2.1. Primary hypothyroidism

Hypothyroidism in dogs occurred mainly due to acquired primary thyroid destructive processes, like idiopathic thyroidal atrophy (end stage immune mediated process) and lymphocytic thyroiditis (autoimmune disease) (Chastain, 1982; Shaw, 1985).

The most commonly encountered causes of hypothyroidism included primary-thyroid atrophy, lymphocytic thyroiditis (90 per cent) and secondary/tertiary, congenital/acquired hypothyroidism (10 per cent) (Baker and Thomsett, 1990).

According to Jeffers (1990) primary hypothyroidism due to an inadequate production of thyroxine ($T_4$) or triiodothyronine ($T_3$) from thyroid gland accounted for more than 90 per cent of the cases of hypothyroidism and concept of dog's inability to convert the storage form of thyroid hormone ($T_4$) to the biologically active form ($T_3$) was no longer accepted.

Nelson and Ihle (1987a) stated that lymphocytic thyroiditis and thyroid gland atrophy were the major causes of primary hypothyroidism.

Primary hypothyroidism accounted for more than 95per cent of the cases of canine hypothyroidism and characterised by decrease in circulating and pituitary $T_4$ and $T_3$ concentrations with a concurrent increase in TSH secretion (Panciera, 1997b).

Evaluation of serum total $T_4$ or free $T_4$ concentration in series with serum TSH concentration had high specificity because the combination of low $T_4$ and high TSH concentrations was unusual in dogs that did not have primary hypothyroidism (Peterson *et al.*, 1997).

#### *2.2.1.1. Lymphocytic thyroiditis*

Canine hypothyroidism was commonly caused by lymphocytic thyroiditis with invasion of the thyroid gland by lymphocytes, plasma cells and macrophages with destruction of follicles (Baker, 1986).

Lymphocytic thyroiditis and idiopathic follicular atrophy were the main causes of hypothyroidism in dogs (Panciera, 1997b).

Dixon (2001) stated that the most commonly recognised underlying cause of hypothyroidism was lymphocytic thyroiditis in which the thyroid gland becomes progressively infiltrated with lymphocytes, macrophages and plasma cells.

#### *2.2.1.2. Idiopathic follicular atrophy*

The cause of idiopathic follicular atrophy was unknown, but it was postulated as a primary degenerative process (Gosselin *et al.*, 1981).

Muller *et al.* (1989) and Dixon (2001) concluded that idiopathic thyroid necrosis and atrophy was an end stage of lymphocytic thyroiditis.

### 2.2.2. Secondary hypothyroidism

According to Jeffers (1990), secondary and tertiary hypothyroidism resulted from a deficiency of thyroid stimulating hormone (TSH) from the pituitary gland and thyrotropin-releasing hormone (TRH) from hypothalamus respectively.

Secondary hypothyroidism resulted from loss of pituitary TSH secretion secondary to neoplasia, trauma or congenital disease, (Panciera, 1997b).

### 2.2.3. Tertiary hypothyroidism

Bush (1991), Catherine *et al.* (2000) and Panciera *et al.* (2000) reported that the tertiary hypothyroidism due to lack of thyrotropin-releasing hormone had not been recognised in the dogs.

## 2.3. EPIDEMIOLOGY

### 2.3.1. Prevalence

According to Panciera (1994a) and Dixon (2001) the prevalence of canine hypothyroidism was 0.2 per cent and 0.2 to 0.64 per cent respectively.

Chakrabarti *et al.* (2001) observed that out of the 56 alopecic dogs, six were related to hypothyroidism (10.71 per cent).

### 2.3.2. Age

Belshaw and Rijnberk (1979) observed that coefficient of regression of plasma $T_4$ on age was significant, but the predicted decrease in plasma $T_4$ with age was very small (0.07 µg/100 ml per year).

The age of onset of clinical signs varied but usually four to six years. Large and giant breed dogs developed clinical signs at earlier age (2 to 3 years), low risk breeds showed a linear increase in risk up to nine years of age (Nelson and Ihle, 1987a).

The age of onset of clinical signs might be at any age, but usually of middle to old age (6-10 years), and little earlier in the giant breeds (Baker and Thomsett, 1990).

Jeffers (1990) reported that eventhough hypothyroidism affects dogs of any age; it typically affects dogs of four to ten years of age.

Hypothyroidism occurred most commonly in 4 to 8 years old large sized pure bred dogs with mean age of 7.2 years (Panciera, 1997a).

According to Peterson *et al.* (1997) age of affected dogs ranged from 2 to 13 years with a mean age of six years.

Hypothyroid dogs with thyroiditis tended to be younger than those without thyroiditis (Dixon, 2001).

Hypothyroidism was commonly found in 4 to 8 year old mid to large-sized purebred dogs (McKeown, 2002) and in dogs between 6 to 10 years of age (Mueller, 2003).

### 2.3.3. Sex

There was no significant difference in concentrations of $T_3$ and $T_4$ values between normal males and females (Belshaw and Rijnberk, 1979).

There was no sex predisposition in canine hypothyroidism as reported by Nelson and Ihle (1987a).

Neutered dogs regardless of sex were found to have a significantly higher risk of hypothyroidism compared with sexually intact dogs (Panciera, 1994a).

Both entire and neutered males and females were affected by canine hypothyroidism (Dixon, 2001).

### 2.3.4. Breeds

Doberman pinschers, Great Danes, Poodles, Irish Setters and Boxers accounted for 50 per cent of the hypothyroid dogs (Nesbitt, *et al.*1980).

Middle to large sized pure bred Spaniels, Doberman Pinschers, Irish Setters, Pomeranians, Dachshunds, and Golden retrievers were most commonly affected with hypothyroidism (Chastain, 1982).

Golden retrievers, Doberman pinschers, Boxers, Irish setters, Airdales, Great Danes and old- English sheep dogs were reported to be at increased risk to hypothyroidism (Panciera, 1997a).

## 2.4. CLINICAL SIGNS

Chastain (1982) stated that the early signs of hypothyroidism in more than 90 per cent of cases were confined to skin such as dry scaly skin, dull brittle hair, and failure to regrow of clipped hair or bleaching of normal hair colour.

The most common clinical signs of hypothyroidism were related to a generalized slowing of cellular metabolism and dermatological abnormalities like alopecia, hyperkeratosis, myxedema and pyoderma (Nelson and Ihle, 1987a).

Clinical signs of canine hypothyroidism included lethargy, weight gain, dermatological abnormalities and anaemia (Peterson *et al.*, 1997).

Clinical hypothyroidism developed only after approximately 75 per cent of the tissue was destroyed and therefore thyroid pathology could be present even for months or years before clinical signs of hypothyroidism become apparent (Dixon, 2001).

The most common classical signs associated with hypothyroidism were dermatological abnormalities such as alopecia, seborrhea and hyperpigmentation (McKeown, 2002).

The hypothyroidism should be differentiated from hyperadrenocorticism, alopecia-X, follicular dysplasias, seasonal flank alopecia and alopecia areata (Mueller, 2003).

### 2.4.1. Dermatological manifestations

Cutaneous manifestations were described as marked increase in the thickness of the skin folds of the neck, reduced body temperature, dry coat, lustreless and coarse with readily epilated hair and accentuation of skin folds of the face with a tragic/pitiful expression (Baker and Thomsett, 1990).

Jeffers (1990) reported that about 90 per cent of hypothyroid dogs were presented with a skin problem. Seborrhoea sicca, seborrhoea oleosa and seborrhoic dermatitis were common clinical features of canine hypothyroidism.

According to Panciera (1997a) alopecia and seborrhoea were the most frequent findings in at least 60 per cent of hypothyroid dogs. Alopecia was frequently bilaterally symmetrical, although hair loss in areas undergoing friction was common.

Pruritus did not occur in canine hypothyroidism unless complicated with *Malassezia* or bacterial pyoderma (Rosychuk, 1997).

### *2.4.1.1. Pattern of alopecia*

According to Jeffers (1990), as the disease progressed, hair loss spread to the entire trunk and proximal limbs, typically sparing the head, lower extremities except in giant breeds where it might begin on the distal extremities and spread towards the trunk.

Endocrine dermatoses predisposed the animal to seborrheic changes in the skin (Rhodes, 1990).

Shanley (1990) stated that well known clues of endocrine dermatoses included a dull, dry coat with bilaterally symmetrical alopecia, delayed regrowth of hair after clipping, later secondary pyoderma and seborrhoea developed due to inadequate protection provided by a thinning of coat, changes in the skin barrier and immunological defence mechanisms.

Alopecia usually begins on the tail, around the neck and a bilaterally symmetric pattern of hair loss involving the trunk and sparing the extremities occur in dogs with prolonged hypothyroidism (Panciera, 1997a).

Hair loss occurred in a bilaterally symmetrical pattern and it initially occurs in areas of friction such as the tail and around the neck (Panciera, 1999).

Dermatologic abnormalities like hair thinning particularly affecting the flanks, tail and thighs, dry or poor coat quality, skin hyperpigmentation, seborrhoea and superficial pyoderma were observed in 80 per cent cases of hypothyroidism (Dixon, 2001).

### 2.4.2. Other clinical manifestations

Cardiovascular abnormalities in hypothyroid dogs included bradycardia, weak pulse, low-voltage electrocardiogram complexes, arrhythmias including first-degree atrio- ventricular block and atrial fibrillation (Panciera, 1994b).

Panciera (1997a) reported that reproductive abnormalities in female dogs included infertility, prolonged or irregular estrum, short estrum, poor libido, foetal death and abortion. The authors also opined that reproductive function was not affected in hypothyroid male dogs.

Obesity, lethargy, exercise intolerance, and weakness were manifestations of decreased metabolic rate in hypothyroid dogs (Greco *et al.*, 1998).

Other clinical signs reported in hypothyroid dogs were generalized neuropathy, megaesophagus, laryngeal paralysis and myasthenia gravis (Panciera, 1999).

## 2.5. DIAGNOSIS

### 2.5.1. Clinicopathologic changes

#### *2.5.1.1. Haematological changes*

Haematological changes in hypothyroid dogs included normochromic, normocytic anaemia and lowered haemoglobin concentration (Baker and Thomsett, 1990).

Panciera (1994a) and Catharine *et al.* (2000) observed mild non-regenerative anaemia in 30 per cent of hypothyroid dogs.

Chakrabarti *et al.* (2001) observed that there was reduction in Hb (g/dl) 10.06 ± 0.93 and PCV (33.33 ± 3.02 per cent) in hypothyroid dogs.

Studies comparing the routine biochemical and haematological tests from hypothyroid dogs showed that the most reliable abnormalities that specifically

helped to identify hypothyroidism were decreased red cell count, increased gamma-glutamyl transferase, hypercholesterolemia and neutropenia (Dixon, 2001).

***2.5.1.2. Serum cholesterol***

Manning *et al.* (1973) reported that hyperlipoproteinaemia and hypercholesterolemia were associated with primary hypothyroidism in dogs.

According to Chastain (1982), hypercholesterolemia (>500 mg/dl) observed in 2/3 of the canine hypothyroid patients were due to the decrease in cholesterol clearance.

A serum cholesterol value of >15.6 nmol/l following starvation for 24 hours, was highly suggestive of hypothyroidism (Baker and Thomsett, 1990).

Panciera (1994a) reported hypercholesterolemia (70 per cent of cases) with mean serum cholesterol of 417 mg/dl and hypertriglyceridaemia in dogs having hypothyroidism.

Kaneko (1997) reported that the diagnostic accuracy of serum cholesterol estimation for the diagnosis of hypothyroidism in dogs was about 66 percent, however when the concentration was very high, >500 mg/dl (>12.9 mmol/L), and diabetes mellitus was eliminated, serum cholesterol's diagnostic accuracy was greatly increased.

Catharine *et al.* (2000) observed fasting hypercholesterolemia in about 75 per cent cases of hypothyroid dogs.

Chakrabarti *et al.* (2001) observed a mean cholesterol value of 344.83 ± 29.12 mg/dl in hypothyroid dogs and in control group it was 140 ± 8.99 mg/dl.

According to Gomathy *et al.* (2004), the cholesterol concentration was found to be twice in hypothyroid dogs than in normal dogs because the low level of $T_3$, $T_4$ could have affected the transport of cholesterol to peripheral tissue for epidermal lipogenesis.

## 2.5.2. Hormonal estimation

### *2.5.2.1. Method of estimation*

Belshaw and Rijnberk (1979) stated that the inherently greater sensitivity of radioimmunoassay makes it suitable for measurement in dogs and there were no major departures from RIA methods which had been used in man.

A radioimmunoassay kit for total $T_4$ designed for human samples was unable to detect total $T_4$ in 35 per cent of normal canine serum tested since the kit being designed to measure total $T_4$ over the normal human range which was four times the canine normal range (Eckersall and Williams, 1983).

Radioimmunoassay method for hormone analysis is based on the inhibition of binding of radioactive hormone (tracer) to anti-hormone antibody by hormone in the standard and sample (Young *et al.*, 1985).

Radioiodine uptake studies did not accurately reflect thyroid gland function, but simply determine the turnover of iodine in the thyroid gland (Wolfsheimer and Brady, 1995).

Measurement of serum total $T_4$ concentration by radioimmunoassay remains a useful screening test for hypothyroidism. (Panciera, 1997b).

Chakrabarti *et al.* (2001) used radioimmunoassay techniques for estimation of $T_4$, $T_3$ and TSH.

### *2.5.2 .2 .Total $T_4$ estimation*

The study conducted by Kelley and Oehme (1974), found that there was a significant difference between the mean thyroxine (displacement) [$T_4$ (D)] and thyroxine-resin $T_3$ index ($T_4$-$RT_3$ index) of the adult and puppies and puppies having higher values.

According to Harless *et al.* (1981), the serum $T_4$ values changed inversely with age at a rate of 0.23 ng/ml per year and in a study of 180 dogs with a mean age of 6.8 years, 70 per cent of the dogs had serum $T_4$ values of 9.6 to 26.6 ng/ml.

Thyroxine concentration in normal dogs ranged from 1.52 to 3.60 µg/100 ml and the predicted decrease in plasma $T_4$ with age was very small (0.07 µg/ml/year) (Eckersall and Williams, 1983).

Measuring patient's total $T_4$ and $T_3$ (protein –bound plus free hormone) by radioimmunoassay was a common method for diagnosing hypothyroidism (Jeffers, 1990).

According to the study conducted by Nelson *et al.* (1991) in 172 dogs, the measurement of serum $T_4$ concentration provided best assessment of thyroid gland function.

Ferguson and Peterson (1992) reported that in dogs with hyperadrenocorticism, a subgroup had reduced serum $T_4$ binding and another group had low values for all iodothyronines consistent with secondary hypothyroidism.

Wolfsheimer and Brady (1995) stated that dogs with normal total $T_4$ concentration and low total $T_3$ concentrations have non-thyroidal illnesses.

Dixon *et al.* (1996) suggested that the $tT_4$/cTSH ratio may be more sensitive than individual parameter analysis.

