PATHOLOGY OF HYPOTHYROIDISM IN PIGS

By

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THESIS

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DECLARATION

I hereby declare that this thesis entitled **PATHOLOGY OF HYPOTHYROIDISM IN PIGS** is a bonafide record of research work done by me during the course of research and that this 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 this thesis entitled **PATHOLOGY OF HYPOTHYROIDISM IN PIGS** is a record of research work done independently by Smt K S Prasanna under my guidance and supervision and that this has not previously formed the basis for the award of any degree, fellowship or associateship to her

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Dedicated to My
Beloved Husband and
Loving Brother

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Introduction

INTRODUCTION

The thyroid gland is unique among the endocrine glands and its product thyroxine containing 70 to 80 per cent of total body iodine, significantly influences every tissue in the body It has been well established that iodine and thyroid functions are closely related and want of a little of iodine could adversely affect the growth and production of the animals

The existence of endemic goiter in man and animals due to absolute or relative deficiency of iodine has been well established since long Kelly and Snedden (1960) while discussing the geographical distribution of endemic goiter in Asia have identified certain regions of India including coastal areas of Kerala as endemic zones of goiter

The iodine content of soil varies with geochemistry of the land and climatic conditions In heavy rain fall areas iodine deficiency occurs because of leaching of surface soil Kerala therefore is bound to have iodine deficiency in soil due to heavy rainfall The tendency to use nitrogenous fertilizers injudiciously in the fields is also likely to induce hypothyroidism in animals

The role of goitrogenic substances widely distributed in nature may also play a role in precipitating hypothyroidism in the animal population Therefore there is need to make a detailed investigation on this problem to understand the influence of sub-clinical hypothyroid state on the health and growth of animals

There has been a few detailed investigations on the problem of thyroid disorders in cattle and goats in India However there has not been any published reports on thyroid disorders in pigs in India Incorporation of cassava rubber seed meal and sorghum as feed ingredients in pig feed is a common practice in Kerala These contain goitrogenic substance and when fed for a long spell it can induce sub clinical hypothyroidism

In order to assess the functional status of the thyroid the thyoxine level of some of the pigs slaughtered at the Meat plant at Mannuthy and Koothattukulam was estimated at random Besides this an experimental study was designed to assess the sequence of pathological changes in hypothyroid state and its influence on the animal health and production in pigs Thiourea a chemical goitrogen was used for inducing hypothyroidism in pigs in this study and the results obtained have been presented and discussed

Review of Literature

REVIEW OF LITERATURE

1. Historical Resume

The chinese recognized diseases of thyroid as early as the second Millennium B C The name Thyroid for the gland was first suggested by Wharton (1658) King (1836) recognized thyroid as an organ of internal secretion Cooper (1936) first studied the role of thyroid in various metabolic activities of the body Kocher (1883) observed development of myxoedema like syndrome following thyroidectomy Bauman (1896) demonstrated the presence of considerable quantities of iodine in the thyroid Kendall (1915) isolated an iodinated amino acid from the thyroid of animals and named it as thyroxine The identification and synthesis of thyroxine was first achieved by Harington and Barger in 1926 Kimbal (1937) noted the association of hypothyroidism and endemic goiter Gross and Pitt-Rivers (1952) identified triiodo thyronine (T_3) in the gland and in plasma Thyroglobulin was classified as a glycoprotein and most of the carbohydrate was found accounted by glucosamine and mannose (Gottschalk and Adam 1954) The chemical characteristics of purified thyroglobulin were discussed (Rac et al 1968) Immunohistochemical studies revealed that the thyroid gland was formed on day nine of the gestation by the central out pocketing of the foregut between the first and second branchial pouches The ultimorbranchial body was derived from the fifth pouch and fused with thyroid on twelth day of gestation (Taniguchi _et al_ 1990)

2 Thyroid Hormone synthesis

The synthesis of thyroid hormone was unique among endocrine glands because the final assembly of the hormone occurred extracellularly within the follicular lumen The iodide for the synthesis of thyroid hormone was trapped by follicular cells from the plasma, transported rapidly against a concentration gradient to the lumen and oxidised by a peroxidase in the microvillus membrane to iodine

The active protease within the thyroid gland cleaved the iodinated aminoacid from thyroglobulin (De Robertis, 1941) Thyroglobulin is a polypeptide, synthesised by follicular cells on the ribosome of endoplasmic reticulum The constituent aminoacids and carbohydrate were derived from the blood Newly synthesised thyroglobulin leaving the golgi apparatus was packed into apical vesicles and extruded into the follicular lumen (Edelhoch, 1960)

Out of the 5650 aminoacid residues in the thyroglobulin molecule 125 were tyrosyl units (Edelhock and Rall, 1964) Iodide was bound to tyrosyl residue in the thyroglobulin at the apical surface of the follicular cell to form successively monoiodotyrosine and diiodotyrosine These combined to form the two biologically active iodothyronines (thyroxine and triiodothyronine) secreted by the thyroid (Jubb et al 1993)

3 Thyroid function

The primary function of the thyroid hormone was considered as regulation of cellular oxidation and stimulation of oxygen consumption for normal growth and development (Barker 1951) Oxygen consumption was increased in the heart liver muscle, kidney and in white blood cells after the administration of thyroxine Tissues like the brain did not share in this response (Barker and Schwartz 1953) The activities of hexokinase cytochrome reductase cytochrome oxidase and other respiratory enzymes were influenced considerably along with the pentose phosphate pathway for glucose oxidation (Necheles and Beutler 1959)

Berman (1960) reported that the thyroid hormone regulated the basal metabolic rate It also influenced the development of hair and pigmentation in animals In conjunction with other hormones it exerted control over growth and development of young animals temperature regulation intermediary metabolism and reproduction (Bush 1969)

Barker (1971) reported that thyroxine was essential for full translation of genetic message into the ribonucleic acid and ribosomal synthesis of protein Metabolic processes were regulated such as protein breakdown carbohydrate and lipid turnover and calcium metabolism Gorbman and Bern (1979) observed that nervous function at all levels was influenced by the thyroid Exchange of water and salts, between cell and body fluids spontaneous electrical activity threshold of sensitivity to a variety of stimuli and reflex time motor behaviour were also under the control of the thyroid gland May <u>et al</u> (1979) reported that reduced function of the thyroid resulted in immunological depression in swine

4 Pathological conditions associated with the thyroid gland

Bush (1969) classified thyroid disease capable of producing clinical signs as goiter, hypothyroidism hyperthyroidism thyroditis and thyroid neoplasia

<u>4 1 Goiter</u>

Cohr (1966) defined the term goiter as non inflammatory non-neoplastic enlargement of the thyroid gland He classified goiter as

1 Atoxic goiter (including sporadic form)

2 Goiter with functional change which may be athyroid or hypothyroid goiter and hyperthyroid goiter

Kaneko (1970) classified goiter as

1 Nontoxic goiter (Simple goiter with normal level of hormones or hypothyroid with less than normal level of hormones)

2 Toxic goiter (hyperthyroid goiter)

Jones and Hunt (1983) classified goiter on the morphological basis as

1 Colloid goiter
2 Hyperplastic goiter
3 Nodular goiter
4 Exophthalmic goiter

4 1 1 Endemic goiter

The main etiology for endemic goiter was considered as iodine deficiency Mc Carrison (1913) related goiter in Himalayas to water pollution Stott et al (1931) pointed out the association between high goiter rate and dolomitic lime in India He also noted that hard water with high calcium content was of importance in causing goiter in Himalayan endemic zones

Levine et al (1933) identified that elemental iodine and inorganic iodine themselves in large doses were goitrogenic

Wilson (1941) suggested that excessive intake of fluorine might be a causative agent for endemic goiter in Punjab Stanbury et al (1954) stated that there was an inverse correlation between the quantity of iodine excreted in the urine of patients in endemic area

Kelly and Snedden (1960) suggested that mountain slopes of Himalaya Alps and Pyrenese were the world s most notorious foci of endemic goiter Scrimshaw (1964) reported that cold climate influenced the prevalence of endemic goiter in border line iodine supply regions as a result of increased demand for thyroid hormone

Halik and Zavadsky (1978) reported goiter in breeding lambs in endemic areas Gilbert (1984) stated that consumption of cassava could be a key factor in causing endemic goiter in areas where there were iodine deficiency in the diet of people Ghergaria et al (1987) reported an outbreak of endemic goiter in new born piglets This group had a mortality rate of 25-30 per cent The outbreak was controlled by intra muscular injection of potassium iodide to sows three or four times during late pregnancy and a high dose to three day old piglets Boyages and Halper (1993) described the pathophysiological changes observed in endemic cretinism They included foetal hypothyroidism which led to the neurological damages Targovnik et al (1993) reported that defective or impaired thyroglobulin synthesis resulted in congenital goitrous hypothyroidism

4 1 2 Colloid goiter

Follis (1959) suggested that colloid goiter was an involutionary phase of hyperplastic goiter This type of goiter was asymptomatic Means et al (1963) noted that the gland was symmetrically enlarged and was soft or spongy to feel The gland was not able to return to its normal size even after the demand for thyroxine was met Follicles were packed with colloid and there was greater variation in their size and sometimes they coalesced to form cysts Jubb et al (1993) stated that colloid goiter developed even after sufficient amount of iodide was added to the diet of animals In older animals this condition was seen after the requirement of thyroxine had diminished Some involuted follicles in colloid goiter had remnants of the papillary projections of follicular wall Inter follicular capillaries were less well developed than those with diffuse hyperplastic goiter

4 1 3 Parenchymatous goiter

Wilson (1975) pointed out that an early characteristic sign of stimulation of the gland by thyroid stimulating hormone was hyperplasia of the thyroid epithelium, and appearance of vacuoles around the periphery of the colloid