The mean $T_4$ by radioimmunoassay method in dogs was 2.3 ± 0.8 µg/dl (29.6 ± 10.3 nmol/L) with an observed range of 0.6 to 3.6 µg/dl (7.7- 46.3 nmol/l) (Kaneko, 1997).

Serum $T_4$ concentration was rarely normal in hypothyroid dogs or below normal in dogs with normal thyroid function because of perturbation of protein binding as well as the effects of certain drugs and non-thyroidal illness. Mean resting serum $T_4$ and triiodothyronine concentration in hypothyroid dogs were 7.4

nmol/l (normal - 19-51 nmol/l) and 0.68 nmol/l (normal- 1.23 to 3.0 nmol/l) respectively (Panciera, 1997b).

Measurement of serum $T_4$ concentration remained a useful screening test for hypothyroidism and it was infrequently normal in hypothyroid dogs although early hypothyroidism resulted in a low- normal $T_4$ (Peterson *et al.*, 1997).

Measurement of basal total thyroxine ($T_4$) had been frequently used to assess thyroid function, but its concentration reduced in a number of non- thyroidal disease states and also by concurrent use of certain drugs like prednisolone and sulphonamides. If the concentration of total thyroxine ranges from 0-14 nmol/l and TSH >0.6 mg/ml it is considered as hypothyroid/sick euthyroid/with concurrent therapy (Ramsey, 1997).

Low serum total or free $T_4$ with elevated serum TSH concentrations were suggestive of hypothyroidism, although dogs with non-thyroidal illness might have thyroid function tests similar to those found in hypothyroid dogs (Ramsey *et al.*, 1997).

Use of $T_4$ in combination with TSH increased the accuracy of diagnosis of hypothyroidism. (Scott-Moncrieff *et al.*, 1998).

Total thyroxine estimation was an inexpensive and sensitive marker for hypothyroidism, but decreased values were also observed in non-thyroidal illness and therapy with steroids, barbiturates, non-steroidal anti-inflammatory drugs and sulphonamides (Dixon, 2001).

Study conducted by Gomathy *et al.* (2004) revealed that, $T_4$ values were reduced from 2.52 ± 0.04 µg/dl to 1.28 ± 0.06 µg/dl in hypothyroid dogs.

### *2.5.2. 3. Total $T_3$ estimation*

Kelley and Oehme (1974) observed no significant difference between the values for resin triiodothyronine uptake ($RT_3U$) in adults and puppies.

Walsh and Brown (1980) reported that bound $T_4$ was not immediately available to peripheral cells and unbound (free) $T_4$ that reached the peripheral cells was acted up on by an enzyme that removed one iodine from the molecule, producing $T_3$.

Serum $T_3$ concentration decreased in severe hypothyroidism, but lowered serum $T_3$ concentrations were more often caused by non-thyroidal illness since 80 per cent of serum $T_3$ was produced by peripheral deiodination of serum $T_4$ by 5-deiodinase (Chastain, 1982).

Abnormalities in the conversion of $T_4$ to $T_3$ have not been documented in human beings, dogs or cats. These "poor converters" are patients with concurrent illnesses or patients receiving drugs that influence serum $T_3$ concentrations (Nelson and Ihle, 1987b).

Beale *et al.* (1992) stated that serum $T_3$ concentration was not accurate in predicting thyroid function since most of the euthyroid and hypothyroid dogs with skin disease had serum $T_3$ concentrations within the normal range and generalized dermatologic disease in the absence of systemic illness did not affect serum thyroid hormone concentration.

The mean concentration of $T_3$ by radioimmunoassay was 107 ± 18 ng/dl (1.6 ± 0.3 nmol/l) with an observed range of 82-138 ng/dl in normal dogs (1.26-2.12 nmol/l) (Kaneko, 1997).

Most of the circulating $T_3$ was derived from peripheral deiodination of $T_4$. Therefore serum $T_3$ concentration was a poor indicator of thyroid function, often being in the normal range in hypothyroid dogs (Panciera, 1997b).

Peterson *et al.* (1997) stated that the measurement of baseline $T_3$ concentration was of little value in differentiating hypothyroidism from euthyroid dogs since there was little difference in serum $T_3$ concentrations between clinically normal dogs, dogs with hypothyroidism and euthyroid dogs with nonthyroidal diseases.

Under the stimulation by TSH, the thyroid gland preferentially secretes $T_3$, which account for the normal serum $T_3$ concentration in hypothyroid dogs (Panciera, 1999).

Gomathy *et al.* (2004) reported that the mean $T_3$ levels in control dogs and hypothyroid dogs were 0.92 ± 0.054 ng/ml and 0.45 ± 0.062 ng/ml respectively.

***2.5.2.4. TSH estimation***

The measurement of high concentrations of TSH with low $T_4$ in patients with clinical signs of hypothyroidism indicated primary hypothyroidism (Wolfsheimer and Brady, 1995).

Dixon *et al.* (1996) stated that cTSH concentrations were within the reference range in some naturally occurring cases of canine hypothyroidism.

According to Williams *et al.* (1996) serum cTSH estimation was more helpful in the differential diagnosis of primary, secondary and tertiary hypothyroidism and in monitoring response to thyroid hormone replacement therapy.

Ramsey (1997) opined that if the clinical history and physical examination (including routine blood tests) of a dog were suggestive of hypothyroidism, then a combination of tT4 and cTSH concentrations should be used to support the clinical suspicion of hypothyroidism.

While using the human TSH-RIA assay method for the dogs, it was found that the normal values were 5.9 ± 4.1 µU/ml (Kaneko, 1997).

According to Panciera (1997b), 60 to 80 per cent of hypothyroid dogs have elevated TSH whereas elevated TSH was found only in 15 per cent of euthyroid dogs with nonthyroidal illness.

Serum TSH concentration was high in most of the dogs with naturally developing hypothyroidism (> 2.0 ng/ ml). But in 24 per cent of hypothyroid dog had concentrations within the reference range and 9 per cent had concentrations low-

normal concentrations. The author had pointed out that one cannot exclude a diagnosis of hypothyroidism on the basis of a normal or low normal TSH concentration, because, the assay detects some , but not all , isoforms of circulating TSH (Peterson,*et al.*, 1997).

According to Ramsey *et al.* (1997) cTSH concentration was 0.41 ng/ml determined after storage of the samples at -20$^0$C for a maximum of 12 months .The author suggested that normal cTSH concentration in the naturally occurring cases of canine hypothyroidism was due to later diagnosis and disruption of the feed back pathway by down-regulation or exhaustion of cTSH production by the pituitary thyrotrophs in case of prolonged periods of low thyroid hormone concentrations.

The combination of reduced $T_4$ and increased cTSH values were highly specific for hypothyroidism although normal in 20 per cent of hypothyroid dogs (Dixon and Mooney, 1999).

Kooistra *et al.* (2000) demonstrated pulsatile secretion of TSH in dogs during hypothyroidism and suggested that the low TSH values occasionally found in dogs with spontaneous primary hypothyroidism in some cases may be as a result of ultradian fluctuations.

### *2.5.2.5. Free $T_4$ Estimation ($fT_4$)*

Determination of free thyroid hormone concentrations reflected thyroid gland function of animals more accurately than determination of total thyroid hormone concentrations, which involves measuring bound and free hormone concentrations (Peterson and Ferguson, 1989).

Significant difference in mean serum $fT_4$ concentration was not evident between dogs with hypothyroidism and euthyroid dogs with hyperadrenocorticism or peripheral neuropathy. So measurement of serum $fT_4$ concentration using the single-stage radioimmunoassay did not provide additional information about thyroid gland function other than gained by measurement of serum $T_4$ concentration (Nelson *et al.*, 1991).

The most accurate method of measurement for serum free $T_4$ is modified equibrilium dialysis techniques (Ferguson, 1995).

The $fT_4$ concentration in clinically normal dogs was 0.52-2.7 ng/dl (6.7-34.7 pmol/l) (Kaneko, 1997).

Serum free $T_4$ was a better test of thyroid function than total $T_4$ concentrations because it was less affected by factors that alter protein binding (Peterson *et al.*, 1997).

Free $T_4$ measurement was less affected by non-thyroidal illnesses and drug therapy than total $T_4$ (Dixon and Mooney, 1999).

***2.5.2.6. TSH stimulation test***

Lorenz and Stiff (1980) stated that TSH stimulation test was the best clinical procedure for presumptive diagnosis of canine hypothyroidism and the study revealed the fact that the failure to double control $T_4$ values after TSH administration was associated with good response to thyroid medication whereas the doubling of the control values after TSH administration was associated with negative response to thyroid medication.

Study conducted by Peterson *et al.* (1984) in dogs with untreated spontaneous hyperadrenocorticism revealed that reduced basal serum concentrations of $T_4$ and $T_3$ were found in 58 (57 per cent) and 53(52 per cent) cases respectively and decreased response to TSH stimulation test in dogs with hyperadrenocorticism.

Laurberg (1989) stated that paradoxically subnormal serum $T_4$ and $T_3$ in dogs after prolonged excessive TSH stimulation of the thyroid were due to post-cAMP refractoriness of thyroid hormone secretion.

In case of early hypothyroidism, level of T4 can be low, yet the thyroid gland may contain enough reserves for thyroid hormone to respond normally to the TSH stimulation (Jeffers, 1990).

Beale *et al.* (1992) reported that 1 IU of TSH induced serum $T_4$ concentrations over baseline, and the increase was significantly less than that in response to a 5 IU dose at 6 hours after the administration of TSH and concluded that the response to TSH was not a dose related phenomenon.

TSH stimulation test should be considered in cases in which moderate to severe concurrent illness could not be resolved before testing (Panciera, 1997b).

According to Ramsey (1997) dogs had a post stimulation$T_4$ concentration greater than 1.2 times the pre stimulation $T_4$ concentration were normal.

Scott-Moncrieff *et al.* (1998) stated that the measurement of serum total $T_4$ before and six hours after intravenous administration of 0.1 IU/Kg bovine TSH was the recommended protocol for TSH response test in dogs.

***2.5.2.7. TRH response test***

Lothorp *et al.* (1984) reported that a useful procedure for pituitary-thyroid function testing was serum thyroxine measurement before and six hours after TRH (0.1 mg/kg) stimulation.

The largest increase in the serum $T_4$ concentration occurred 4 hours after intravenous administration of 200 µg of thyrotropin-releasing hormone (Evinger *et al.*, 1985).

Kaufman *et al.* (1985) reported that TRH challenge test was of limited value in evaluating canine pituitary gland function, since the response was too variable among individual animals.

Jeffers (1990) stated that the TRH stimulation test, offered the advantages of potentially diagnosing primary, secondary and tertiary hypothyroidism, where as the TSH stimulation test could only diagnose primary hypothyroidism.

Measurement of TSH after TRH administration could be useful in cases in which serum TSH and $T_4$ or free$T_4$ are not diagnostic (Panciera, 1997b).

### *2.5.2.8. Thyroglobulin antibodies*

In the study conducted by Haines *et al.* (1984), thyroglobulin autoantibodies were found in 59 per cent of 34 clinically hypothyroid dogs, 43 per cent of 65 dogs with nonthyroidal endocrine diseases, 47 per cent of 64 healthy dogs and 13 per cent of 1057 canine hospital patients without endocrine disorders.

Thyroglobulin is highly antigenic and damage to the thyroid gland results in the production of thyroglobulin antibodies, which can interfere with RIA of thyroid hormones if the titre was high enough to bind a considerable fraction of the radiolabelled hormone used in the RIA procedure (Chastain *et al.*, 1989).

Muller *et al.* (1989) stated that anti-thyroglobulin antibodies were demonstrable in over 50 per cent cases of naturally occurring canine hypothyroidism and the important applications were detecting family members that could develop hypothyroidism and helping to differentiate primary hypothyroidism ( antibody positive) from secondary and tertiary hypothyroidism ( antibody negative).

Autoantibodies against $T_3$ occurred with greater frequency than those against $T_4$ in dogs because the structural similarity of $T_3$ with canine thyroglobulin which is the antigenic source, $T_3$ was more exposed to immunorecognition than $T_4$ (Kemppainen and Young, 1992).

Gaschen *et al.* (1993) reported that thyroglobulin auto-antibodies (TgAA) and $T_3$ auto-antibodies ($T_3$AA) should be considered as the indicators of lymphocytic thyroiditis in dogs and direct linear correlation existed between $T_3$AA concentration and apparent serum $T_3$ concentration.

The measurement of thyroglobulin antibodies had the potential value of early recognition of lymphocytic thyroiditis (Wolfsheimer and Brady, 1995).

The presence of autoantibodies to thyroid hormone could confuse the diagnosis of hypothyroidism which resulted in elevation of total $T_3$, total $T_4$ and free$T_4$ concentrations when measured using an analog RIA (Kemppainen *et al.*, 1996).

Thyroglobulin antibodies were produced during the development of lymphocytic thyroiditis, which provide no assessment of thyroid functional status. (Dixon, 2001).

### *2.5.2.9. Thyroid hormone autoantibodies*

Great Danes, Irish Setters and Old English Sheep dogs had an increased occurrence of autoantibodies against thyroid hormone and it was not influenced by age or sex (Haines *et al.,* 1984).

Chastain *et al.* (1989) reported that the reason for more frequent detection of $T_3$ antibodies than that of $T_4$ antibodies in the dogs was due to the binding of proteins to $T_3$ in thyroglobulin or serum may create a more effective antigenic complex than those bound to $T_4$.

Nachreiner and Refsal (1992) stated that the adequate $tT_4$ concentration with subnormal $tT_3$ concentration in some dogs was due to the presence of $T_3$ autoantibody which produced false lowering of the assay results.

Mean serum $T_4$ concentration was not significantly different between sera with low or high $T_3AA$ concentration (Gaschen *et al.,* 1993).

The presence of thyroid hormone antibodies resulted in elevation in the concentration of $tT_3$ and $tT_4$ (Wolfsheimer and Brady, 1995).

Iverson *et al.* (1998) reported that the prevalence of thyroglobulin auto antibodies (TGAB) in hypothyroid dogs with lymphocytic thyroiditis was 91 per cent and in dogs with dermatological diseases without lymphocytic thyroiditis was 3 per cent.

### *2.5.2.10. Factors affecting thyroid hormone measurement*

Considerable change in total serum $T_4$ concentration was observed due to changes in protein binding which increased by oestrogen and pregnancy and decreased by androgens, glucocorticoids, hypoproteinemia and chronic hepatitis (Chastain, 1982).

Non thyroidal illness results in impaired protein binding decreased tissue uptake, decreased metabolism and reduced activity of 5- deiodinase and reduction in serum $T_4$ and $T_3$ concentration. The author also reported that drugs like anti-convulsants, frusemide, salicylates, phenylbutazone, radiographic contrast agents were suspected of altering thyroid function or thyroid hormone concentration (Shaw, 1985; Panciera, 1997b).

Abnormal canine triiodothyronine- binding factor interfered with the radioimmunoassay for total $T_3$ resulted in an apparent increase in values for $T_3$ concentration (Young *et al.*, 1985).

According to Moriello *et al.* (1987) dexamethasone had no effect on the response to TSH.

The testing method also was affected by a nonthyroidal illness since the recovering sick dog might have a rebounding TSH before the $T_4$ starts to increase back to normal, leaving one with an impression of primary hypothyroidism (Wolfsheimer and Brady, 1995).

Drugs like steroids, sulphonamides containing drugs, barbiturates interfere with thyroid hormone concentrations and assessment of thyroid function should be postponed for around six weeks after such medication had been stopped. (Dixon, 2001).

Kantrowitz *et al.* (2001) reported that the mean serum concentrations of total $T_4$ , free $T_4$ and total $T_3$ concentrations reduced (i.e. in the hypothyroid range) in dogs with moderate to severe non-thyroidal disease, but serum TSH concentrations was more likely to remain within the reference range in sick dogs.

### 2.5.3. SERUM ENZYMES

Panciera, (1994a) observed that there was elevated activity of creatinine kinase in 18 per cent of hypothyroid dogs and alkaline phosphatase in 30 per cent of hypothyroid dogs than the reference range.

Chakrabarti *et al.* (2001) observed an elevation in alkaline phosphatase activity (B.U.- 12.5 ± 1.31) in hypothyroid dogs and in control dogs it was 1.83 ± 0.3 B.U.

Dixon (2001) reported increased gamma-glutamyl transferase activity in hypothyroid dogs.

2.5.4. SKIN BIOPSY

Skin biopsy of dog suspected of hypothyroidism revealed hyperkeratosis and follicular plugging (Nesbitt *et al.*, 1980).

Examination of skin biopsy specimens resulted in misleading conclusion since most biopsies only confirm the recognised dermatologic problem without indicating its endocrine cause (Kaelin *et al.*, 1986).

Skin biopsy of a hypothyroid dog revealed orthokeratotic hyperkeratosis, melanosis, telogen arrest, follicular atrophy, dilatation and keratosis of the hair follicles and a thickened dermis with increased dermal mucin (Baker and Thomsett, 1990).

Follicular atrophy, orthokeratotic hyperkeratosis, epidermal melanosis, a predominance of hair follicle in telogen, dermal thickening, vacuolation of arrector pili muscles and inflammatory changes were the typical histological picture of the skin in canine hypothyroidism (Rosychuk, 1997).

According to Krishnamurthi and Rajan (2002), the skin biopsy examination in hypothyroid dogs revealed the thinning of epidermis, atrophy and collagen degeneration of dermal appendages.

Skin biopsy examination in hypothyroid dogs revealed hypertrophy and vacuolization of arrector pili muscles and increased dermal mucin (Mueller, 2003).

2.5.5. THYROID BIOPSY

Muller and Kirk (1976) reported that early cases of hypothyroidism were characterised by leucocytic infiltration and fibrosis, followed by follicular collapse and atrophy of the thyroid tissue.

Histopathological changes of thyroid gland were characterized by diffuse infiltration of the gland by lymphocytes, plasma cells and macrophages with destruction of thyroid follicles and the formation of lymphoid follicles whereas in idiopathic follicular atrophy, thyroid gland was replaced by adipose tissue (Lucke *et al.*, 1983).

### 2.5.6. SCINTIGRAPHY

Dogs with normal thyroid function had a thyroid –salivary (T: S) ratio of approximately one at both 20 and 60 minutes after injection of 99M Tc-pertechnetate (Catharine *et al.*, 2000).

## 2.6. PROGNOSIS

According to Forrester and Monroe (1997), the prognosis of hypothyroid dogs was good to excellent. Clinical signs and laboratory abnormalities were reversible with appropriate treatment, although neuromuscular and reproductive problems might take up to one year to resolve.

Hypothyroid dogs were potentially at risk of developing immune mediated endocrinopathies known as polyglandular syndromes and most common syndromes in dogs was hypothyroidism in association with diabetes mellitus or hypoadrenocorticism (Dixon, 2001)

## 2.7. TREATMENT

Hightower *et al.* (1973) stated that dosage required for replacement therapy for induced hypothyroidism in dogs, were 12.8 µg/kg body weights for triiodothyronine ($T_3$) alone and 32 µg/kg for thyroxine ($T_4$) alone. Concentration of $T_3$ (18 µg/kg) and $T_4$ (4.5 µg/kg) respectively for $T_3$ and $T_4$ together.

Synthetic $T_3$ and combination of $T_3$-$T_4$ products have no established therapeutic advantages to synthetic $T_4$ and the dose should be correlated with metabolic rate than with body weight (Chastain, 1982).

The initial dosage of levothyroxine for dogs is 20µg/kg body weight every 12 hours orally and when the clinical signs improved, reduce the frequency of administration to once daily (Nelson and Ihle, 1987b).

Baker and Thomsett (1990) recommended thyroxine (Eltroxin®,Glaxo) orally at a dose rate of 10-20 µg/kg twice daily for three weeks and patients should be reassessed after that for signs of over dosage.

Levothyroxine (Synthetic $T_4$) given at rate of 17 to 22 µg/kg or 0.5 µg/$m^2$ twice a dosing orally considered as the treatment of choice of canine hypothyroidism (Jeffers, 1990).

Larger dogs tended to have lower therapeutic hormone concentrations at a given dosage and peak concentrations occurred at 4 to 6 hours after dosing and levothyroxine –v (veterinary) achieving higher concentrations than levothyroxine-h (human).On doubling the dosage the serum concentration of $fT_4$ increased only by 59 per cent (Nachreiner *et al.*, 1993).

Levothyroxine converted to triiodothyronine ($T_3$) through deiodination of $T_4$ and $T_3$ became more metabolically active in peripheral tissues (Panciera, 1997c).

Ramsey (1997) used L- thyroxine (Soloxine) at a dosage of 20 µg /kg orally twice daily for the treatment of hypothyroidism.

2.7.1. RESPONSE TO THERAPY

Improvement in mental dullness, physical activity, regrowth of hair, cessation of seborrhoea and normal values of Hb, PCV and serum cholesterol indicate a favourable response to treatment. (Chastain, 1982).

Excessive supplementation of thyroid hormone could promote excessive grooming with subsequent alopecia (Rhodes, 1990).

Mental dullness and lethargy were the first clinical signs to improve usually within one to two weeks of the start of therapy and the coat and skin improve only after one to five months of therapy. Dermatologic signs took four to six weeks of supplementation to show improvement and although some hair usually regrows within the first month, complete regrowth and a significant reduction in hyperpigmentation of the skin took several months (Nelson and Ihle, 1987b).

In effective treatment the $T_4$ value should be above normal in serum samples drawn after four to eight hours after medication and the ultimate proof of effective therapy by the resolution of clinical signs of hypothyroidism after the stoppage of drug therapy (Jeffers, 1990).

Single administration of L-thyroxin resulted in triiodothyronine concentrations above the physiologic range for a number of hours, where as concentration closer to physiological ranges was achieved by use of divided doses and dose was higher than human beings due to the short biologic half life of thyroxine in dogs (Nachreiner *et al.*, 1993).

The presence of lethargy frequently overlooked in hypothyroid dogs by the owners and thyroid hormone supplementation resulted in an increase in activity and alertness (Panciera, 1994a). Mentation may improve within 2 weeks, but alopecia may take up to 3 months. If there is no significant improvement even after 3 months of therapy, the trial should be deemed a failure and the drug should be withdrawn (Ramsey, 1997).

The peak circulating total $T_4$ concentration values of approximately 60 to70 mmol/l after thyroid hormone supplement was usually associated with excellent clinical control; peak $tT_4$ concentration of less than 35 nmol/L indicated the need for an increase in dose. Dermatologic abnormalities took longer time for improvement, but most dogs were essentially clinically normal within 12 weeks of starting therapy (Dixon, 2001).

### 2.7.2 TREATMENT FAILURE

According to Jeffers (1990), possible reasons for thyroid supplementation treatment failures were poor absorption or rapid excretion of drug, outdated product, inadequate dose or frequency, presence of antibodies to $T_3$ or $T_4$, defect in 5-deiodinase,peripheral tissue resistance (never proved)or incorrect diagnosis.

According to Dixon (2001) thyroid administration to dogs with "normal" thyroid function resulted in physiological effects that were easily interpreted as a clinical response and adequately treated hypothyroid dogs were failure to respond completely also considered as useful evidence of a misdiagnosis.

# *Materials and Methods*

# 3. MATERIALS AND METHODS

The present study was carried out in the Department of Clinical Medicine, College of Veterinary and Animal Sciences, Mannuthy during the period from June 2004 to May 2005. The prevalence of cutaneous disorders in relation to thyroid dysfunction was studied in dogs that were presented to veterinary college hospitals Mannuthy and Kokkalai during that period.

## 3.1 DESIGN OF THE STUDY

Fifty-four suspected cases of hypothyroidism were selected at random and utilized for the present study. These animals were grouped into groups I and II depending on the concentrations of $T_3$, $T_4$ and TSH, so that each group consisted of eight animals.

The study consisted of apparently eight healthy animals, between the age group of five to seven years as control.

## 3.2. SOURCE OF CLINICAL CASES

Dogs presented to the University Veterinary Hospitals, Mannuthy and Kokkalai of College of Veterinary and Animal Sciences, Kerala Agricultural University with clinical signs of dermatological disorders were included in this study. A total of fifty four dogs brought to the college hospitals with skin lesions not primarily due to bacteria, fungi or mites were chosen for the study. Signalment and a short previous history of the cases were recorded. Age, sex, breed, general medical and dermatological history, location of lesion, appearance, onset and rate of progression, presence and degree of pruritus, information regarding the feeding practices, bathing and grooming practices, method of disinfection of kennel, drugs used for deworming and previous medication applied also were recorded as suggested by Muller *et al.* (1989). Breeding history including intactness, details of breeding control procedures, status and regularity of oestrus cycle in female animals was also collected. Eight apparently healthy animals between the age group of five

to seven years brought for vaccination were selected at random and utilized as control animals.

## 3.3. CLINICAL EXAMINATION

Clinical examination involving the pattern of distribution, location and configuration of the lesions and relationship to each other, body surface temperature, texture, elasticity and thickness of the skin were carried out as suggested by Houston *et al.* (2000). Microscopic examination of skin scraping was also done to rule out the possible involvement of mites and fungi. Other clinical signs associated with endocrine dermatoses like polyuria, polydipsia, obesity and cardiovascular abnormalities were also recorded.

## 3.4. COLLECTION OF CLINICAL MATERIAL

### 3.4.1. Collection of Blood for Haematological Assay

About three milliliter of blood was collected from recurrent tarsal or cephalic vein of affected dogs in dry glass vials containing EDTA as anticoagulant @ 2 mg/ml of blood and the specimen examined within one hour of collection. The blood samples were collected after six weeks to note the response to treatment.

A drop of blood was taken on clean grease free glass slide to prepare a blood smear (Benjamin, 1985).

### 3.4.2. Collection of Blood for Biochemical and Hormonal examination

Five milliliter of blood was collected in another clean and dry test tube for separating serum. The separated serum after slow centrifugation at 3000 rpm for ten minutes without disruption of clot was transferred to a serum vial. Sera thus separated were stored at –20°C till further analysis.

Disposable clean plastic micropipette tips were used to draw serum from the vials for various biochemical and hormonal estimations.

## 3.5. EVALUATION OF CLINICAL MATERIALS

### 3.5.1. Haematological Parameters

The following haematological parameters were estimated.

#### *3.5.1.1. Haemogram*

**Haemoglobin (Hb)**

Haemoglobin was estimated by acid- haematin method using Sahli's haemoglobinometer and expressed as gram percentage (Schalm *et al.,* 1975).

**Volume of packed red cells (VPRC)**

Volume of packed red cells (VPRC) was estimated by Wintrobe's method as per Coles (1986) and expressed as per cent.

#### *3.5.1.2. Leukogram*

**Total Leukocyte Count (TLC)**

Total WBC count was estimated using Thoma's fluid as per Coles (1986) and value expressed as X $10^3$ cells/$mm^3$ of blood.

**Differential Leukocyte Count (DLC)**

Blood smear was stained by Leishman's stain and 100 leukocytes were counted under oil immersion objective and differential counts were expressed as percentage (Benjamin, 1985).

### 3.5.2. Serum Biochemical Parameters

#### *3.5.2.1. Serum Cholesterol*

Serum cholesterol[1] was estimated by modified CHOD- PAP method described by Allain *et al.* (1974) using Merck200 spectrophotometer with commercially available kit.

#### *3.5.2.2. Serum Alkaline phosphatase (ALP)*

Estimation of serum alkaline phosphatase[2] was carried out according to the recommendations of Bergmeyer (1972) using Merck200 spectrophotometer with commercially available kits.

#### *3.5.2.3. Serum Gamma glutamyl transferase (GGT)*

Gamma glutamyl transferase[3] was estimated according to the recommendations of Persijn and Van der Silk (1976) using Merck200 spectrophotometer with commercially available kits.

#### *3.5.2.4. Serum hormonal estimation*

Serum concentrations of Thyroxine ($T_4$) and Triiodothyronine ($T_3$) were estimated using gamma coated $T_4$ and $T_3$ radioimmunoassay commercial kit[4] and value expressed in µg/dl and ng/ml respectively.

Thyroid stimulating hormone was estimated using gamma coated TSH-IRMA commercial kit[5] and value expressed in mU/L.

[1] Merck Ecoline Cholesterol
[2] Merck Ecoline Alkaline phophatase
[3] Merck Ecoline Gamma GT
[4] M/s Diasorin, Minnesota,USA
[5] M/s Diasorin, Minnesota,USA

## 3.6. HISTOPATHOLOGY

Tissue collected was processed, embedded in paraffin, four micrometer sections were made and stained with haematoxylin and eosin (Bancroft and Cook, 1984).

## 3.7. THERAPEUTIC TRIALS

Samples were collected from suspected cases of hypothyroidism, hormonal assays were performed and animals found to be hypothyroid were treated with Eltroxin®[6] (100 µg) orally at a dose rate of 20 µg/Kg body weight BID for six weeks. The serum samples were collected again after six weeks to note the response to treatment.

Response to treatment was assessed by hormonal estimation and evaluating the clinical improvement of the conditions after six weeks.

## 3.8. STATISTICAL ANALYSIS

The data obtained in the present study were subjected to statistical analysis as per the procedure described by Snedecor and Cochran (1980).

[6] Glaxo Levothyroxine Sodium 100mcg tab

# Results

# 4. RESULTS

In the present study the prevalence of cutaneous disorders in dogs in relation to thyroid dysfunction were assessed. In order to evaluate the functional status of thyroid gland in suspected cases, serum $T_4$, $T_3$ and TSH concentrations were estimated. Treatment was carried out in ten positive cases.

## 4.1. PREVALENCE

Data on the prevalence of dermatitis collected from the University Hospitals at Mannuthy and Kokkalai from June 2004 to May 2005 are presented in Table (1) and Fig (I).