Jubb _et al_ (1993) reported that the major factors responsible for the development of thyroid hyperplasia were iodine deficient diet goitrogenic compounds that interfered with thyroxine synthesis dietary iodide excess and genetic enzyme defects in the biosynthesis of thyroid hormones All these factors resulted in inadequate thyroxine synthesis and decreased blood levels of thyroxine and triiodothyronine This stimulated the hypothalamus and pituitary resulting in hypertrophy and hyperplasia of the follicular cells

4 1 4 Nodular goiter

Jones and Hunt (1983) reported that the nodular goiter was frequent in older animals They described well defined nodules in one or both thyroid lobes Many follicles were distended with colloid while others were small and devoid of colloid Jubb _et al_ (1993) reported that nodular hyperplasia in thyroid glands of horses cats and dogs appeared as multiple white to tan nodules of varying size Nodular goiter consisted of multiple foci of hyperplastic follicular cells sharply demarcated from the adjacent thyroid parenchyma but not encapsulated

4 2 Hypothyroidism

Marine and Lonhart (1910) reported congenital hypothyroidism occurring in an endemic area of iodine deficiency In conditions associated with low levels of thyroid hormones they observed defects in foetal development also

Ruminant hypothyroidism mainly occurred in areas of endemic goiter (Hojer 1931) Ferguson et al (1956) pointed out that hypothyroidism had an adverse effect in the young growing animals as it caused interference with the overall growth, than in mature animals Reproductive disorders associated with iodine deficiency were characterised by loss of libido in male and suboestrum in females (Calderbank 1963)

Wallach (1965) pointed out that hypothyroidism was generally characterised by lowered body temperature and growth retardation Mason and Wilkinson (1973) classified hypothyroidism into following categories

1 Primary hypothyroidism due to lack of functioning of the thyroid

2 Secondary hypothyroidism due to pituitary insufficiency

3 Hypothyroidism due to iodine deficiency
4 Hypothyroidism due to ingestion of goitrogen
5 Hypothyroidism due to dyshormonogenesis
6 Hypothyroidism due to autoimmune thyroiditis
7 Hypothyroidism due to neoplasia

Wilson (1975) summarised the effects of hypothyroidism in ruminants as follows

1 Retention of placenta
2 Infertility
3 Lowered milk production
4 Lowered resistance to infection
5 Increased susceptibility to ketosis
6 Late abortion still birth and weak offspring

4 2 1 Hypothyroidism due to iodine deficiency

Iodine deficiency in the environment caused simple hypothyroidism (Southcott 1945) Four per cent of the total incidence of non-toxic goiter was due to other causes Calderbank (1963) pointed out that there was no correlation between the iodine content of soil and pasture growing on it But the iodine content of drinking water was found to be low in endemic goiter region

Scrimshaw (1964) reported that heavy rainfall played an important role in leaching of surface soil, leading to iodine deficiency Means et al (1963) stated that the soil contained more iodine than the rocks from which they were produced This was partly because of the retention of iodine by plant life growing on the soil

Wilson (1975) observed that high protein diet interfered with utilisation of iodine An epidemiological survey undertaken in Germany, revealed that upto ten percentage of cattle and sheep in farms and fifteen percentage of swine herds were affected with iodine deficiency This was due to the presence of nitrates thiocyanates or glucosinate in the diet (Blood and Radostitis 1987)

4 2 2 Hypothyroidism due to goitrogens

Presence of goitrogenic substances in the feed stuffs caused hypothyroidism in animals Calderbank (1963) reported two types of goitrogens A thiocyanate type which inhibited thyroidal uptake of iodine This blocking effect was overcome by simultaneous administration of iodine The thiouracil type which interfered with organic binding of iodine in the thyroid and this effect was reversed by the administration of thyroxine

Greer et al (1966) showed that thiocyanates were about 25 times more potent than nitrates in inhibiting thyroid function Two basic types of goitrogens have been described Those like thiouracil described as organic goitrogens and anionic goitrogens represented by thiocyanate and nitrate (Catt 1970)

4 2 2 1 Natural goitrogens

Sharpless *et al* (1939) reported that soyabean flour meal in rats produced enlarged thyroid Kennedy and Purves (1941) demonstrated the goitrogenic effect of Brassica seeds in rats They observed hyperplasia of thyroid glands and the weight of the glands was found to be increased by 300 times Rapid proliferative changes occurred in the second and third weeks after the treatment All the halogens if present in excess were capable of displacing iodine and caused iodine deficiency (Wilson, 1941)

Astwood *et al* (1945) found that the seeds of *Ochlearia* and *Conringia orientalis* contained 5 5-dimethyl-2 thioxazolidone a goitrogenic substance Astwood *et al* (1949) isolated L-5 vinyl-2 thioxazolidine (goitrin) from turnips

A marked decrease in follicular colloid and decrease of follicular epithelium were observed in sheep and goat fed cauliflower leaves (Spisni and Gravalglia 1954) Clements and Wishart (1956) demonstrated that milk from cows fed on narrow stemmed kale (*Brassica oleracea moellerii*) interfered with uptake of 131_{I} in man and animals

Sinclare and Andrews (1958) noted that feeding a heavy diet of kale to pregnant ewes caused high incidence of goiter and hypothyroidism in new born lambs Greer and Whalton (1961) isolated 5-phenyl-2-thioxazolidone from the seeds of Barbarea vulgaris Greer (1962) isolated goitrin from turnips and Brassica seeds

Purushothaman et al (1985) reportedthat castor bean meal had a mild goitrogenic effect when fed to sheep Simple goiter and hypothyroidism were observed in ruminants fed Brassica seed and Brussel sprints (Blood and Radostitis 1987) Ramirez et al (1987) observed that large fall in protein bound iodine value occurred in cattle fed Leuceana leuocephala

Ratnakumar (1989) observed increase in the body weight and reduction in fur weight in cassava fed rabbits The serum thyroxine level in the experimental animals was reduced considerably

Rajan et al (1990) reported that rubber seed cake induced mild hypothyroidism in goats when fed at 20 per cent level for six months Rajan et al (1991) experimentally proved that Leuceana leucocephala was a mild goitrogen when fed to goats at the rate of 1 kg/day for six months Histologically the thyroid gland revealed pronounced hyperplastic changes

4 2 2 2 Chemical goitrogen

Goitrogenic substances like thiourea are commonly employed to induce hypothyroidism experimentally Chemically thiourea is H_2N $CS-NH_2$ Mayberry and Astwood (1961) described the mode of action of thiourea and related compounds These inhibited the formation of iodothyronine and their coupling to form diido thyronine Thus they diminished the inorganic iodine content of the thyroid and the iodide pump was inhibited

Kennedy (1942) observed three times enlargement of the thyroid in rats treated with thiourea The follicles were almost devoid of colloid in the thyroid of experimental group The pituitary showed an increase in basophil cells and loss of acidophil cells Bauman and Marine (1945) observed a decrease in adrenal size in rats fed thiourea

Jones _et al_ (1946) noted resorption of foetus in rats treated with thiouracil and observed hypertrophy of the thyroid congestion of thyroid vessels and depletion of colloid in the follicles of the thyroid Involution of the adrenal cortex occurred in rats fed thiouracil (Zarrow and Money 1949) Sellers and Ferguson (1949) observed exophthalmus in rats treated with thiouracil

Administration of propylthiouracil caused thyroid hyperplasia in the guinea pig (D Angelo _et al_ 1951) Swanson and

Boatman (1953) observed symptoms of hypothyroidism in dairy bulls after treatment with thiouracil The weight of the thyroid gland in the treated animals was twice the weight of the normal Histologically the follicles were filled with colloid and lined by low cuboidal epithelial cells

Goldberg et al (1957) observed enlarged thyroid glands with tall columnar cells, numerous mitotic figures, scanty colloid, papillary infoldings and increased vascularity in rats fed with propylthiouracil In the pituitary, hyperplasia and hypertrophy of the beta cells with characteristic granularity and vacuolation and disappearance of granules from the alpha cells were observed

Lascelles and Setchell (1959) noticed goiter in the offspring of Merino sheep treated with methylthiouracil at the dose rate of 0 5, 1 5 and 4 5 g daily In hamster, colloid goiter was produced by thiouracil administration Extensive thyroid hyperplasia and loss of colloid were noted in the first week after thiouracil administration (Follis, 1959) Mc Carthy et al (1959) reported adrenal atrophy among rats fed thiouracil and tapzole

Nangia et al (1975) observed high blood levels of protein and cholesterol in methimazole treated birds Sreekumaran and Rajan (1977a) induced hypothyroidism in kids by feeding various dose levels of thiourea Stunted growth and reduction in body weight were observed in all the kids An increase in the relative weight of the thyroid was a consistent feature in the study

Prasad and Singh (1979) reported decreased plasma protein bound iodine in methimazole treated hypothyroidism in birds Burstein et al (1979) observed significant drop in the level of the growth hormone in propylthiouracil treated rats

Reddy and Rajan (1985a) experimentally produced hypothyroidism in goats by feeding thiourea The experimental animals showed marked decrease in the serum protein bound iodine level

Abraham and Rajan (1986) induced hypothyroidism in calves giving thiourea orally They observed irregular shedding of hair on the belly, thigh and neck, and slight to moderate edema on the face below the eyelid, jaw region and lower parts of the body Ratnakumar (1989) reported reduced serum thyroxine level in propyl thiouracil fed rabbits

Gupta et al (1990) reported that thiourea was more effective in inducing hypothyroidism in goats than methyl thiouracil Bello and Oovian (1991) observed that high sodium chloride intake (above 4m eq) in rats resulted in reduced level of protein bound iodine and radioactive iodine uptake, both the experimental and control group had similar weight of the thyroid Vijayan et al (1992) observed colloid changes in the thyroid of calves treated with superchlorinated water

Jamillah et al (1992) reported that propyl thiouracil induced hypothyroidism in monkey resulted in atrophy of the motor neurons

Swollen mitochondria and lysis of the cristae, rupture of the myofilaments in the myofibrils, lesser concentration of granules in the perinuclear area, abundant granular interstitial tissue and separation of myofibrillar collagen were the ultra structural changes in propyl thiouracil treated rats (Lopez et al 1993)

4 3 Dyshormonogenesis

Falconer (1966) described a condition in which the thyroid was not able to produce normal quantities of the thyroid hormone, because of the congenital defect in Merino sheep Thyroid stimulating hormone was released resulting in hyperplasia of the thyroid gland Rac et al (1968) observed congenital goiter with thyroid enlargement in Merino sheep There was considerable increase in the cholesterol level in the affected animals Mayo and Mulhearn (1969) pointed out that abnormal iodo protein formation by an autosomal recessive gene with high penetrance and variable expressivity caused congenital goiter in Merino sheep.

Poulose *et al* (1984) indicated the involvement of a genetic factor in the causation of goiter and hypothyroidism in man, apart from iodine deficiency and cassava factor in Kerala Ricketts *et al* (1987) reported hereditary goiter in Afrikander cattle caused by mutation, unmasking the alternative splicing of thyroglobulin transcripts

Jubb *et al* (1993) suggested that an impairment in the thyroglobulin synthesis due to reduction in the concentration of m RNA coding for thyroglobulin, led to congenital goiter in animals

5 Radiothyroidectomy

Goldberg and Chaikoff (1951) produced an early state of hypothyroidism in rats by injecting various doses of ^{131}I Hypertrophy and hyperplassia of the basophil cell and degranulation of acidophils were the changes observed in the pituitary Lewis (1956) observed a drop in protein bound iodine from 6 7 to 0 8 mg per cent in Jersey Bull after subcutaneous injection of carrier free ^{131}I Bustad *et al* (1957) produced thyroid adenoma, fibroma and fibrosarcoma in sheep following daily administration of ^{131}I at different levels

Potter et al (1960) indicated papillary and follicular carcinoma in rats by single ^{131}I injection Administration of radio iodine in goats caused damage of the thyroid gland and reduction in the rate of radio active iodine uptake by the thyroid (Ayoub 1968) Cons et al (1975) recorded high plasma thyroid stimulating hormone level in radio thyroidectomised rats

6 Thyroid status and Reproduction

Mc Kenzie and Berliner (1937) reported that summer sterility in rams was associated with thyroid status Reineke et al (1941) noticed reduced gonadotropic potency of the pituitary in thyroidectomised young male goats Complete lack of libido was noticed in thyroidectomised bull calves with normal development of gonads (Peterson et al 1941)

Chu and You (1944) reported that feeding small doses of desiccated thyroid to thyroidectomised rabbit prevented the hypertrophy of ovarian follicle while large doses had inhibitory action Spielman et al (1946) observed absence of external signs of oestrus in thyroidectomised female though they were cycling regularly

Schultze and Davis (1946) noted a decrease in conception rate sperm motility and greater resistance of spermatozoa in bulls fed iodinated casein Daily subcutaneous injection of propyl thiouracil disturbed the oestrus rhythm of adult albino mice causing prolonged irregular cycles (Krohn 1947) Kumaran and Turner (1949) induced mild hypothyroidism in birds by feeding 0 6 per cent thiouracil and observed a progressive depression of secretion of Interstitial Cell Stimulating Hormone (ICSH)

Maqsood (1952) demonstrated that the thyroid gland has an important role in the maintenance of fertility with thyroxine supplementation There was increased sex libido and improvement in the semen picture in iodine deficient bulls

Hignett (1952) noted a decline in libido and deterioration of semen quality in iodine deficient bulls Soliman and Reinke (1952) observed that thiouracil fed mice had ovaries packed with follicles but there was absence of any corpora lutea Brownstand and Fowler (1959) reported that sows maintained on 0 15 per cent thiouracil had lowered ovulation rate Moberg (1959) described retention of placenta in bovines associated with sub optimal iodine intake

Brooks and Ross (1962) observed that exogenous administration of L thyroxine in feed at 0 2 0 3 and 0 4 mg per cent concentration failed to have any significant effect on the adverse influence of high ambient temperature on the semen quality in rams Mahtiev (1966) recorded an improvement in fertility and semen picture following iodine supplementation in infertile rams maintained in iodine deficient areas

Prasad and Singh (1971) observed four fold increase in the weight of testes in propyl - thiouracil fed chicks This group of birds showed tightly arranged coils of seminiferous tubules as compared with the loose arrangement of tubules in normal birds Sharma and Singh (1975) recorded more coiled seminiferous tubules lined with two or more layered germinal epithelium in hypothyroid birds as against single layer of epithelium in the control groups

Sreekumaran and Rajan (1977 b) observed that the seminiferous tubules contained only a few primary and secondary spermatocytes in experimentally induced hypothyroidism in male kids There was complete absence of spermatozoa and germinal layer in some of the tubules The lumen of the tubules contained only a net work of fibres and scattered round cells

Srinivas (1979) reported very low concentration of protein bound iodine (PBI) among buffaloes with cystic ovarian degeneration The mean value was 1 68+0 04 mg per cent The highest concentration of PBI was seen in animals with uterine infection Vadodaria et al (1980) observed less active thyroid follicles in the ovulatory phase compared to luteal phase

Reddy and Rajan (1984) observed a significant decrease in the relative weight of the testis in goats fed thiourea A reduction in the relative weight of the epididymis and accessory sexual glands were also observed in this group Histologically the seminiferous tubules were slightly smaller in size and the lining cells were scanty

Ratnakumar and Rajan (1989) observed that propylthiouracil fed rabbits showed very few spermatogonial cells in the testis and mild degenerative changes in the ovaries in female rabbits

Ghosh et al (1993) reported that hypothyroidism played a role in the etiology of polycystic ovarian syndrome There was lowering of the sex hormone binding globulin and an increment in the free testosterone, which might be directed to the overproduction of estriol

Cooke et al (1993) observed that 0 006 per cent of 6-propyl-2-thiouracil concentration was optimal for maximally increasing the testicular growth and daily sperm production in rats

7 Incidence of hypothyroidism in pigs

Ferguson et al (1956) reported that hypothyroidism caused interference in the overall development of the body and and this condition was seen more in young immature animals than in adult animals Moustgard and Sorenson

(1957) studied thyroid function in pigs Lucas *et al* (1959) studied the relationship of altered thyroid activity to various reproductive phenomena in gilts Brumstad (1959) reported embryonic mortality in thiouracil fed gilts

Thoonen *et al* (1959) reported that the ratio of follicular diameter to the height of the epithelium of thyroid follicle was not related to the sex or weight gain and it was related to carcass quality

Griem (1959) noted hyperaemic changes in the thyroid gland in pigs affected with liver dystrophy Frape *et al* (1959) reported that both hypo and hyper vitaminosis A resulted in lowered rate of thyroid secretion in pigs Pearson *et al* (1966) reported that thiouracil at low doses caused fattening in pigs

Kaszubkiewiez (1968) studied morphological changes in the thyroid of pigs fed a ration containing rape seed meal Oliver and Neher (1971) studied the clinical changes in experimentally induced athyreosis in swine Smirnov (1975) reported that morphometric changes in the skeletal bones in pigs were associated with hypothyroidism

May *et al* (1979) observed a depression in the immunological status of pig fed methyl thiouracil Schone *et al* (1984) reported hypothyroidism in pigs after feeding rape seed meal and potatoes Slebodzinski and Tratwal (1988) reported that early sub clinical atrophic rhinitis was associated with uncompensated hypothyroidism

Materials and Methods

MATERIALS AND METHODS

1 Design of the Experiment

Twelve, clinically healthy, two to three months old male Large white Yorkshire piglets were selected randomly from the University Pig Breeding Farm, Mannuthy for the study All the animals were maintained on concentrate ration and water was given ad libitum The animals were divided into control and experimental groups of six animals each All the animals were dewormed and kept under observation for a week before the start of the experiment

2 Dose of Thiourea

Experimental hypothyroidism was induced by the daily oral administration of thiourea (H_2NCSNH_2 Sarabhai-M-chemicals) at a dose level of 50 mg/kg body weight for a period of three months

3 Clinical Parameters Studied

Body weight, haemogram (total RBC, WBC, differential leucocyte count, packed cell volume, E S R haemoglobin content, MCV, MCH and MCHC), serum cholesterol, total plasma protein and serum thyroxine level of all the animals were recorded before the commencement of the experiment and subsequently at fifteen days intervals The pigs were observed daily and clinical symptoms if any manifested were observed and recorded

The study covered the following aspects

1 Weight gain and growth rate

2 Observation of clinical symptoms

3 Haemogram values

4 Estimation of plasma protein

5 Estimation of serum cholesterol

6 Determination of serum thyroxine

8 Histopathology

2 Techniques

2 1 Clinical symptoms and weight gain

Both the control and experimental group of animals were weighed at the commencement of the experiment and there after at fifteen days intervals The animals were observed daily for clinical symptoms if any, and recorded

2 2 Collection of blood samples for laboratory estimation

Blood samples were collected from the anterior venacava aseptically using Ethylene Diamine Tetra Acetic acid (EDTA) as the anticoagulant Dipotassium salt of EDTA was used as the anticoagulant at the rate of 1 mg/ml of blood, for haematological studies Five milliliter of blood was also collected separately in sterile test tubes without adding anticoagulant for serum separation

Erythrocyte sedimentation rate and packed cell volume were estimated by using the method described by Wintrobe (1981) Acid haematin method was employed for the estimation of haemoglobin (Schalm, 1965)

Erythrocyte count, total leucocyte count and differential leucocytic count were made by the method of Schalm (1965)

Total protein content of blood plasma

The Biuret assay method of Inchiosa (1964) was adopted for the estimation of plasma protein