Dermatological problems constituted 10.28 per cent of dog cases presented to the University Veterinary Hospitals. The overall prevalence of hypothyroidism in the present study was 1.23 per cent of the total dermatological cases presented to the University Veterinary Hospitals. This accounted for 0.13 per cent of the total canine cases presented in the two hospitals taken up for the study.

The present study revealed that the hypothyroidism accounted for about 29.6 per cent of the suspected cases of endocrine dermatoses in dogs.

### 4.1.1. Age

Age-wise prevalence of hypothyroidism revealed that dogs of 7 to 10 years of age (50 per cent) were more frequently affected followed by 3 to 7 years (25 per cent), 2 to 3 years (18.75 per cent) and 1 to 2 years (6.25 per cent) (Table 2).

### 4.1.2. Sex

The prevalence of canine hypothyroidism was higher in males (56.25 per cent) than in females (43.75 per cent) (Table 3).

Table 1. Prevalence of dermatological disorders in dogs presented to University Veterinary Hospitals during June 2004 to May 2005

| | Number of cases | Percent incidence out of dermatological cases | Percent incidence out of total canine cases |
|---|---|---|---|
| Canine cases presented | 11991 | | |
| Canine cases with dermatological disorders | 1233 | | 10.28 |
| Bacterial dermatitis | 192 | 15.57 | 1.60 |
| Fungal dermatitis | 285 | 23.12 | 2.38 |
| Ectoparasitic infestations | 626 | 50.77 | 5.22 |
| Demodicoses | 76 | 6.16 | 0.63 |
| Suspected cases of endocrine dermatoses | 54 | 4.38 | 0.45 |
| Hypothyroidism in suspected cases of endocrine dermatoses | 16 | 1.23 | 0.13 |

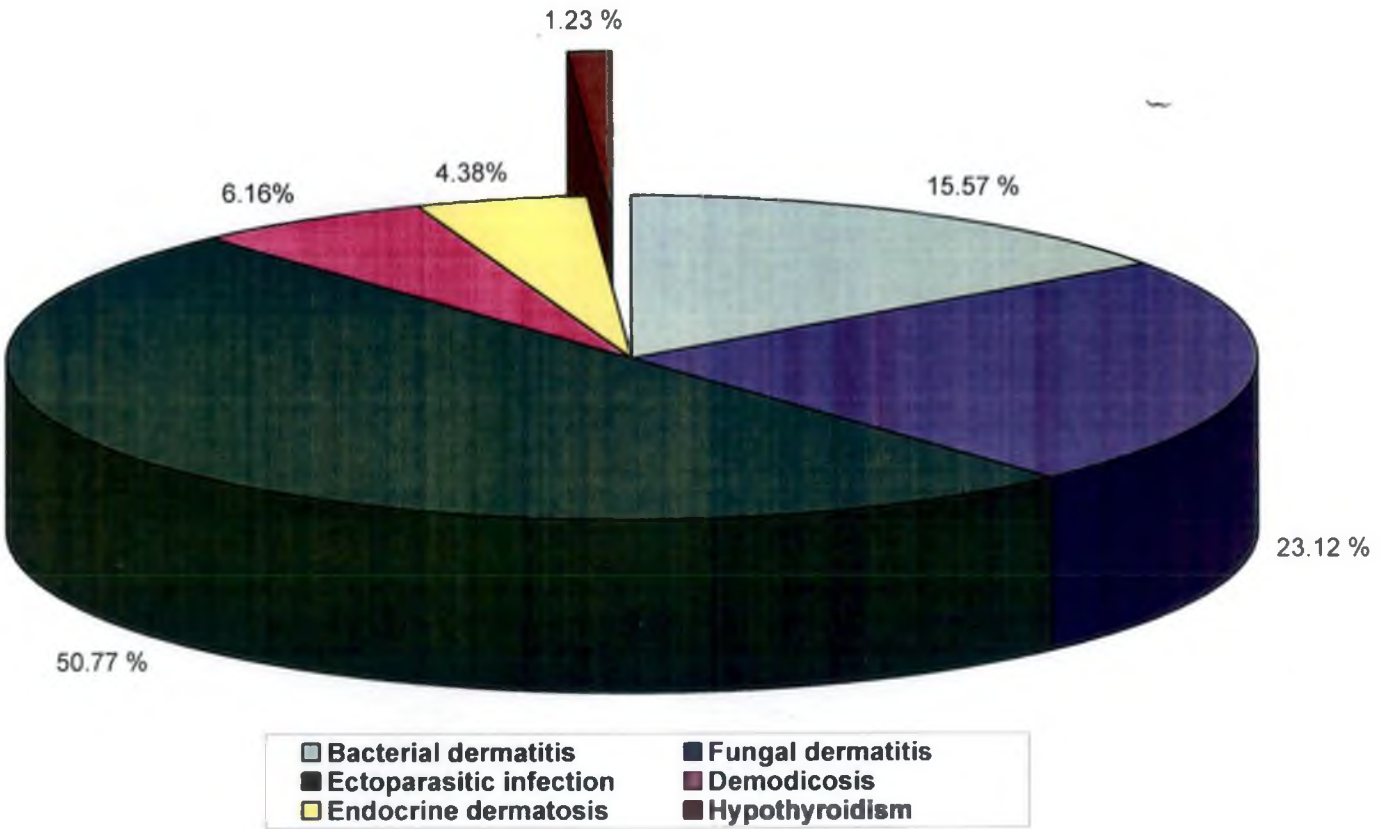



Fig.1. Prevalence of dermatological disorders in dogs presented to University Veterinary Hospitals during June 2004-May 2005

Table 2. Age-wise prevalence of hypothyroidism in dogs

| Age | Cases with hypothyroidism | Percentage |
|---|---|---|
| 1-2 years | 1 | 6.25 |
| 2-3 years | 3 | 18.75 |
| 3-7 years | 4 | 25 |
| 7-10 years | 8 | 50 |

Table 3. Sex-wise prevalence of hypothyroidism in dogs

| Sex | Number |
|---|---|
| Male | 9 (56.25 per cent) |
| Female | 7 (43.75 per cent) |

Table 4. Breed-wise prevalence of hypothyroidism in dogs

| Breed | Number | Percentage |
|---|---|---|
| German Shepherd | 5 | 31.25 |
| Dachshund | 4 | 25.00 |
| Spitz | 3 | 18.75 |
| Labrador | 2 | 12.50 |
| Doberman | 1 | 6.25 |
| Non-descript | 1 | 6.25 |

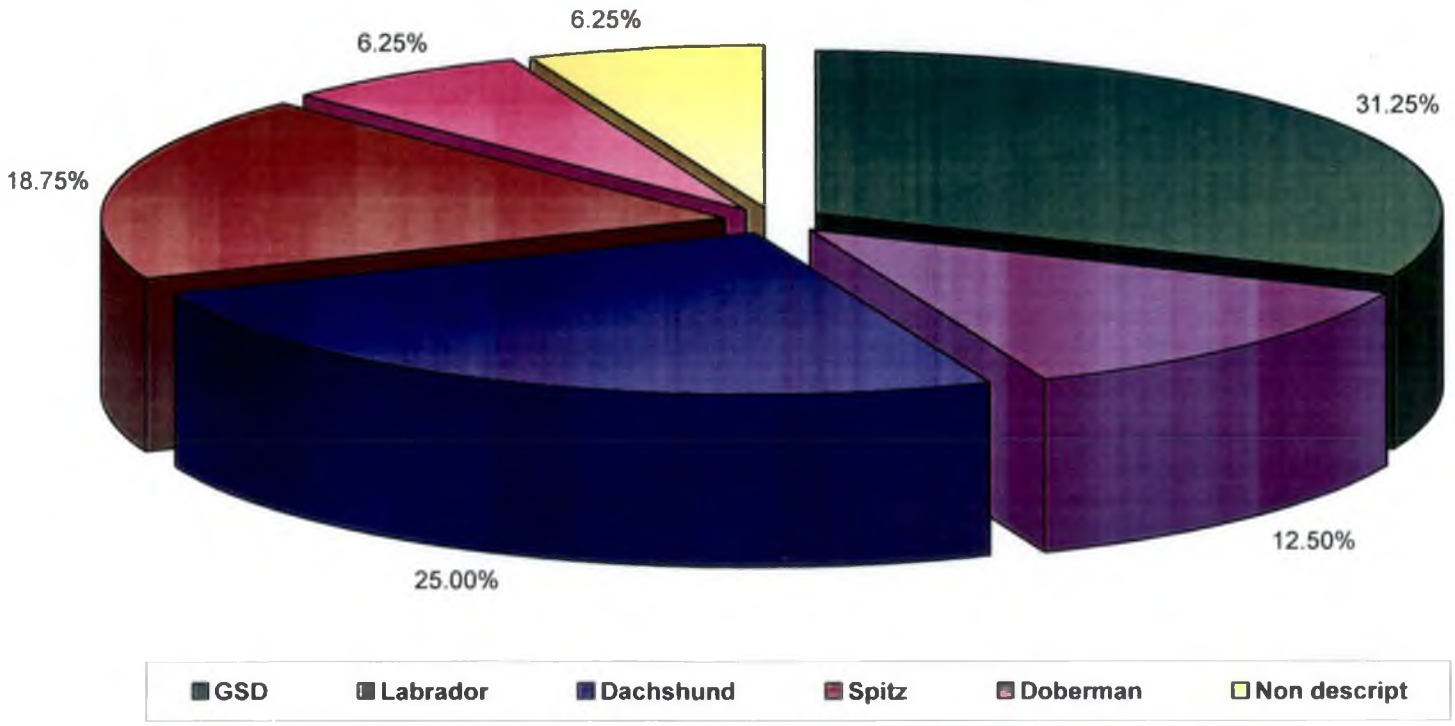



Fig.2. Breed-wise prevalence of hypothyroidism in dogs

### 4.1.3. Breed

The breed wise prevalence indicated that German Shepherd dogs were more prone to hypothyroidism (31.25 per cent) followed by Dachshunds (25 per cent), Spitz (18.75 per cent), Labrador (12.50 per cent) Non-descript dog (6.25 per cent) and Doberman (6.25 per cent) (Table 4) (Fig 2).

## 4.2. SYMPTOMATOLOGY IN ENDOCRINE DERMATOSES

Fifty four dogs presented to the veterinary hospitals with clinical signs of endocrine dermatoses were selected. The most common clinical features of endocrine dermatoses were bilaterally symmetrical alopecia of ventrolateral abdomen and extremities (57.41 per cent), hyperpigmentation of the area of hair loss (40.74 per cent) and coat changes (81.48 per cent). The coat changes included dryness, dullness, dandruff, coarseness and sparseness. Pruritus was observed in 44.40 per cent of the suspected cases due to secondary bacterial or *Malassezia* infection. Pyoderma (35.18 per cent) and *Malassezia* (22.22 per cent) were observed due to secondary infection. Abnormal cyclical activity was observed in nine out of 28 female dogs (16.6 per cent). Otitis and seborrhoea were reported in 13 (24.07 per cent) and 19 (35.18 per cent) cases respectively (Table 5).

Out of the fifty four endocrine dermatoses cases, hypothyroidism was confirmed in 16 cases based on serum levels of $T_3$, $T_4$ and TSH and they were grouped into two so that each group consisted of eight animals. Dogs of group I (n=8) had low serum thyroxine ($T_4$), tri-iodothyronine ($T_3$) and high thyroid stimulating hormone (TSH) values. In group II (n=8) there was low serum thyroxine ($T_4$)), normal tri-iodothyronine ($T_3$) and normal thyroid stimulating hormone (TSH) values.

## 4.3. CLINICAL SIGNS IN CANINE HYPOTHYROIDISM

### 4.3.1. Cutaneous signs of hypothyroidism

The common dermatological changes exhibited by hypothyroid dogs included seborrhoea (n=10, 62.50 per cent), alopecia which usually began on the

Table 5. Skin lesions of endocrine dermatoses in dogs

| Number | Skin lesions | Number of cases | Percentage of occurrence |
|---|---|---|---|
| 1 | Bilaterally symmetrical alopecia | 31 | 57.41 |
| 2 | Hyperpigmentation | 22 | 40.74 |
| 3 | Coat changes* | 44 | 81.48 |
| 4 | Pruritus | 24 | 44.40 |
| 5 | Pyoderma | 19 | 35.18 |
| 6 | *Malassezia* infection | 12 | 22.22 |
| 7 | Otitis | 13 | 24.07 |
| 8 | Seborrhoea | 19 | 35.18 |

* Coat changes included dryness, dullness, coarseness and sparseness.

dorsal, proximal or distal aspect of the tail causing a "rat-tail appearance", around the neck (n=7, 43.75 per cent) and bilaterally symmetrical pattern of hair loss of ventrolateral abdomen and extremities (n=8, 50 per cent). In German Shepherd and Labrador, the alopecia was most commonly observed in the extremities rather than on the trunk. Coat changes such as dryness, dullness, dandruff, scaliness, coarseness and sparseness were observed in 14 dogs (87.75 per cent) out of 16 cases.

Sub acute superficial pyoderma was found in lateral abdomen and dorsal part of the body (German Shepherd) in four dogs and chronic superficial pyoderma in digits and lateral flank was found in other three dogs. All these animals responded to appropriate antibiotic therapy, but recurrence was noticed after one month.

Hyperpigmentation in the areas of hair loss was observed in 11 (60.75 per cent) out of sixteen cases. Out of sixteen dogs, four dogs were infected with *Malassezia*. Pruritus was noticed in 11 out of 16 cases due to secondary bacterial or *Malassezia* infection. In 10 (62.50 per cent) out of 16 cases, seborrhoea was reported (Table 6).

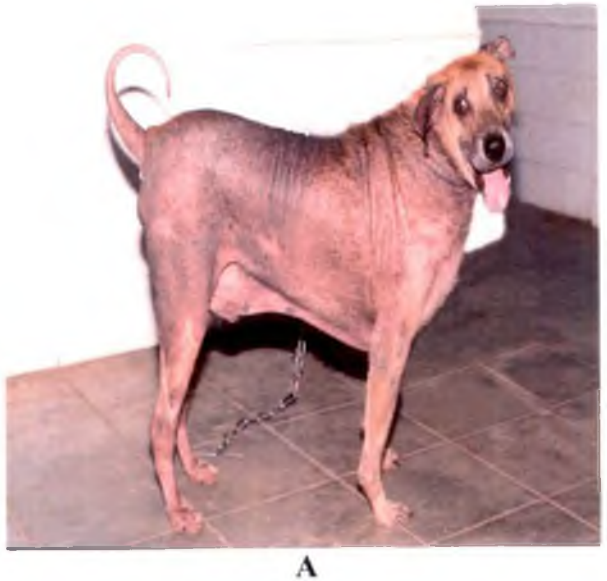
**4.3.2. Non -cutaneous signs of hypothyroidism**

Lethargy was observed in three out of 16 dogs and four dogs were obese. But obesity was generally mild. Heat seeking behavior was observed only in two cases. Six dogs out of sixteen dogs (37.50 per cent) had chronic ceruminous otitis. There was response to appropriate therapy within one week. But recurrence occurred after a short period of normalcy.

Ocular abnormalities such as corneal ulceration, chronic lacrimation and blepheritis in both eyes were observed in three cases (18.75 per cent). Reproductive abnormalities such as prolonged anoestrum were observed only in one out of seven female hypothyroid dogs (Table 6).

Table 6. Clinical signs in canine hypothyroidism

| Serial No. | Symptoms | Total no. of cases | Percentage |
|---|---|---|---|
| 1 | Bilaterally symmetrical alopecia | 8 | 50.00 |
| 2 | Rat tail | 7 | 43.75 |
| 3 | Seborrhoea | 10 | 62.50 |
| 4 | Coat changes | 14 | 87.50 |
| 5 | Pyoderma | 7 | 43.75 |
| 6 | Lethargy | 3 | 18.75 |
| 7 | Obesity | 4 | 25.00 |
| 8 | Heat seeking behaviour | 2 | 12.50 |
| 9 | Ceruminal otitis | 6 | 37.50 |
| 10 | Hyper pigmentation | 11 | 60.75 |
| 11 | *Malassezia* infections | 4 | 25.00 |
| 12 | Ocular abnormalities | 3 | 18.75 |
| 13 | Reproductive abnormalities | 1 | 6.25 |



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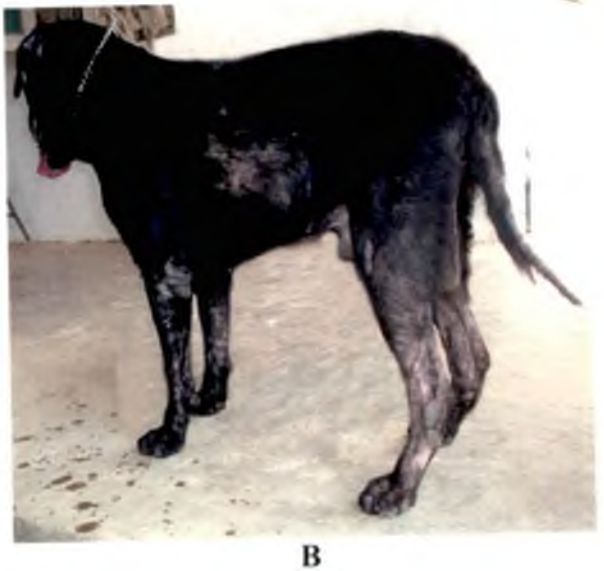

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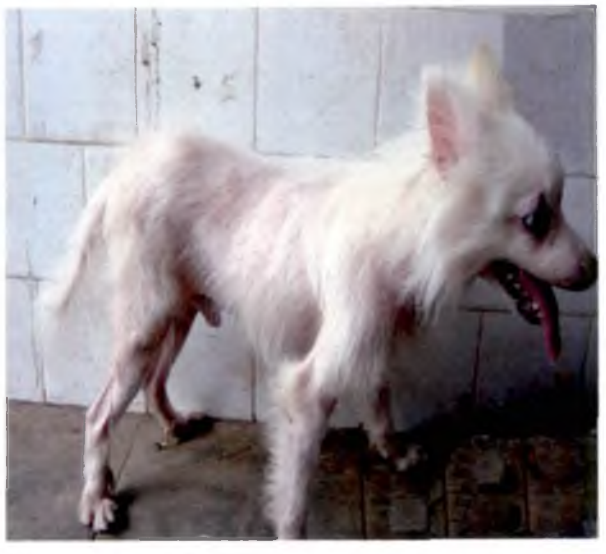

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**Plate 1. Dermatological manifestations of Hypothyroidism in dogs**

**A. Extensive alopecia with Hyperpigmentation** **B. Rat tail**

**C. Bilaterally symmetrical alopecia**

## 4.4. CLINICAL PATHOLOGY

The following haematological and biochemical parameters were estimated in dogs with hypothyroidism.

### 4.4.1. Haemogram

#### *4.4.1.1. Haemoglobin (Hb)*

The mean haemoglobin values of animals of group I and II were 10.40 ± 0.74 g/dl and 10.85 ± 1.50 g/dl respectively. In control group it was 11.58 ± 1.28 g/dl. The reduction in the haemoglobin concentration obtained in the present study was not statistically significant when compared with control (Table 7).

#### *4.4.1.2. Volume of Packed Red Cells (VPRC)*

The mean values of volume of packed red cells in animals of group I and II were 33.25 ± 3.88 per cent and 35.75 ± 6.78 per cent respectively and corresponding value for the control group was 39.13 ± 3.14 per cent. No significant difference in the mean values of the diseased and control groups could be observed. However seven out of 16 cases showed low VPRC values ranging from 25 per cent to 34 per cent suggestive of mild anaemia. The VPRC values did not correlate consistently with $T_4$ or $T_3$ values (Table 7).

### 4.4.2. Leucogram

#### *4.4.2.1. Total Leucocyte Count (TLC)*

The mean total leucocyte count of animals of group I and II were 9675 ± 1911 /mm$^3$ and 11237.5 ± 2162 / mm$^3$ respectively and for the control group it was 9668.75 ± 1821 /mm$^3$. Statistical analysis showed no significant differences in the mean total leucocyte count of diseased groups when compared to the control group (Table 7).

*4.4.2.2. Differential leucocyte count*

**4.4.2.2.1. Neutrophil count**

The mean values of neutrophil count in animals of group I and II were 69.75 ± 6.58 per cent and 67.50 ± 3.30 per cent respectively. For the control group, it was 67.63 ± 3.42 per cent. Statistical analysis revealed no significant differences in the mean neutrophil counts of diseased groups when compared to the control group (Table 7).

**4.4.2.2.2. Lymphocyte count**

The mean values of lymphocyte count in animals of group I and II were 27.75 ± 6.30 per cent and 29.88 ± 3.70 per cent respectively. In the case of control group it was 30.75 ± 3.20 per cent. No statistically significant differences were observed between mean values of diseased and control groups (Table 7).

**4.4.2.2.3. Monocyte count**

The mean values of monocyte count in animals of group I and II were 1.71 ± 0.30 and 1.64 ± 0.21 per cent respectively. In the case of control it was 1.48 ± 0.25 per cent. No statistically significant differences were observed between mean values of diseased and control groups (Table 7).

**4.4.3. Serum biochemical parameters**

*4.4.3.1. Serum Cholesterol*

The mean values of serum cholesterol in animals of group I and II were 361.1 ± 84.08 mg/dl and 299.5 ± 69.56 mg/dl respectively. For the control group it was 221.5 ± 41.96 mg/dl. A statistically significant increase ($P<0.05$) was obtained in serum cholesterol value of the diseased groups when compared to control group (Table 8).

Table 7. Haematological values in normal and hypothyroid dogs (values expressed as Mean ± SD)

| Haematological parameters | | Group I (n = 8) | Group II (n = 8) | Control group (n = 8) |
|---|---|---|---|---|
| Haemoglobin (g %) | | 10.40 ± 0.74 | 10.85 ± 1.50 | 11.58 ± 1.28 |
| VPRC (%) | | 33.25 ± 3.88 | 35.75 ± 6.78 | 39.13 ± 3.14 |
| WBC (per $mm^3$) | | 9675 ± 1911 | 11237.5 ± 2162 | 9668.75 ± 1821 |
| Differential leukocyte count | N (%) | 69.75 ± 6.58 | 67.50 ± 3.30 | 67.63 ± 3.42 |
| | L (%) | 27.75 ± 6.30 | 29.88 ± 3.70 | 30.75 ± 3.20 |
| | M (%) | 1.71 ± 0.30 | 1.64 ± 0.21 | 1.48 ± 0.25 |

Table 8. Serum biochemical values in normal and hypothyroid dogs (values expressed as Mean ± SD)

| Biochemical parameters | Group I (n=8) | Group II (n=8) | Control group (n=8) |
|---|---|---|---|
| Serum cholesterol (mg/dl) | 361.1±84.08$^b$ | 299.5 ± 69.56$^b$ | 221.5 ± 41.96$^a$ |
| Serum Alkaline phosphatase (U/L) | 217.6±127.50 | 170.1±109.90 | 123.5 ± 44.40 |
| Serum Gamma glutamyl transferase (U/L) | 5.9±3.01 | 3.8 ± 2.49 | 3.5 ± 1.69 |
| Serum thyroxine (µg/dl) | 0.48±0.28$^b$ | 0.63 ± 0.08$^b$ | 1.04 ± 0.14$^a$ |
| Serum tri-iodothyronine (ng/ml) | 0.74±0.31 | 1.14 ± 0.39 | 1.26 ± 0.66 |
| Serum thyroid stimulating hormone (mU/L ) | 8.7±2.50$^b$ | 6.6 ±1.59$^a$ | 5.3 ± 1.19$^a$ |

a, b = between groups means with different superscripts are differ significantly within same row ($P<0.05$)

#### *4.4.3.2. Serum Alkaline Phosphatase (ALP)*

The mean serum alkaline phosphatase activity in animals of group I and group II were 217.6 ± 127.50 U/L and 170.1 ± 109.90 U/L respectively. For the control group it was 123.5 ± 44.40 U/L. No significant differences were observed in the mean values of the diseased and control animals. But five out of 16 cases (31.25 per cent) showed an elevation in serum alkaline phosphatase activity (Table 8).

#### *4.4.3.3 Serum Gamma Glutamyl Transferase (GGT)*

The mean serum gamma glutamyl transferase (GGT) activity in animals of group I and II were 5.9 ± 3.01 U/L and 3.8 ± 2.49 U/L respectively. For the control group it was 3.5 ± 1.69 U/L. No significant differences were observed in the mean values of the diseased animals when compared to the control. But four out of 16 cases (25 per cent) showed an elevated gamma glutamyl transferase (GGT) activity (Table 8).

#### *4.4.3.4. Serum Thyroxine ($T_4$)*

Mean serum thyroxine levels in animals of group I and II were 0.48 ± 0.28 µg/dl and 0.63 ± 0.08 µg/dl respectively. For the control group it was 1.04 ± 0.14 µg/dl. A statistically significant decrease ($P \leq 0.05$) was obtained in serum thyroxine ($T_4$) value of diseased groups when compared to control animals (Table 8) (Fig 3).

#### *4.4.3.5. Serum Tri-iodothyronine ($T_3$)*

Mean serum tri-iodothyronine levels in animals of group I and II were 0.74 ± 0.31 ng/ml and 1.14 ± 0.39 ng/ml respectively. For the control group it was 1.26 ± 0.66 ng/ml. No significant differences were observed in the mean values of group II and control group. Group I had lower concentration of $T_3$ (0.74 ± 0.31 ng/ml) compared to control group (1.26 ± 0.66 ng/ml) (Table 8) (Fig 4).

#### *4.4.3.6. Serum Thyroid Stimulating Hormone (TSH)*

Mean thyroid stimulating hormone levels in animals of group I and group II were 8.7 ± 2.50 mU/L and 6.6 ± 1.59 mU/L respectively. For the control group it