Serum cholesterol

Serum cholesterol was estimated using the method of Zak (1957

Serum thyroxin

Radio Immunoassay (RIA) method of Abraham (1977) was employed for the estimation of serum thyroxine The RIA kits were obtained from the Bhabha Amomic Research Centre, Bombay

Post mortem examination

The piglets were slaughtered at the end of the experiment The carcass was weighed A detailed autopsy was conducted following the autopsy procedure advocated by FAO/SIDA (1968) Immediately after slaughter, thyroid pituitary and adrenals were dissected out and weighed after removing the loose fat and fascia Testes were separated from the epididymis and weighed The endocrine glands and the visceral organs were examined for gross lesions

Histopathology

Appropriate samples of tissues were collected in 10 per cent buffered neutral formalin for histopathological examination Tissues were processed by the routine paraffin embedding technique (Armed Forces Institute of Pathology, 1968) Paraffin sections cut at five to six microns thickness were stained routinely with haematoxylin and eosin (H&E) method of Haris as described by Disbrey and Rack (1970

3 Assessment of the thyroid status of pigs from different parts of Kerala

The thyroid status of pigs was assessed at random using T_4 as a marker Seventyfive blood samples were collected from pigs brought for slaughter at the Meat Products of India, Koothattukulam and also from pigs reared at the University Pig Breeding Farm, Mannuthy

Results

RESULTS

Symptoms

The experimental group consisted of six male Large White Yorkshire piglets of 2-3 months age All were dosed with 50 mg/kg body weight of thiourea daily orally, uniformly mixed in the feed The experiment was for three months

The animals in the experimental group were active and clinically normal for the first one month Thereafter the condition of the animals slowly deteriorated The hair coat became rough Moderate degree of alopecia was noticed on the lateral aspect of the neck, shoulder and thigh regions (Fig 8) All the animals showed progressive weakness and stunted growth The animals were sacrificed after three months of observation, to study the gross and histopathological changes in different organs

Weight gain and loss

The data on weight gain and loss during the experimental period are shown in Fig 4 All the experimental animals recorded gradual increase in weight during the first one month Subsequently there was a gradual and progressive reduction in the body weight The control animals recorded a progressive increase in weight

Fig 1 BODY WEIGHT GAIN (kg)