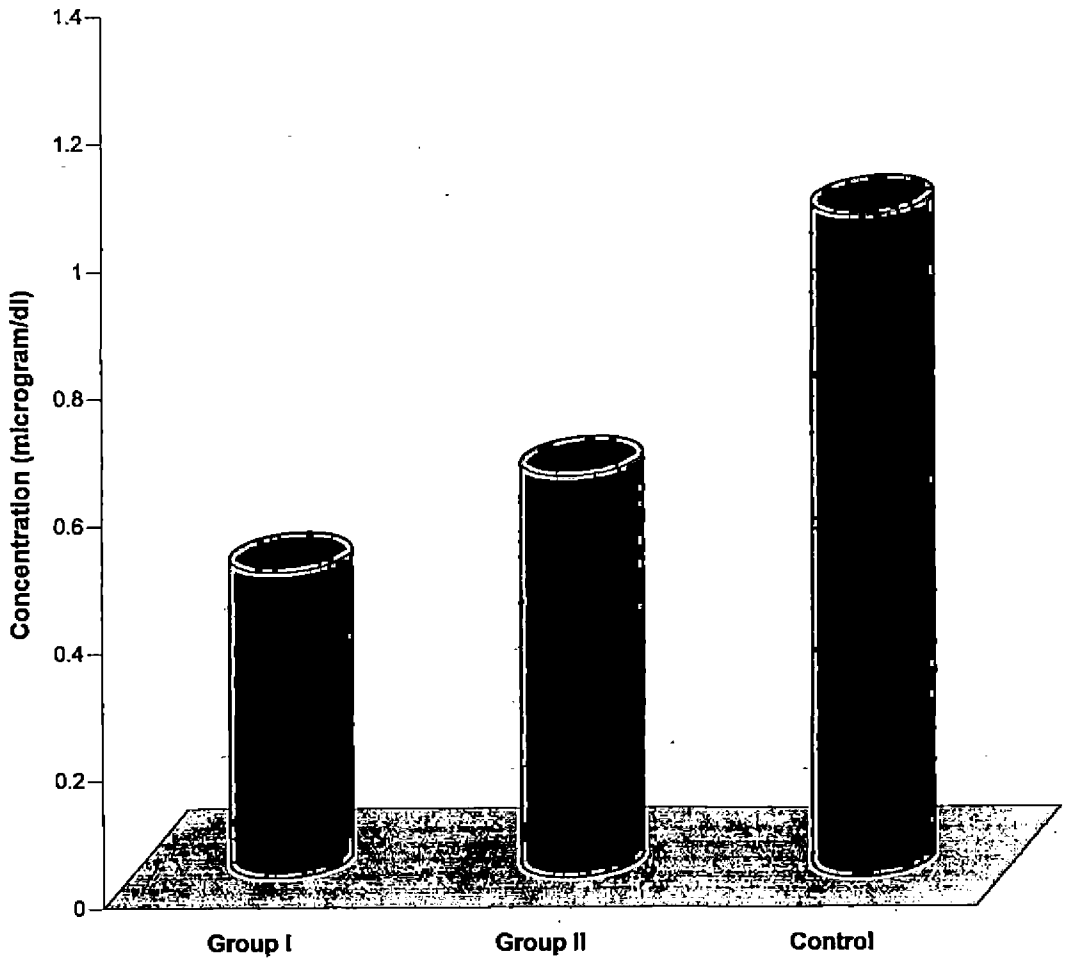



Fig. 3. Comparison of serum thyroxine levels in different groups

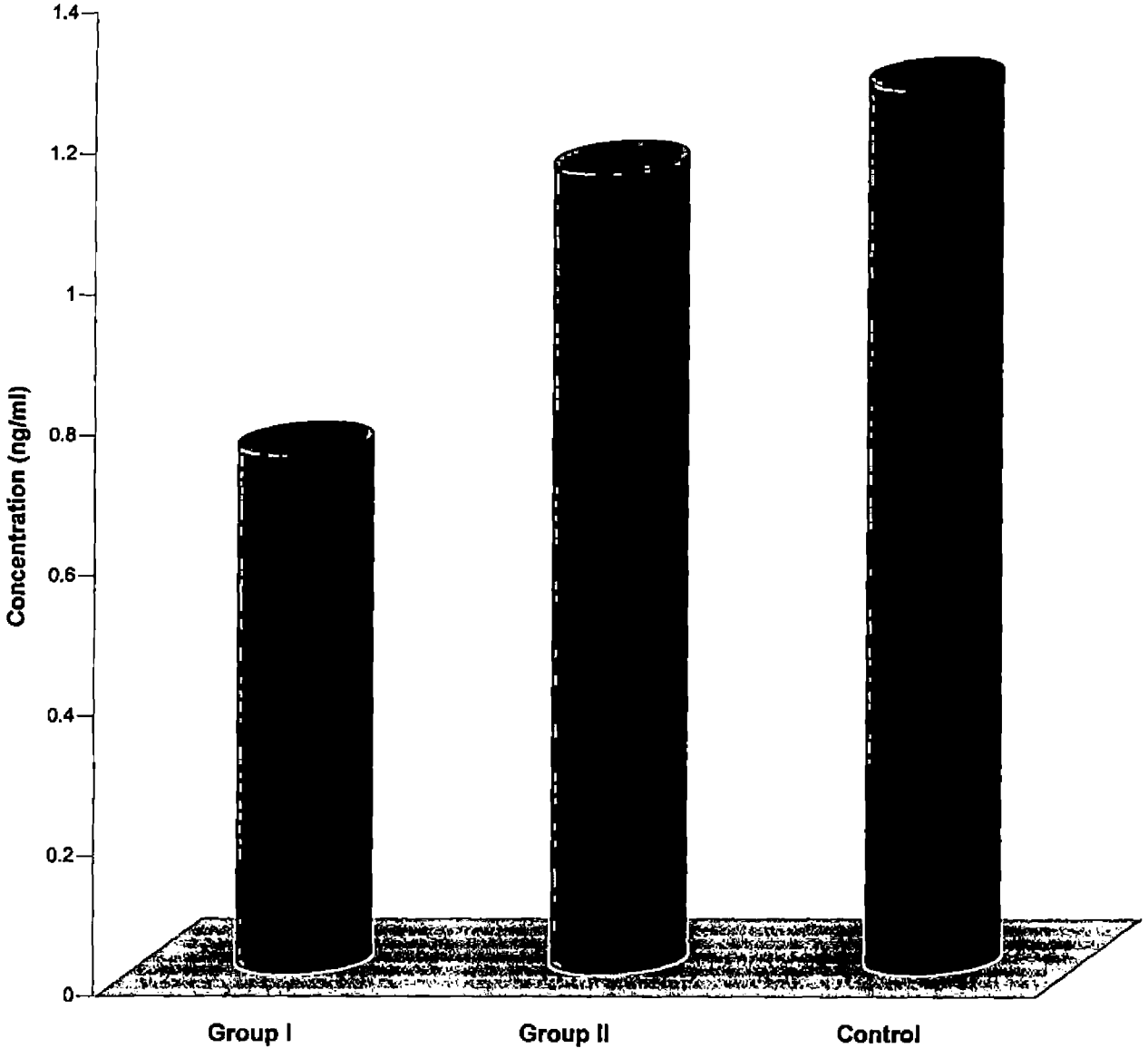



Fig. 4. Comparison of serum tri-iodothyronine levels in different groups

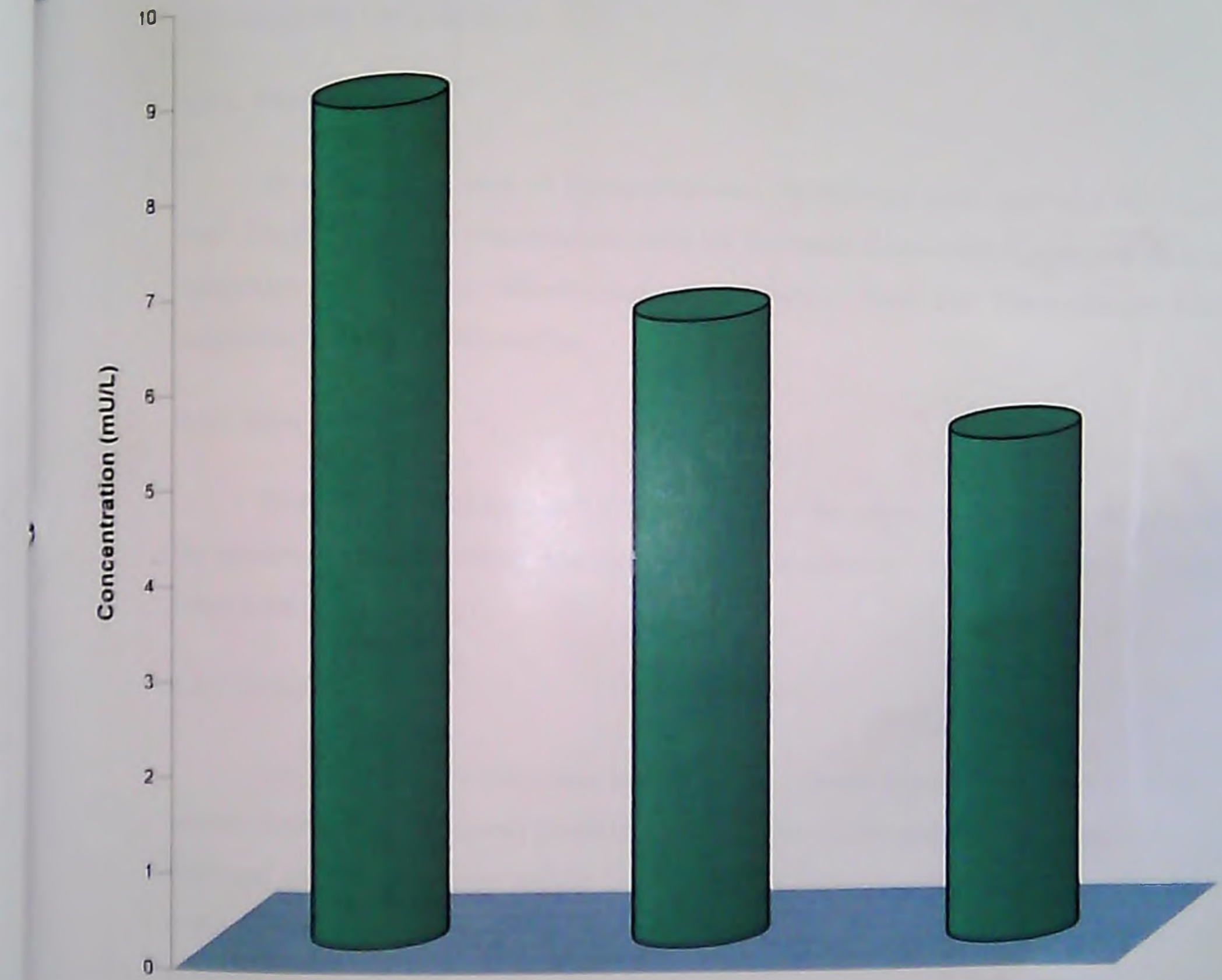



Fig. 5. Comparison of serum thyroid stimulating hormone levels in different groups

was 5.3 ± 1.19 mU/L. Group I showed significant increase ($P<0.05$) in the serum TSH concentration from the control group and group II did not show any significant differences ($P>0.05$) from the control group (Table 8) (Fig 5).

## 4.5. HISTOPATHOLOGY

### 4.5.1. Thyroid Biopsy

In a confirmed case of hypothyroidism, the thyroid gland appeared small and hard. Histopathological examination revealed follicular degeneration, necrosis, diffuse congestion and moderate inflammatory cell infiltration (Plate 2A). These changes were suggestive of moderate thyroiditis.

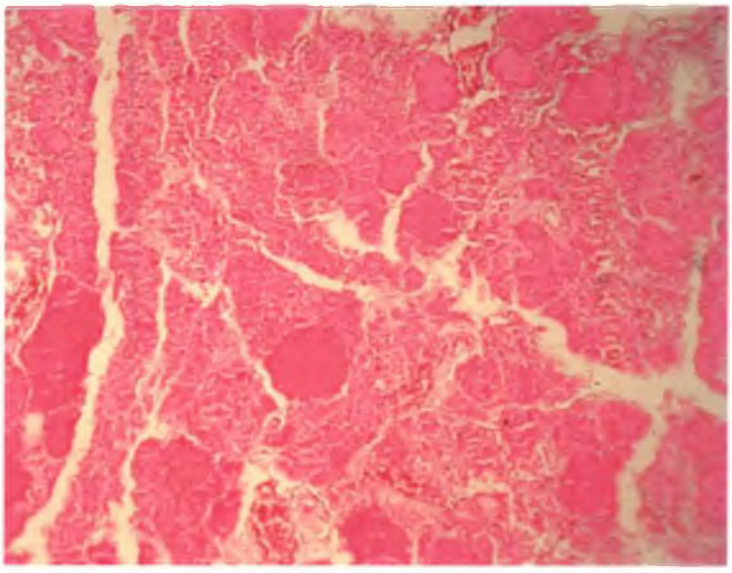
### 4.5.2. Skin Biopsy

Histopathological examination of the skin in one of the cases showed thinning of the epidermal layers, atrophy and moderate dermal sclerosis (Plate 2B). Hair follicles were absent.

## 4.6. THERAPY

Ten out of 16 positive cases having typical signs of hypothyroidism, like rat tail, severe alopecia and recurrent pyoderma were selected and treated with Eltroxin® at a dose rate of 20 µg/kg body weight twice daily for six weeks. Follow up results were obtained only in six cases. In four cases (66.66 per cent) there was an excellent response obtained in four to six weeks after therapy. Increased hair loss was evident early in treatment in some cases. Regrowth of hair, cessation of seborrhoea and improvement in coat condition were noticed in cases which responded to treatment within six weeks (Plates 3 and 4).

Thyroid hormone levels were estimated after six weeks in treated cases. Samples were taken 12 hours post treatment and hormone levels were found to be in the normal ranges in responded cases. In two cases, poor response to therapy was obtained.



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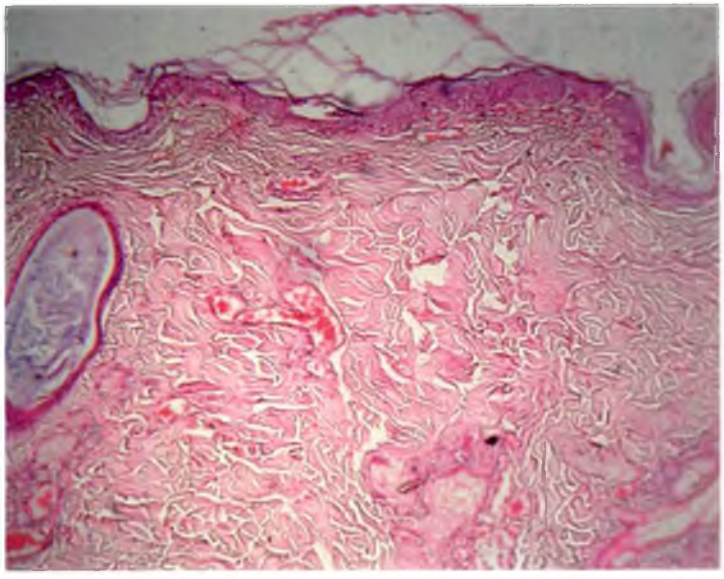


B

**Plate 2. Histopathology - H & E 400 X**

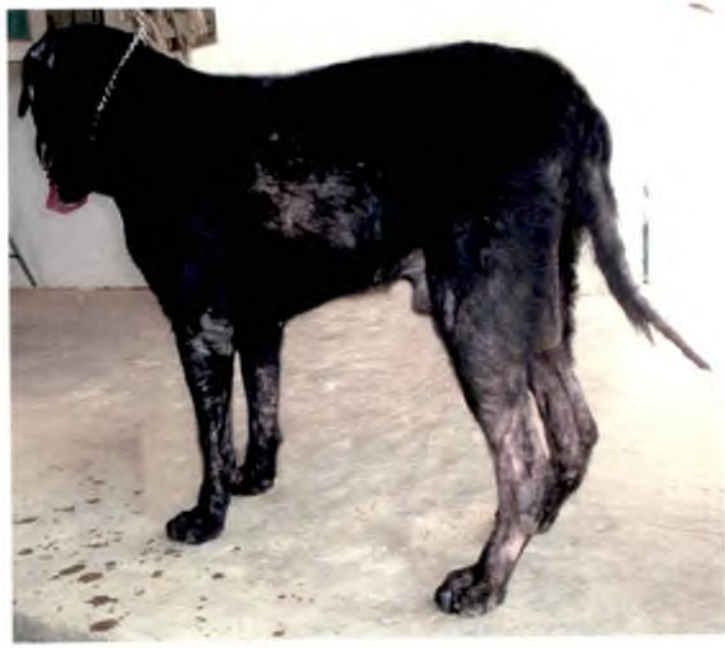
**A. Thyroid Gland - Follicular degeneration, congestion, infiltration of inflammatory cells - Moderate Thyroiditis**

**B. Skin- Hypoplasia of epidermis, Dermal sclerosis**

Among these, one had normal thyroxine value, low tri-iodothyronine and high TSH values and the other had low $T_4$, $T_3$ and high TSH concentration after six weeks of therapy. In one case, after discontinuing the treatment, there was recurrence of clinical signs (Table 9).