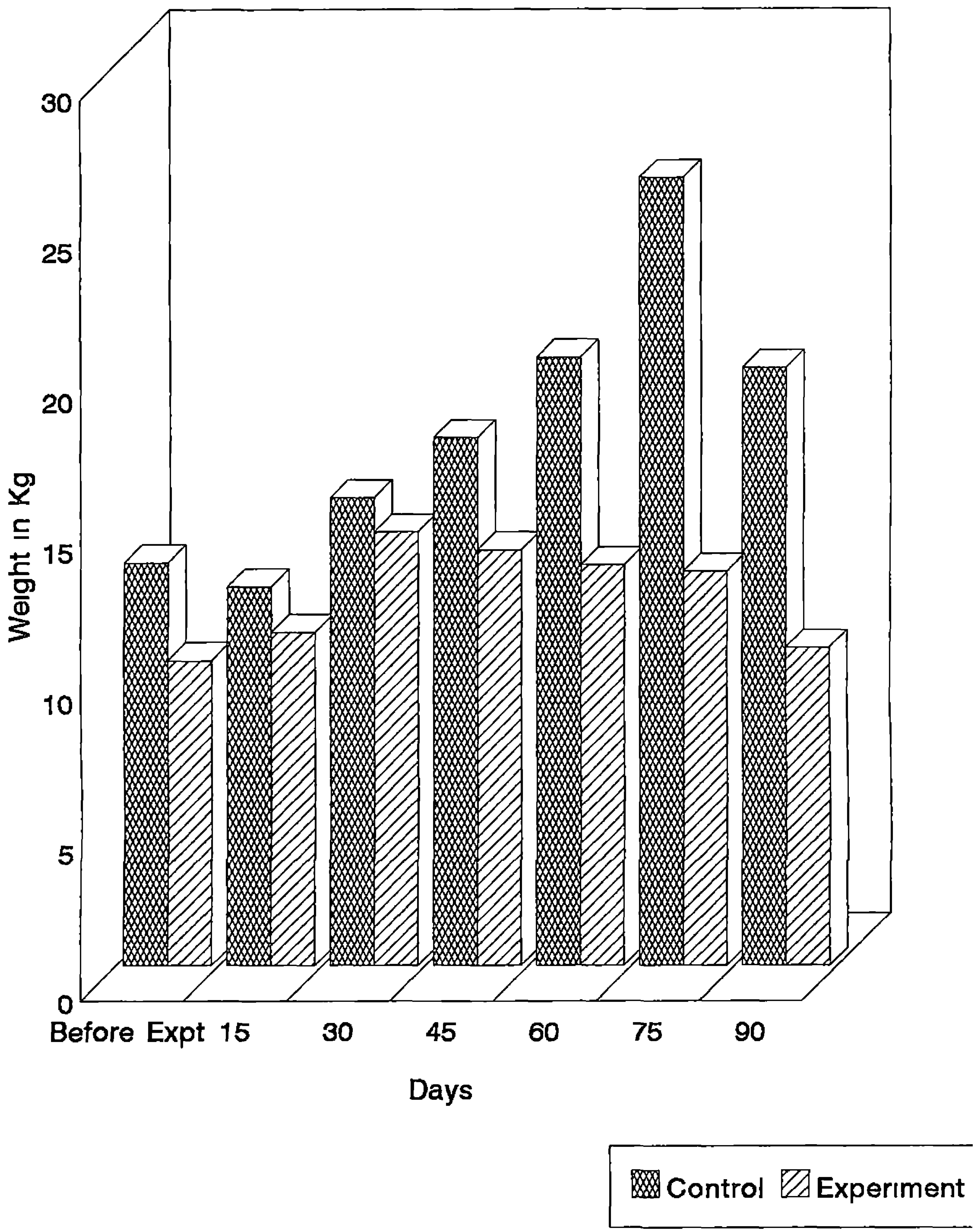


Fig.2 Hb LEVEL IN CONTROL ANIMALS

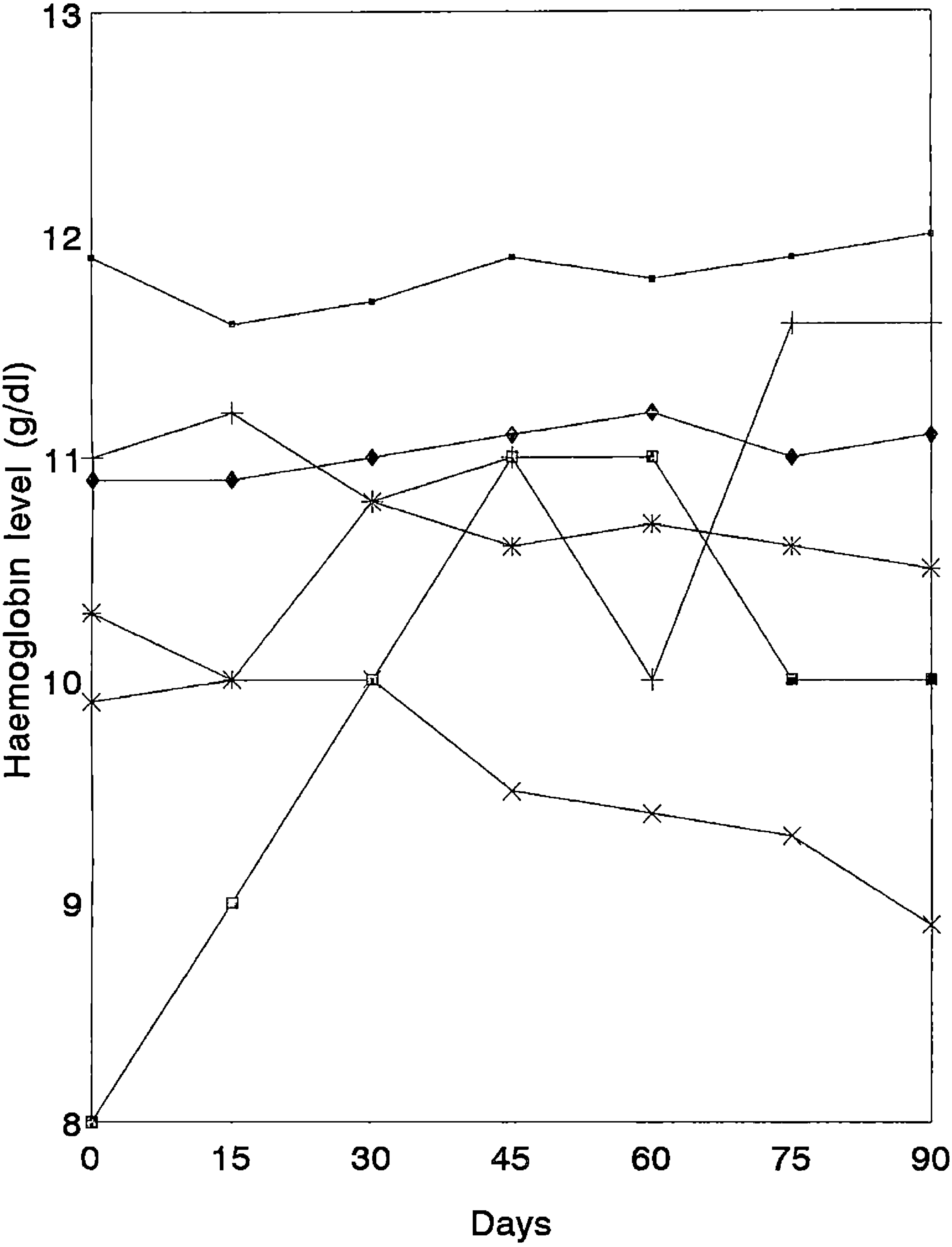
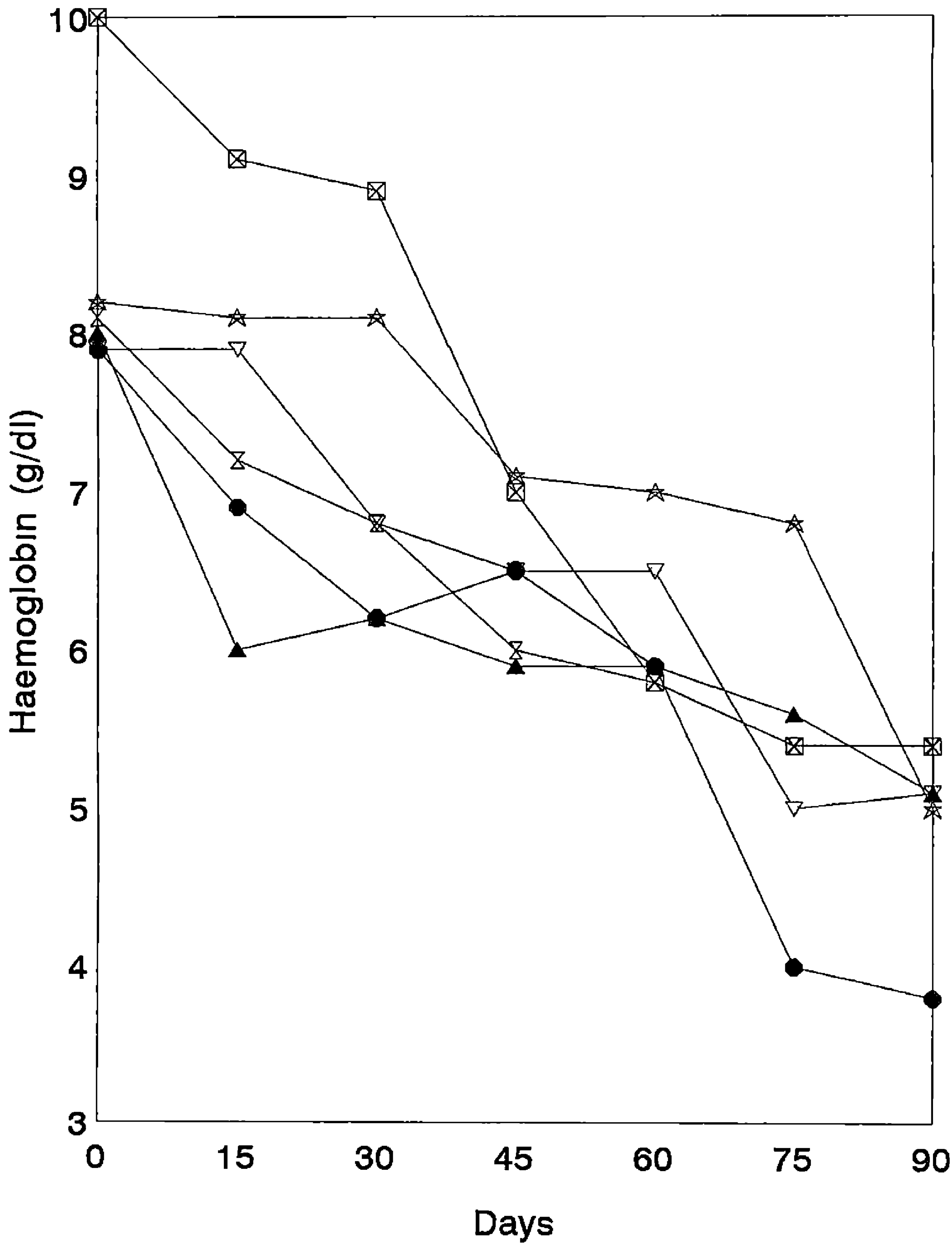


Fig.3 Hb LEVEL IN EXPERIMENTAL ANIMALS



Haemogram

The haemogram of the individual animals in both the groups during the experimental period is presented in table 1-12 and Fig 2 and 3 The experimental animals showed normocytic hypochromic anemia characterised by reduction in the hemoglobin and total erythrocyte count The leucogram did not record any significant change

Serum Cholesterol

The data on serum cholesterol level of the animals are presented in Fig 4 The serum cholesterol level in the experimental group of animals markedly increased from the 30th day onwards There was no significant variation in the control group

Total Plasma Protein

The data on plasma protein level are presented in Fig 5 The level of plasma protein in experimental animals increased gradually from the second month onwards Plasma protein level in the control group maintained almost a steady level

Serum thyroxine

The data on serum thyroxine level of the animals during the experimental period are presented in Fig 6 There was

Fig 4 SERUM CHOLESTEROL LEVEL (mg/dl)

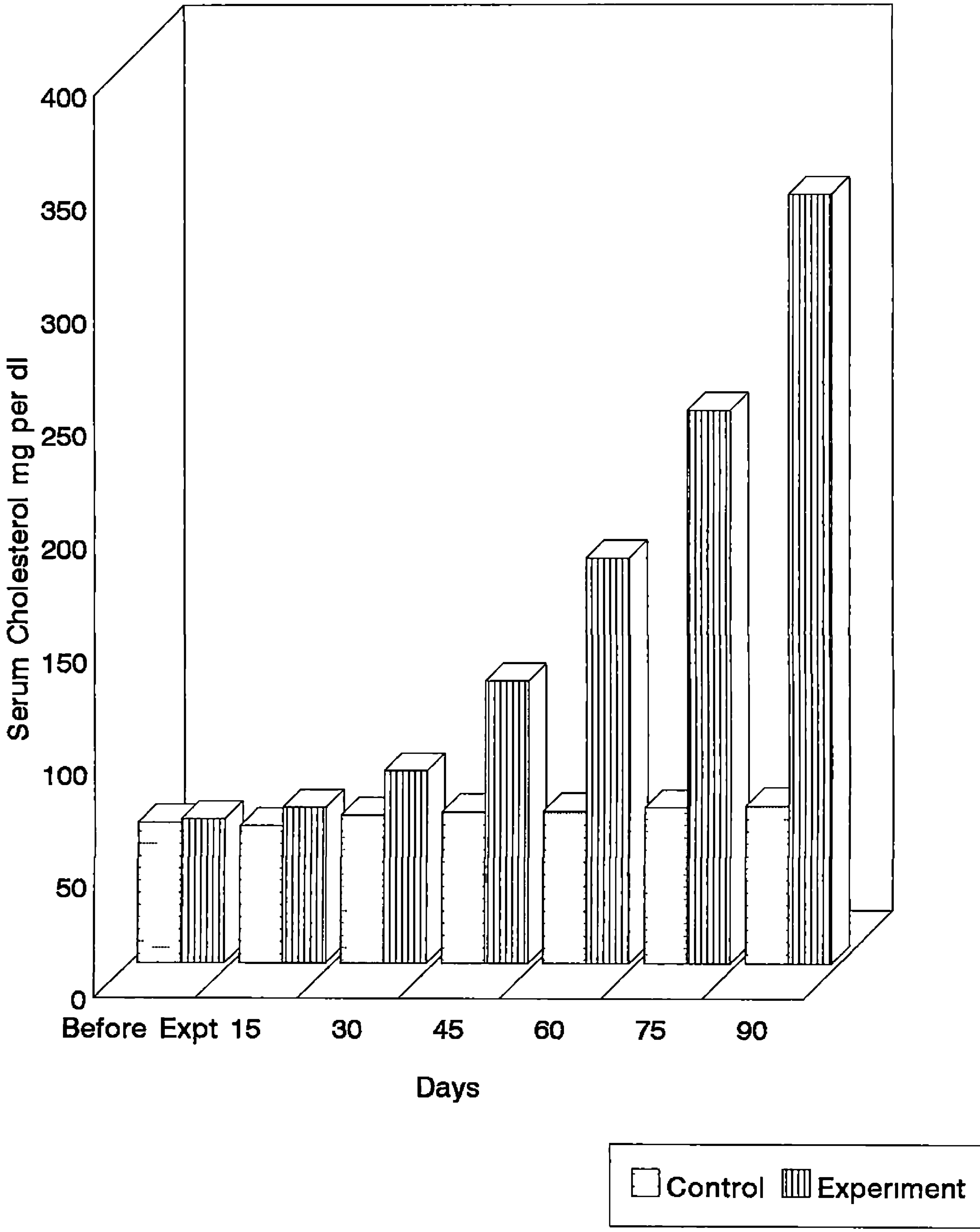


Fig 5 PLASMA PROTEIN LEVEL (g/dl)

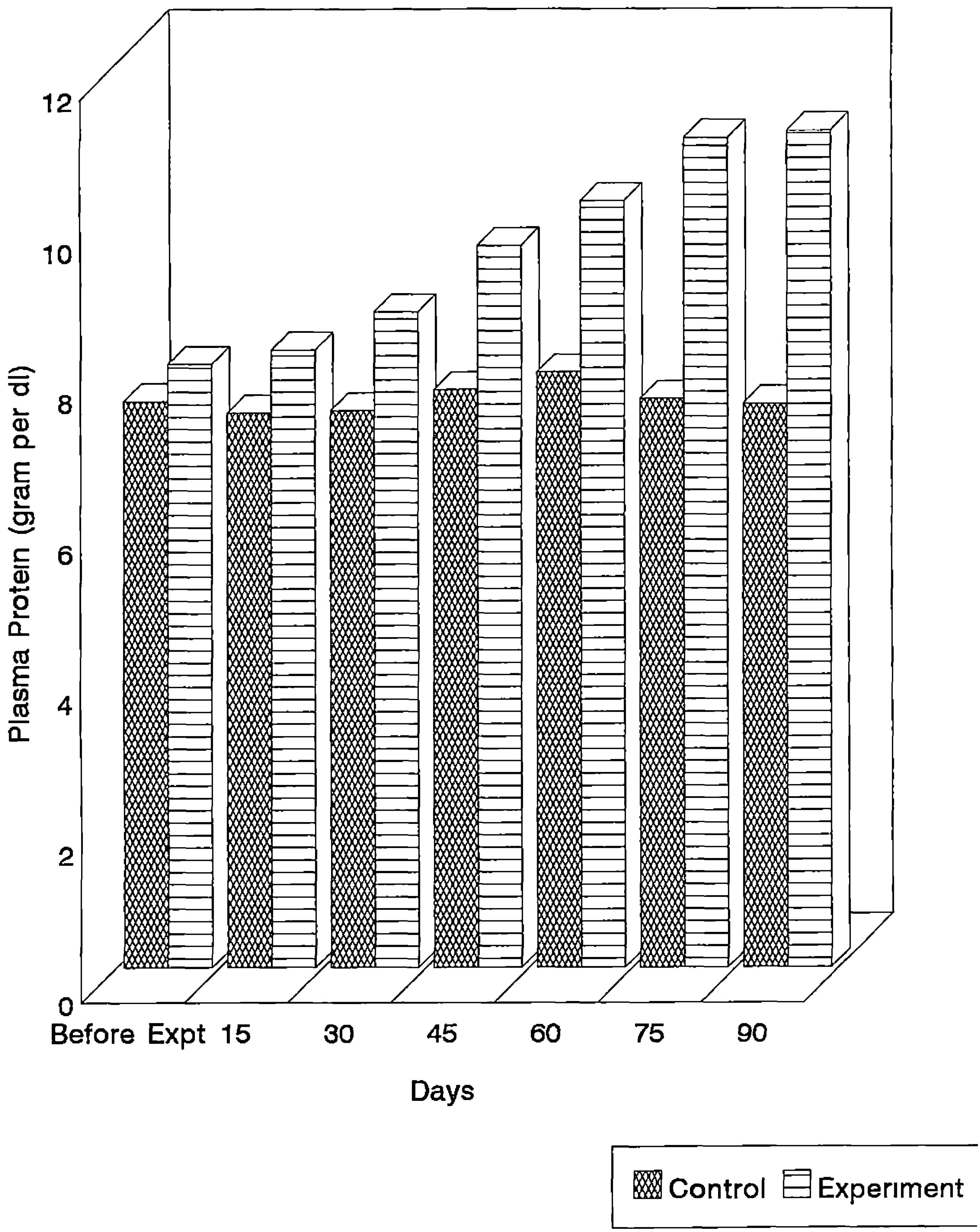


Fig 6 SERUM THYROXINE LEVEL (micro g/dl)

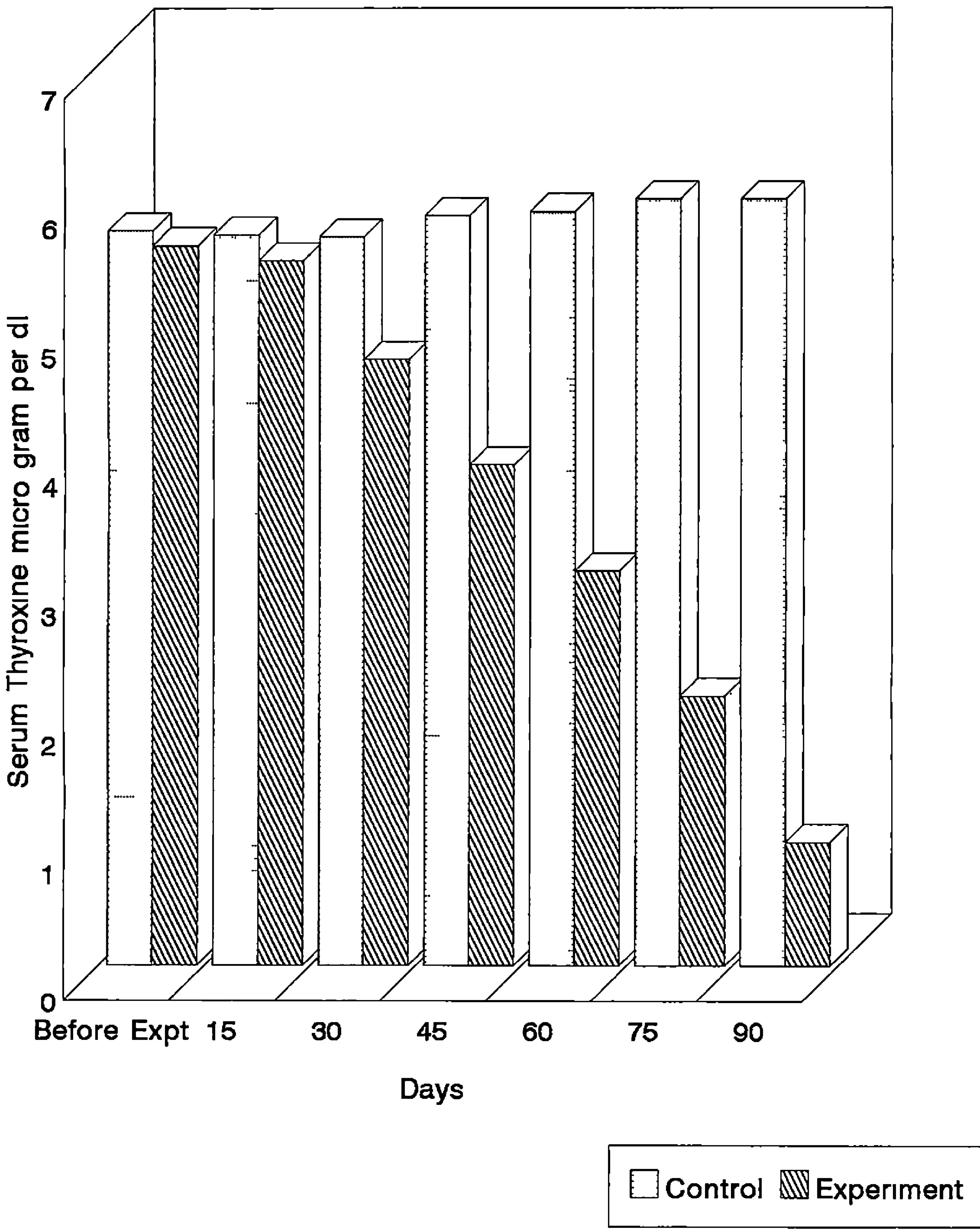


Table 1 Haemogram of Control Group - Animal No. 1.

Parameters	Before Expt	Ist fort-night	2nd fort-night	3rd fort-night	4th fort-night	5th fort-night	6th fort-night
RBC million/cmm	5 85	5 90	5 90	6 00	5 80	6 10	6 20
Hb g/dl	11 70	11 80	11 70	11 80	11 95	12 00	12 10
ESR mm/h	3 00	4 00	4 00	3 00	4 00	3 00	4 00
PCV %	30 00	28 00	29 00	31 00	30 00	28 00	29 00
MCV fl	51 28	47 46	49 15	51 67	51 72	32 79	46 47
MCH pg	20 00	20 00	20 00	19 60	20 60	19 67	19 00
MCHC %	39 00	42 00	40 00	38 00	39 00	42 00	41 00
Leucocytes thousand/cmm	13 55	14 00	13 85	14 05	13 50	13 80	14 00
Differential count							
Lymphocytes %	61 00	62 00	55 00	57 00	60 00	62 00	58 00
Neutrophils %	30 00	28 00	36 00	33 00	31 00	30 00	32 00
Monocytes %	4 00	5 00	5 00	5 00	4 00	4 00	5 00
Eosinophils %	4 00	5 00	4 00	5 00	5 00	4 00	4 00
Basophils %	1 00	0 00	0 00	0 00	0 00	0 00	1 00

Table 2 Haemogram of Control group -Animal No. II.

Parameters	Before Expt	Ist fort-night	2nd fort-night	3rd fort-night	4th fort-night	5th fort-night	6th fort-night
RBC million/cmm	5 70	5 76	5 70	5 20	5 60	5 70	5 73
Hb g/dl	11 20	10 80	10 70	10 80	10 75	10 20	11 05
ESR mm/h	4 00	5 00	6 00	4 00	6 00	5 00	5 00
PCV %	28 00	28 00	29 00	30 00	29 00	30 00	30 00
MCV fl	49 00	48 00	50 00	57 00	50 00	52 00	52 00
MCH pg	19 60	18 00	18 70	20 76	19 19	17 89	19 28
MCHC %	25 00	25 92	36 45	36 00	26 97	34 00	36 83
Leucocytes thousand/cmm	15 85	15 00	16 05	15 25	15 60	16 00	15 80
Differential count							
Lymphocytes %	58 00	46 00	62 00	57 00	47 00	58 00	47 00
Neutrophils %	33 00	37 00	30 00	34 00	42 00	33 00	43 00
Monocytes %	5 00	9 00	7 00	4 00	7 00	4 00	6 00
Eosinophils %	4 00	7 00	1 00	5 00	4 00	5 00	4 00
Basophils %	0 00	1 00	0 00	0 00	0 00	1 00	0 00

Table 3 Haemogram of Control group - Animal No. III.