Table 9. Pre and post treatment concentrations of thyroid hormones in treated cases

| Serial no | Pretreatment | | | Post treatment | | |
|---|---|---|---|---|---|---|
| | $T_4$ (µg/dl) | $T_3$ (ng/ml) | TSH (mU/L) | $T_4$ (µg/dl) | $T_3$ (ng/ml) | TSH (mU/L) |
| 1 | 0.40 | 0.8 | 8.0 | 1.1 | 1.4 | 6.0 |
| 2 | 0.30 | 0.6 | 10.0 | 1.2 | 1.1 | 5.8 |
| 3 | 0.30 | 0.7 | 10.4 | 1.0 | 0.9 | 6.2 |
| 4 | 0.20 | 0.6 | 9.0 | 0.9 | 1.2 | 4.4 |
| 5 | 0.80 | 0.5 | 8.2 | 1.0 | 0.6 | 7.2 |
| 6 | 0.70 | 0.4 | 9.4 | 0.8 | 0.5 | 8.7 |



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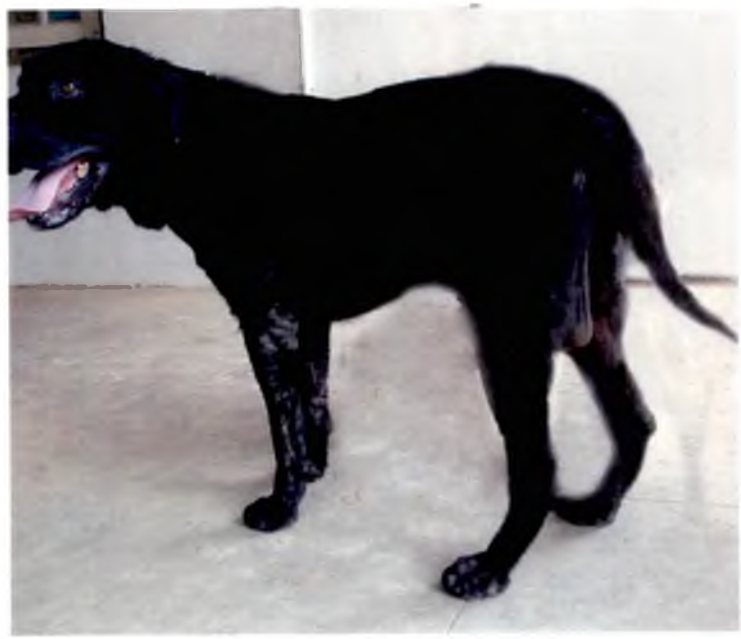
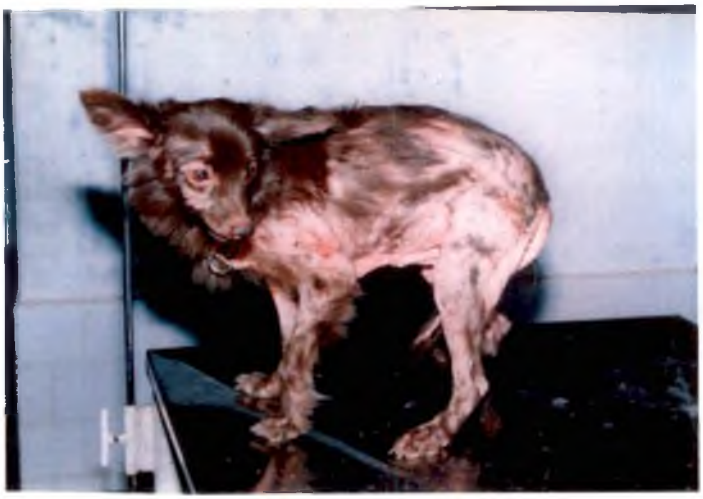


B

**Plate 3. Rat tail with generalized alopecia in a hypothyroid dog.**

**A. Before treatment** **B. 4 months after treatment**



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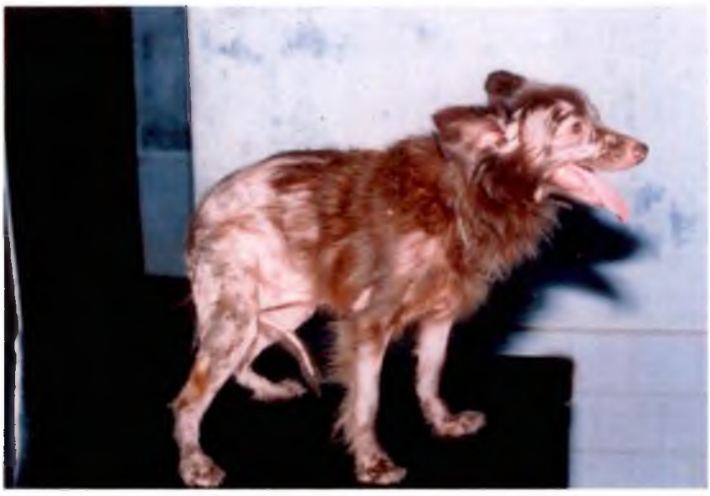

B

C

**Plate. 4. Dog with advanced hypothyroidism showing alopecia, scaliness and pyoderma**

**A. Before treatment B. 6 weeks after treatment**

**C. 6 months after treatment**

# *Discussion*

# 5. DISCUSSION



Dermatological disorders constitute a major problem in canine practice. Endocrine deficiencies/imbalances are one of the major causes of chronic skin diseases in pets.

Hypothyroidism was one of the most commonly diagnosed endocrinopathies in dogs (Kaufman *et al.*, 1985). Early signs of hypothyroidism in more than 90 per cent of cases were confined to the skin such as dry scaly skin, dull brittle hair, failure of growth of clipped hair or bleaching of normal hair colour (Chastain, 1982).

Dogs presented to University Veterinary Hospitals with clinical signs suggestive of endocrine dermatoses were subjected to detailed anamnesis, clinical examination and laboratory investigations.

## 5.1. PREVALENCE

The overall prevalence of dermatological disorders in the canine population as per the hospital records, during the study period was 10.28 per cent. This is in agreement with the findings of Thushara (2003) and Udayasree (2004) who reported that dermatological problems constitute 10.19 per cent and 18.93 per cent respectively of the total canine cases presented to the Veterinary Hospitals.

The dermatological disorders due to hypothyroidism constitute 0.13 per cent of the total canine cases. The incidence of hypothyroidism in the present study is in agreement with the observations of Panciera (1994a) and Dixon (2001) who reported a prevalence of 0.2 per cent and 0.2 to 0.64 per cent respectively. But the incidence rate was less than that reported by Chakrabarti *et al.* (2001).

### 5.1.1. Age

The analysis of the percentage of dogs suffering from hypothyroidism in various age groups revealed that the age group between seven to ten years (50 per cent) had the highest incidence followed by three to seven years (25 per cent).

Baker and Thomsett (1990), Panciera (1997a) and Mueller (2003) also reported similar observations.

Nelson and Ihle (1987a) reported that the age of onset of clinical signs in canine hypothyroidism varied, but usually four to six years. Large and giant breed dogs tend to develop clinical signs at an earlier age (two to three years), low risk breeds show a linear increase in risk up to nine years of age.

Jeffers (1990) reported that although hypothyroidism affects dogs of any age, it typically affects dogs of four to ten years of age.

**5.1.2. Sex**

Sex-wise prevalence of canine hypothyroidism showed that 56.25 per cent were males and 43.75 per cent were females. But Nelson and Ihle (1987a) and Jeffers (1990) reported that there was no sex predisposition in canine hypothyroidism.

According to Panciera (1997a) neutered dogs regardless of sex were found to have a significantly higher risk of hypothyroidism compared with sexually intact dogs. In the study conducted by Nesbitt *et al.* (1980), out of 108 dogs with hypothyroidism, the number of males (55) approximated to the number of females (53).

The higher incidence of hypothyroidism within males observed in the present study could be attributed to the large number of males in canine population.

**5.1.3. Breed**

In the present study, the hypothyroidism has the highest occurrence in German Shepherd dogs (31.25 per cent) followed by other breeds which included Dachshunds (25 per cent), Spitz (18.75 per cent), Labrador (12.50 per cent), Doberman (6.25 per cent) and Non-descript (6.25 per cent).

Chastain (1982) and Panciera (1997a) reported that Spaniels, Doberman Pinschers, Irish setter, Pomeranians, Dachshund and Golden retrievers were most

commonly affected with hypothyroidism. Nelson and Ihle (1987a) and Jeffers (1990) reported that German Shepherds, Mongrels, Springer spaniels and Beagles appeared to have less chance of developing hypothyroidism.

But in the present study, less incidence of hypothyroidism was noticed in Doberman Pinschers and high incidence in German Shepherd dogs where as a comparatively high incidence was noticed in Dachshunds. A detailed demographic study involving a wide range of breeds would be required for a proper conclusion.

## 5.2. SYMPTOMATOLOGY IN ENDOCRINE DERMATOSES

In veterinary medicine endocrine dermatoses are a common, multi-faceted and frequently confusing problem. Well-known clues of endocrine dermatoses include a dull, dry coat with bilaterally symmetric alopecia, poor regrowth of hair after clipping and chronic course (Shanley, 1990).

In the present study, the most common clinical features of endocrine dermatoses were bilaterally symmetrical alopecia, hyper pigmentation of the area of hair loss and coat changes such as dryness, dullness, dandruff, coarseness and sparseness. The pattern of dermatological disorders in the present study was in accordance with the findings of Shaw (1985), Baker (1986) and Mueller (2003).

Pyoderma with pruritus as observed in the suspected cases of endocrine dermatoses was in agreement with the findings of Shanley (1990), who opined that secondary pyoderma and seborrhoea developed in endocrine dermatoses were due to inadequate protection provided by a thinning of coat, changes in the skin barrier and immunological defence mechanisms. Endocrine dermatoses predisposed the animals to seborrheic changes in the skin (Jeffers, 1990).

## 5.3. CLINICAL SIGNS OF CANINE HYPOTHYROIDISM

### 5.3.1. Cutaneous signs of hypothyroidism

The most common dermatological changes of hypothyroid dogs in the present study included, seborrhoea (62.50 per cent), alopecia on the tail and around the neck (43.75 per cent) and bilaterally symmetrical pattern of hair loss of ventrolateral

abdomen and extremities (50 per cent). The dermatological manifestations of hypothyroidism in the present study was in accordance with the reports of previous workers, Walsh and Brown (1980), Nelson and Ihle (1987a), Jeffers (1990), Panciera (1997a), and Dixon (2001).

Nelson and Ihle (1987a) reported that most common clinical signs of hypothyroidism were related to a generalized slowing of cellular metabolism and dermatological abnormalities like alopecia, hyper keratosis, myxoedema and pyoderma and according to McKeown (2002), the most classical signs associated with hypothyroidism were dermatological abnormalities such as alopecia, seborrhoea and hyper pigmentation.

Coat changes such as dryness, dullness, dandruff and coarseness were observed in 87.75 per cent of the hypothyroid dogs. Nesbitt *et al.* (1980) and Baker and Thomsett (1990) also observed similar changes in coat conditions in dogs affected with hypothyroidism.

In most of the cases, the alopecia began on the tail and around the neck and then progressed to bilaterally symmetrical pattern of dermatoses. According to Jeffers (1990) early dermatological signs of hypothyroidism might appear as alopecia on the dorsal, proximal or distal aspect of the tail causing a "rat-tail appearance" and when the disease progresses, hair loss spread to the entire trunk and proximal limbs, and typically sparing the head and lower extremities except in giant breeds where it may begin on the distal extremities and spread towards the trunk. The alopecia in hypothyroidism was due to cessation of hair production and atrophy of hair follicles (telogen stage) (Baker, 1986).

Seborrhoea was observed in 62.50 per cent cases in the present study. These findings were similar to those reported by Jeffers (1990) and Rhodes (1990).

Pyoderma was observed in 43.75 per cent of the cases and this might be due to animal's impaired immune system (Nelson and Ihle, 1987a) or as a result of altered local immunity secondary to seborrhoea or of impaired systemic immunity (Jeffers, 1990; Panciera, 1997a).

The neutrophils of hypothyroid dogs had decreased ability to kill *Staphylococcus aureus*. This altered neutrophil function along with the altered metabolism in dermis may predispose the dog to skin infections (Slade *et al.*, 1984).

Pruritus was reported in 11 out of 16 cases. It was due to secondary bacterial infection or *Malassezia* infection. Rosychuk (1997) reported that pruritus did not occur in canine hypothyroidism unless complicated with *Malassezia* or bacterial pyoderma.

**5.3.2. Non-cutaneous signs of hypothyroidism**

Ocular abnormalities such as corneal ulceration, chronic lacrimation and blepheritis were observed in 18.75 per cent of the cases and this may be probably an effect of hyper lipidemia rather than a direct result of thyroid hormone deficiency (Panciera, 1997a).

Panciera (1994a) and Greco *et al.* (1998) opined that obesity observed in hypothyroid dogs due to decreased metabolic rate. Heat seeking behavior observed in two out of 16 cases and this may probably due to defective thermoregulatory mechanisms in hypothyroid dogs (Panciera (1997a).

Lethargy observed in hypothyroid dogs was a consequence of low metabolic rate and cerebral hypoxia due to low cardiac output and cerebral blood flow (Panciera, 1994a).

It is presumed that the chronic ceruminous otitis observed in few cases in the present study was due to seborrhoea which is developed as a sequelae of defective cutaneous immune system in hypothyroid dogs (Muller *et al.*, 1989)

Reproductive abnormalities like prolonged anoestrum were observed only in one out of seven female hypothyroid dogs. Panciera (1997a) reported that reproductive abnormalities in female dogs had not been well documented in canine hypothyroidism, but might consist of infertility, shortened duration of oestrus, prolonged or irregular anoestrus and abortion. Hyperprolactinemia occurred in severe hypothyroidism due to excess thyrotropin releasing hormone and deficient

hypothalamic dopamine concentration. Hyperprolactinemia might be responsible for infertility in dogs with severe hypothyroidism since prolactin may interfere with gonadotropin releasing hormone or directly with gonadal steroid production.

## 5.4. CLINICAL PATHOLOGY

### 5.4.1. Hemogram

The mean values of haemoglobin in animals of group I and II were found to be 10.40 ± 0.74 g/dl and 10.85 ± 1.50 g/dl respectively. These values did not show any significant difference from the values obtained in control group.

The mean values of volume of packed red cells in animals of group I and II were serum 33.25 ± 3.88 per cent and 35.75 ± 6.78 per cent respectively and corresponding value for control group was 39.13 ± 3.14 per cent. No significant difference in the mean values of the control and diseased groups could be observed. However seven out of 16 cases showed low VPRC values ranging from 25 per cent to 34 per cent, suggestive of mild anaemia. Even though the results of Hb and VPRC values did not show any significant difference when compared to normal values, low normal values are suggestive of mild anemia.

Jeffers (1990), Panciera (1999) and Catherine *et al.* (2000) observed mild non-regenerative anaemia in 25 to 30 per cent of hypothyroid dogs.

Mild non-regenerative anaemia found in hypothyroid dogs was due to decreased erythropoietin production and lack of direct effect of thyroid hormone on erythroid precursors in the bone marrow to stimulate haematopoiesis (Bush, 1991;Panciera *et al.* 2000) and reduced tissue oxygen demand and depressed erythropoiesis at the stem cell level (Raskin, 2000).

Chastain and Panciera (1995) suggested that red cell production was slowed by hypothyroidism to a rate due to inadequate replacement of red blood cells from aging and splenic removal from the circulation. Anemia observed in hypothyroid dogs could have resulted from reduced thyroxine concentration as it can directly

affect erythroid stimulation and indirectly by increasing the cellular oxygen demands of erythropoietic cells (Sullivan *et al.*, 1993).

### 5.4.2. Leucogram

The leucogram of the diseased and control animals did not show any significant difference in the present study. Dixon (2001) reported neutropenia in hypothyroid dogs. The inconsistency of results of the present study with the available literatures could be an incidental finding due to the smaller number of cases diagnosed. Long standing and untreated hypothyroid dogs could develop neutropenia which is not observed in the present study.

Routine blood screenings are important not only as a tool to help the diagnosis of hypothyroidism but also as a means of eliminating other diseases with similar clinical signs. Many diseases such as hyper adrenocorticism, diabetes mellitus, renal failure and hepatic diseases, as well as post anaesthetic and post surgical states, have clinical signs and biochemical abnormalities consistent with that of hypothyroidism.

### 5.4.3. Serum Biochemical Parameters

#### *5.4.3.1. Serum Cholesterol*

The mean values of cholesterol in animals of group I and II were 361.1 ± 84.08 mg/dl and 299.5 ± 69.56 mg/dl respectively. Statistically significant increase ($P \leq 0.05$) was obtained in serum cholesterol values of the diseased animals when compared to control group.