Parameters	Before Expt	Ist fort night	2nd fort-night	3rd fort-night	4th fort-night	5th fort-night	6th fort-night
RBC million/cmm	5 90	5 90	5 85	6 00	6 10	5 90	6 00
Hb g/dl	10 40	10 10	10 20	10 70	10 80	10 75	10 80
ESR mm/h	9 00	5 00	6 00	10 00	9 00	6 00	10 00
PCV %	30 00	32 50	36 00	31 80	32 00	34 00	30 80
MCV fl	50 84	54 91	61 53	53 00	52 45	57 62	51 33
MCH pg	17 62	17 11	18 46	17 83	17 70	18 22	18 00
MCHC %	34 66	31 17	30 02	33 64	33 15	31 61	35 04
Leucocytes thousand/cmm	14 55	14 90	13 15	14 05	13 87	13 90	14 05
Differential count							
Lymphocytes %	55 00	57 00	60 00	62 00	61 00	56 00	59 00
Neutrophils %	35 00	35 00	30 00	28 00	33 00	35 00	28 00
Monocytes %	4 00	2 00	5 00	4 00	2 00	3 00	4 00
Eosinophils %	6 00	6 00	5 00	6 00	4 00	6 00	8 00
Basophils %	0 00	0 00	0 00	0 00	0 00	0 00	1 00

Table 4 Haemogram of Control group - Animal No.IV.

Parameters	Before Expt	Ist fort-night	2nd fort-night	3rd fort-night	4th fort-night	5th fort-night	6th fort-night
RBC million/cmm	4 89	4 50	4 80	4 81	4 76	4 30	4 00
Hb g/dl	8 00	9 60	10 00	10 90	11 00	10 30	10 40
ESR mm/h	9 00	9 00	10 00	12 00	14 00	11 00	14 00
PCV %	20 00	22 00	24 00	23 00	23 00	24 00	24 00
MCV fl	40 89	48 88	50 00	47 81	48 32	55 81	60 00
MCH pg	16 35	21 33	20 83	22 66	23 10	26 00	24 52
MCHC %	40 00	43 63	41 60	47 39	30 91	42 91	43 33
Leucocytes thousand/cmm	12 80	14 10	13 80	14 10	13 90	14 05	13 75
Differential count							
Lymphocytes %	55 00	59 00	47 00	60 00	61 00	62 00	59 00
Neutrophils %	36 00	32 00	43 00	27 00	28 00	29 00	30 00
Monocytes %	5 00	4 00	6 00	8 00	5 00	5 00	4 00
Eosinophils %	4 00	5 00	4 00	4 00	6 00	4 00	5 00
Basophils %	0 00	0 00	0 00	1 00	0 00	0 00	0 00

Table 5 Haemogram of Control Group - **Animal No. V.**

Parameters	Before Expt	Ist fort-night	2nd fort-night	3rd fort-night	4th fort-night	5th fort-night	6th fort-night
RBC million/cmm	4 20	4 30	4 20	3 90	3 40	3 20	3 00
Hb g/dl	10 30	10 20	10 70	10 60	10 80	10 70	10 60
ESR mm/h	8 00	7 00	8 00	6 00	8 00	9 00	9 00
PCV %	27 00	27 20	26 00	25 00	25 00	24 00	20 00
MCV fl	64 20	64 76	51 90	64 10	73 50	75 00	66 66
MCH pg	24 52	23 72	25 47	27 70	31 76	31 25	35 33
MCHC %	38 14	37 50	41 15	42 40	43 20	44 58	53 00
Leucocytes thousand/cmm	12 00	12 80	14 10	13 35	14 20	14 00	13 00
Differential count							
Lymphocytes %	55 00	57 00	58 00	55 00	60 00	61 00	62 00
Neutrophils %	35 00	33 00	33 00	36 00	30 00	30 00	30 00
Monocytes %	6 00	6 00	5 00	5 00	4 00	4 00	5 00
Eosinophils %	4 00	4 00	4 00	4 00	6 00	4 00	5 00
Basophils %	0 00	0 00	0 00	0 00	0 00	1 00	0 00

Table 6 Haemogram of Control group - Animal No. VI.

Parameters	Before Expt	Ist fort-night	2nd fort-night	3rd fort-night	4th fort-night	5th fort-night	6th fort-night
RBC million/cmm	6 10	6 12	6 00	5 50	5 60	5 40	5 00
Hb g/dl	11 10	11 00	11 10	11 20	11 30	11 20	11 30
ESR mm/h	6 00	6 00	5 00	5 00	6 00	5 00	6 00
PCV %	25 00	27 00	26 00	25 00	24 00	23 00	24 00
MCV fl	40 98	44 91	43 33	48 45	42 85	42 51	48 00
MCH pg	18 19	17 97	18 5	20 3	20 17	20 74	22 60
MCHC %	44 40	40 74	42 69	55 00	47 08	40 69	47 08
Leucocytes thousand/cmm	13 00	13 50	13 70	14 20	14 30	14 00	14 50
Differential count							
Lymphocytes %	58 00	57 00	53 00	55 00	59 00	61 00	60 00
Neutrophils %	30 00	36 00	35 00	37 00	30 00	30 00	31 00
Monocytes %	6 00	4 00	5 00	4 00	6 00	4 00	5 00
Eosinophils %	6 00	5 00	6 00	4 00	5 00	4 00	4 00
Basophils %	0 00	0 00	1 00	0 00	0 00	1 00	0 00

Table 7 Haemogram of Experimental group - Animal No. I.

Parameters	Before Expt	Ist fort-night	2nd fort-night	3rd fort-night	4th fort-night	5th fort-night	6th fort-night
RBC million/cmm	4 89	4 50	4 80	4 81	4 76	4 30	4 00
Hb g/dl	8 00	6 30	6 40	6 30	6 40	5 80	5 80
ESR mm/h	9 00	9 00	10 00	12 00	14 00	14 00	14 00
PCV %	20 00	22 00	24 00	23 00	23 00	24 00	23 00
MCV fl	41 60	48 80	50 00	68 29	48 90	55 80	60 00
MCH pg	16 32	14 00	16 00	20 79	14 70	13 48	14 50
MCHC %	28 60	26 60	20 90	20 69	24 16	24 16	21 47
Leucocytes thousand/cmm	15 00	15 85	16 05	15 25	15 60	16 00	16 00
Differential count							
Lymphocytes %	46 00	58 00	62 00	57 00	47 00	47 00	48 00
Neutrophils %	37 00	33 00	30 00	34 00	42 00	43 00	42 00
Monocytes %	9 00	5 00	1 00	5 00	7 00	6 00	6 00
Eosinophils %	7 00	4 00	0 00	1 00	4 00	4 00	4 00
Basophils %	1 00	0 00	0 00	0 00	0 00	0 00	0 00

Table 8 Haemogram of Experimental group Animal No. II.

Parameters	Before Expt	Ist fort-night	2nd fort-night	3rd fort night	4th fort-night	5th fort-night	6th fort-night
RBC million/cmm	4 00	4 10	4 00	3 80	3 30	3 30	3 10
Hb g/dl	8 10	7 50	7 40	6 50	6 10	6 40	6 30
ESR mm/h	10 00	9 00	10 00	11 00	11 00	10 00	11 00
PCV %	28 00	24 00	23 00	23 00	20 00	20 00	20 00
MCV fl	70 00	58 53	77 00	60 52	62 78	60 60	62 25
MCH pg	20 25	18 29	18 50	17 10	18 48	19 39	20 32
MCHC %	28 92	31 25	32 17	28 26	30 50	32 00	31 50
Leucocytes thousand/cmm	14 75	15 00	13 88	14 50	13 54	13 78	14 04
Differential count							
Lymphocytes %	54 00	58 00	50 00	55 00	61 00	60 00	55 00
Neutrophils %	37 00	31 00	38 00	36 00	30 00	30 00	40 00
Monocytes %	4 00	6 00	5 00	5 00	5 00	5 00	3 00
Eosinophils %	5 00	5 00	6 00	4 00	4 00	5 00	2 00
Basophils %	0 00	0 00	1 00	0 00	0 00	0 00	0 00

Table 9 Haemogram of Experimental group - **Animal No. III.**

Parameters	Before Expt	Ist fort night	2nd fort-night	3rd fort-night	4th fort-night	5th fort night	6th fort-night
RBC million/cmm	4 70	4 60	4 65	4 80	4 50	4 45	4 45
Hb g/dl	8 00	7 30	6 40	7 60	6 60	4 80	4 80
ESR mm/h	4 00	3 00	6 00	4 00	5 00	6 00	6 00
PCV %	18 00	18 00	22 00	20 00	21 00	20 00	20 00
MCV fl	38 29	39 13	47 31	43 47	46 66	44 94	44 95
MCH pg	17 02	15 86	13 75	16 23	14 66	10 78	10 78
MCHC %	44 44	40 55	29 09	38 00	31 42	24 00	24 00
Leucocytes thousand/cmm	13 50	14 00	13 85	14 01	13 95	13 55	13 75
Differential count							
Lymphocytes %	47 00	54 00	59 00	61 00	62 00	60 00	62 00
Neutrophils %	40 00	37 00	30 00	30 00	28 00	30 00	27 00
Monocytes %	6 00	5 00	6 00	4 00	4 00	5 00	6 00
Eosinophils %	7 00	4 00	5 00	5 00	6 00	4 00	4 00
Basophils %	0 00	0 00	0 00	0 00	0 00	1 00	1 00

Table 10 Haemogram of Experimental group - Animal No IV

Parameters	Before Expt	Ist fort night	2nd fort-night	3rd fort night	4th fort night	5th fort-night	6th fort-night
RBC million/cmm	4 60	4 30	4 20	3 90	3 40	3 20	3 00
Hb g/dl	8 00	7 30	7 00	6 40	5 60	5 70	5 80
ESR mm/h	8 00	7 00	8 00	6 00	8 00	9 00	9 00
PCV %	27 00	27 00	26 00	25 00	24 00	20 00	20 00
MCV fl	58 60	62 80	62 90	64 00	73 52	75 00	66 00
MCH pg	17 61	16 77	14 67	16 41	16 47	17 81	19 30
MCHC %	29 62	27 63	37 14	25 60	22 40	23 75	34 48
Leucocytes thousand/cmm	14 00	13 35	14 25	14 35	13 000	13 84	13 80
Differential count							
Lymphocytes %	55 00	57 00	58 00	55 00	60 00	61 00	62 00
Neutrophils %	35 00	33 00	33 00	36 00	30 00	30 00	28 00
Monocytes %	6 00	6 00	5 00	5 00	4 00	4 00	5 00
Eosinophils %	4 00	4 00	4 00	4 00	6 00	4 00	5 00
Basophils %	0 00	0 00	0 00	0 00	0 00	1 00	0 00