According to Kaneko (1997) normal serum cholesterol concentrations in dogs ranged from 125 to 250 mg/dl. The mean values of the cholesterol in diseased animals in the present study agree with the findings of Chakrabarti *et al.* (2001) and Gomathy *et al.* (2004) who had also reported serum cholesterol level of 344.8 ± 29.1 mg/dl and 332.6 ± 12.8 mg/dl respectively in hypothyroid dogs.

Chastain (1982), Jeffers (1990), Panciera (1994a) and Catherine *et al.* (2000) observed hypercholesterolemia in 65 to 75 per cent of the cases.

Hypercholesterolemia observed in the present study resulted from decreased peripheral lipoprotein lipolysis, decrease in the low-density lipoprotein receptors, reduced hepatic utilization and augmented hepatic production of cholesterol in hypothyroid dogs (Panciera, 1994a; Panciera, 2000) or decreased degradation of lipid resulted in increased concentration of plasma lipids including cholesterol when compared with the linear decrease in cholesterol synthesis (Chastain, 1982; Forrester and Monroe, 1997).

### *5.4.3.2. Serum Alkaline Phosphatase (ALP)*

The mean values of serum alkaline phosphatase activity in animals of group I and II were 217.6 ± 127.50 U/L and 170.1 ± 109.90 U/L respectively. These values were not statistically significant when compared to normal animals. But five out of 16 cases (31.25%) showed an elevation in serum ALP activity. The observations in the present study agree with the findings of Panciera (1994a) and Chakrabarti *et al.* (2001).

Mild elevation observed in five out of 16 dogs probably due to secondary liver damage associated with hypothyroidism (Bush, 1991) or due to hepatic dysfunction (Panciera, 1994a). Muller *et al.* (1989) stated that ALP elevation presumably resulted from the degenerative myopathies in canine hypothyroidism.

### *5.4.3.3. Serum Gamma Glutamyl Transferase (GGT)*

The mean values of serum gamma- glutamyl transferase (GGT) activity in animals of group I and II were 5.9 ± 3.01 U/L and 3.8 ± 2.49 U/L respectively. For the control group, it was 3.5 ± 1.69 U/L. No significant differences were observed in the mean values of the control and diseased animals. But four out of 16 cases (25 per cent) showed an elevated GGT activity. Dixon (2001) reported an increased GGT activity in hypothyroid dogs.

Leib (1997) and Johnson and Sherding (2000) reported that increased level of cholesterol associated with hypothyroidism resulted in cholestasis and GGT elevation.

The variation observed in the present study may be due to variation in the severity of degree of hypothyroidism.

### *5.4.3.4. Serum Thyroxine ($T_4$)*

Mean serum thyroxine levels in animals of groups I and II were 0.48 ± 0.28 µg/dl and 0.63 ± 0.08 µg/dl. For the control group, it was 1.04 ± 0.14 µg/dl. The mean concentration of serum $T_4$ in control group was similar to that reported by Kaneko (1997).

A statistically significant decrease ($P \leq 0.05$) was observed in serum thyroxine values of diseased animals when compared to control group. The observations in the present study agree with the findings of Jeffers (1990), Nelson *et al.* (1991) and Panciera (1999) who reported that lower the total $T_4$ concentration, higher the likelihood that the dog had hypothyroidism (Fig 3).

### *5.4.3.5. Serum Tri-iodothyronine ($T_3$)*

Mean serum levels of $T_3$ in animals of group I and II were 0.74 ± 0.31 ng/ml and 1.14 ± 0.39 ng/ml respectively. For the control group, it was 1.26 ± 0.66 ng/ml. Group I had lower concentration of $T_3$ compared to control group. Gomathy *et al.* (2004) reported that mean $T_3$ levels in control dogs and hypothyroid dogs were 0.92 ± 0.05 ng/ml and 0.45 ± 0.06 ng/ml respectively (Fig 4)

There was no significant difference in the mean levels in animals of group II and control group. Under stimulation by TSH, the thyroid gland preferentially secretes $T_3$, and in addition much of the circulating $T_3$ is derived from peripheral deiodination of $T_4$. These factors accounted for the finding of a normal serum $T_3$ concentration in the present study (Panciera, 1999).

Progressive loss of thyroid gland function in human patients with hypothyroidism, $T_4$ secretion by the thyroid gland decreased to a greater extent than secretion of $T_3$ and there was evidence of an increase in the rate of conversion of $T_4$ to $T_3$ in peripheral tissues and this may also one of the factors for the normal serum $T_3$ concentrations of the present study (Peterson *et al.*, 1997).

### *5.4.3.6. Thyroid Stimulating Hormone (TSH)*

Mean thyroid stimulating hormone (TSH) levels in animals of group I and group II were 8.7 ± 2.50 mU/L and 6.6 ± 1.59 mU/L respectively. For the control group, it was 5.3 ± 1.19 mU/L. Group I differed significantly ($P \leq 0.05$) from the control group and group II did not show any significant difference from the control group (Fig 5)

Secretion of TSH from the pituitary gland stimulates secretion of $T_4$ and $T_3$, which in turn depresses TSH secretion in a negative feed back manner. These decreased concentrations of $T_4$ and $T_3$ might stimulate the pituitary gland and there by an increased blood TSH levels in the present study (Nelson and Ihle, 1987a; Jeffers, 1990; Panciera, 1997b).

William *et al.* (1996), Peterson *et al.* (1997), Ramsey *et al.* (1997) and Dixon (2001) observed that some naturally occurring cases of canine hypothyroidism had TSH concentrations within the reference range due to later diagnosis or prolonged periods of low thyroid hormones might result in disruption of the feed back pathway by down-regulation or exhaustion of TSH production by pituitary thyrotrophs.

Peterson *et al.*(1997) pointed that one cannot exclude a diagnosis of hypothyroidism on the basis of a normal or low normal TSH concentrations because; the assay detects some, but not all, isoforms of circulating TSH.

## 5.5. HISTOPATHOLOGY

### 5.5.1. Thyroid biopsy

Histopathological changes of the thyroid gland in confirmed case of hypothyroidism is similar to the changes mentioned by Muller and Kirk (1976), Gosselin *et al.* (1981) and Lücke *et al.* (1983). Thyroiditis developed in the present study may be due to thyroglobulin autoantibodies reacting with plasma membrane of the follicular cells, thereby allowing killer lymphocyte acting via antibody-dependent cytotoxicity to injure the target cell.

### 5.5.2. Skin biopsy

The histopathological changes of the skin in the present study agree with the findings of Muller and Kirk (1976) and Krishnamurthi and Rajan (2001) who reported thinning of epidermis, atrophy and collagen degeneration of dermal appendages and degenerating or absence of hair follicles of the skin of hypothyroid dogs.

## 5.6. THERAPY

### 5.6.1. Dose

Ten out of 16 cases were treated with Eltroxin ® @ of 20 µg/kg body weight twice daily for six weeks. This is in accordance with the recommendations of Nelson and Ihle (1987b), Ramsey (1997) and Mueller (2003).

Panciera (1997c) recommended the levothyroxine treatment @22 µg/kg body weight/day or 11to 22 µg/kg body weight twice a day, because twice a day treatment resulted in less fluctuation in daily $T_4$ concentrations. Thyroid hormones have most of their effect through activation of nuclear receptors that induce gene transformation and protein production. Through this mechanism, thyroid hormones have duration of action that exceeds their presence in the plasma and makes once-a-day treatments successful in most cases. Because of the considerable individual variation in pharmacokinetic of thyroid hormones some dogs do not respond adequately to once-a-day treatment. Therefore twice a day treatment at 22 µg/kg body weight is most prudent to ensure highest efficacy with good therapeutic response.

### 5.6.2. Treatment response

The response to treatment in the present study is in agreement with the observations of Chastain (1982), Nachreiner and Refsal (1992) and Panciera (1997c). Increased hair loss was evident during the initial days following treatment in some cases. When the hair follicles entering anagen phase of hair growth, the

telogen hairs will shed, that may be the reason for hair loss following treatment in the present cases (Panciera, 1997c).

Samples were taken 12 hours post treatment and hormone levels were estimated. This is in accordance with the recommendations of Nesbitt *et al.* (1980), Nelson and Ihle (1987b), Muller *et al.* (1989) and Jeffers (1990) since maximal increase from baseline values were observed at six to 12 hours following treatment with $T_4$.

In four cases (66.66 per cent) there was an excellent response obtained in four to six weeks after therapy. In cases showed positive response to treatment, serum $T_4$ concentrations were within normal reference range. These findings are in agreement with the observations of Chastain (1982) and Nelson and Ihle (1987b).

In the present study after thyroxine supplementation, TSH decreased as the dog's serum $T_4$ increased. When exogenous levothyroxine is administered plasma $T_4$ increased. Levothyroxine is converted to tri-iodothyronine ($T_3$) through deiodination of $T_4$, and negative feedback on the pituitary by $T_4$ and $T_3$ resulted in reduced production of TSH (Mckeown, 2002).

Two out of four cases showed positive response to treatment, the $T_3$ concentrations were found to be below the mean $T_3$ values of the control animals. Similar findings were observed by Nachreiner *et al.* (1993) and Panciera (1997c) after treatment with $T_4$ supplement in hypothyroid dogs and this may be due to impaired deiodination of $T_4$ due to nonthyroidal illness or drug administration (Panciera, 1997c).

Nesbitt *et al.* (1980) suggested $T_4$ to $T_3$ conversion problem, if 6-12 hours post treatment $T_4$ values were high and $T_3$ values were low, necessitating a change in the type of thyroid replacement.

One case showed inadequate response to treatment and characterized by low $T_3$ level with above normal TSH concentration. If the response to therapy is inadequate and the serum $T_4$ is below normal, with high TSH level, an increase in the dose of levothyroxine is indicated (Panciera, 1997c).

In one animal which showed poor response to treatment, there were low $T_4$ and $T_3$ values with TSH values higher than the normal range. It may be due to impaired absorption from the intestinal tract or due to irregularity in administration of drug (Nelson and Ihle, 1987b).

# *Summary*

## 6. SUMMARY

The present study, "Thyroid function evaluation in canine dermatoses" was conducted to study the prevalence of thyroid dysfunction in cutaneous disorders, changes in the thyroid hormone levels in dogs affected with dermatological disorders and treatment responses following administration of $T_4$ supplement (Eltroxin®). Prevalence of hypothyroidism was studied among the dogs presented with dermatological disorders at the University Veterinary Hospitals, Mannuthy and Kokkalai during the period from June 2004 to May 2005.

Analysis of the prevalence of the dermatological disorders revealed that overall prevalence was 10.28 per cent among 11,991 canine cases presented during the study period. Among the 1,233 dermatological cases presented, 54 (4.38 per cent) cases suspected to have endocrine dermatoses were selected. Out of 54 suspected cases of endocrine dermatoses, 16 were found to be due to hypothyroidism. This accounted for 0.13 per cent of the total canine cases and 29.6 per cent of suspected cases of endocrine dermatoses presented to the University Veterinary Hospitals taken up for the study.

The most common clinical features in endocrine dermatoses were bilaterally symmetrical alopecia, hyperpigmentation of the area of hair loss and coat changes such as dryness, dullness, dandruff, scaliness, coarseness and sparseness. Pruritus due to *Malassezia* or bacterial infection was observed. Abnormal cyclical activity was observed in few cases.

Out of the 54 endocrine dermatoses cases, hypothyroidism was confirmed in 16 cases based on serum levels of $T_3$, $T_4$ and TSH and the total dogs were grouped in to two groups. Group I (n=8) had low serum $T_4$, $T_3$ values with high TSH values. In group II (n=8), there was low serum $T_4$, normal $T_3$ values and high TSH values.

Dogs between the age group of seven to ten years were more frequently affected with hypothyroidism. Out of the 16 cases, nine were found to be males and the remaining were females. Hypothyroidism was recorded more in German Shepherd breed followed by Dachshund.

The common dermatological changes exhibited by hypothyroid dogs included seborrhea, alopecia which usually began on the tail and around the neck and bilaterally symmetrical pattern of hair loss. In German Shepherd and Labrador, the alopecia was most commonly observed in the extremities rather than on the trunk. Sub acute, superficial pyoderma was found in four dogs and superficial pyoderma in other three dogs.

Obesity observed in the hypothyroid cases was mild. Heat seeking behavior was observed only in two cases. Six dogs out of sixteen dogs had ceruminous otitis. Hyperpigmentation in the area of hair loss was observed in 68.75 per cent of cases. Pruritus was reported in 11 out of 16 cases due secondary bacterial or *Malassezia* infection.

Haematological parameters revealed significant difference between the diseased and control groups. Mild anemia was observed in seven out of sixteen cases.

Serum enzymes such as alkaline phosphatase and gamma glutamyl transferase showed elevation in few cases. Serum cholesterol level showed significant elevation in diseased animals compared with the control group.

Ten out of sixteen positive cases, having rat tail, severe alopecia and recurrent pyoderma were selected and treated with Eltroxin® @ 20 µg/Kg body weight twice daily for six weeks. Four out of six follow up cases showed clinical improvement. Increased hair loss was evident early in treatment in some cases. Regrowth of hair, cessation of seborrhea and improvement in coat conditions were noticed in cases which responded to treatment within one month. Minimum of one month therapy was needed to know the therapeutic response.

Based on the present study, it was concluded that hypothyroidism was frequently associated with canine endocrine dermatoses. $T_3$, $T_4$ along with TSH estimation was helpful in the diagnosis of hypothyroidism. Eltroxin ® was found to be effective in replacement therapy and a minimum of one month therapy was required to evaluate the clinical response.

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# THYROID FUNCTION EVALUATION IN CANINE DERMATOSES

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## ABSTRACT

Prevalence of hypothyroidism was studied among the dogs presented with dermatological problems at the University Veterinary Hospitals, Mannuthy and Kokkalai, during the period from June 2004 to May 2005. Among 1,233 dermatological cases presented, hypothyroidism accounted for 1.23 per cent (16 cases)

Dogs between the age group of seven to ten years were more frequently affected and no significant differences in the incidence rate between male and female dogs were observed. Hypothyroidism was recorded more in German Shepherd breed followed by Dachshunds.

Low serum thyroxine ($T_4$) and high thyroid stimulating hormone (TSH) level with normal or low normal $T_3$ levels were observed in the hypothyroid dogs.

The most common dermatological changes exhibited by hypothyroid dogs included seborrhea, alopecia of tail and around the neck, bilaterally symmetrical pattern of hair loss and coat changes such as dryness, dullness, dandruff, scaliness, coarseness and sparseness.

A significant increase in serum cholesterol concentration was observed in the affected dogs. Serum enzymes such as alkaline phosphatase and gamma glutamyl transferase were showed elevation in few cases.

Replacement therapy using Eltroxin® was found to be effective in treating hypothyroidism. A minimum of one month was needed to evaluate the therapeutic response. Four out of six (66.66 per cent) confirmed cases of hypothyroidism showed an excellent response to replacement therapy.