Table 11 Haemogram of Experimental group - **Animal No. V.**

Parameters	Before Expt	Ist fort-night	2nd fort-night	3rd fort-night	4th fort-night	5th fort-night	6th fort-night
RBC million/cmm	4 60	4 40	4 30	4 20	4 30	4 30	4 20
Hb g/dl	8 20	8 10	8 20	7 70	7 80	7 70	5 80
ESR mm/h	8 00	8 00	8 00	6 00	8 00	9 00	9 00
PCV %	26 00	27 00	25 00	24 00	25 00	25 00	25 00
MCV fl	56 52	61 36	58 20	50 00	57 14	58 20	59 52
MCH pg	17 82	18 41	19 10	18 31	18 13	17 91	11 91
MCHC %	31 53	30 00	32 80	28 51	31 2	30 80	23 20
Leucocytes thousand/cmm	13 20	13 80	14 00	13 85	15 00	15 12	14 00
Differential count							
Lymphocytes %	58 00	55 00	60 00	61 00	55 00	54 00	57 00
Neutrophils %	33 00	36 00	30 00	30 00	35 00	36 00	33 00
Monocytes %	5 00	5 00	4 00	4 00	6 00	5 00	6 00
Eosinophils %	4 00	4 00	6 00	4 00	4 00	5 00	4 00
Basophils %	0 00	0 00	0 00	1 00	0 00	0 00	0 00

Table 12 Haemogram of Experimental group -Animal No. VI.

Parameters	Before Expt	Ist fort-night	2nd fort-night	3rd fort-night	4th fort-night	5th fort-night	6th fort-night
RBC million/cmm	5 00	4 80	4 60	4 60	4 30	4 00	4 00
Hb g/dl	10 00	9 00	8 80	8 00	6 20	5 90	6 10
ESR mm/h	8 00	7 00	8 00	7 00	8 00	7 00	8 00
PCV %	25 00	24 00	20 00	22 00	22 00	20 00	20 00
MCV fl	50 00	35 29	43 40	47 80	51 60	50 00	50 00
MCH pg	20 00	21 42	19 13	17 39	14 41	14 75	15 25
MCHC %	40 00	37 50	44 00	46 36	20 18	29 50	30 05
Leucocytes thousand/cmm	14 00	13 65	13 50	14 50	13 20	14 10	13 50
Differential count							
Lymphocytes %	57 00	55 00	56 00	58 00	61 00	55 00	60 00
Neutrophils %	33 00	35 00	35 00	33 00	30 00	36 00	31 00
Monocytes %	6 00	5 00	4 00	5 00	4 00	5 00	4 00
Eosinophils %	4 00	5 00	5 00	4 00	4 00	4 00	4 00
Basophils %	0 00	0 00	0 00	0 00	1 00	0 00	1 00

significant fall in the serum thyroxine level in the experimental animals from the second fortnight onwards In the control animals the serum thyroxine level did not show any significant variation

Autopsy findings

All the animals were sacrificed on the 90th day and detailed autopsy was conducted

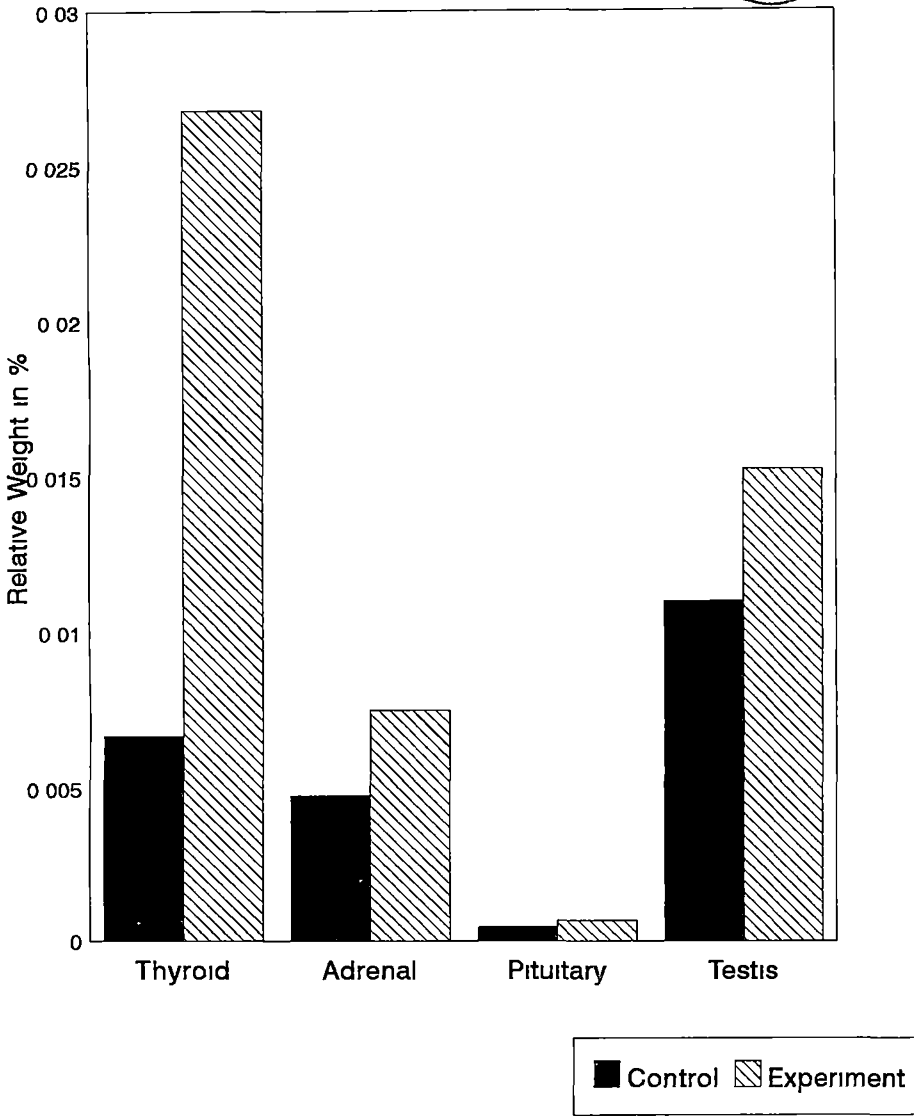
The carcasses were very much emaciated The mucous membrane was pale There was gelatinisation of the subcutaneous fat Hydrothorax of moderate degree was noticed The thyroid glands were enlarged significantly (Fig 9) and dark brown in colour Moderate dilatation of the right ventricle was noticed

Relative weight of Endocrine glands

The relative weight of the endocrine glands and the testes are presented in the Fig 7

An increase in the relative weight of the thyroid glands was observed in animals dosed with thiourea There was slight increase in the relative weight of the adrenal and pituitary glands, when compared to the control animals A mild increase in the relative weight of the testis was noticed in the experimental group

Fig 7 RELATIVE WEIGHT OF ENDOCRINE GLANDS AND TESTIS (%)



8 **Photograph** Thiourea fed animal Alopecia of neck shoulder and thigh regions

9 **Photograph** Enlargement of thyroid gland in thiourea fed animal Gland from the control pig is given adjacently

Histopathology

Thyroid

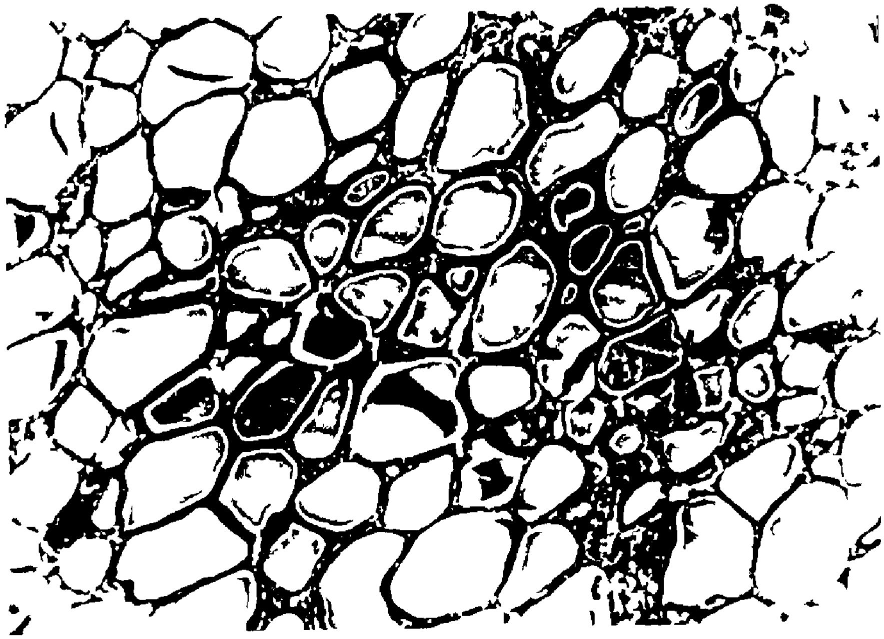
Histological picture of thyroid of control animal is given in Fig 10 The experimental group was characterised by the presence of numerous micro follicles in the thyroid (Fig 11) There was hypertrophy of the lining epithelial cells of the follicles Most of the follicles were lined by tall columnar epithelial cells with a basal nucleus In some of the follicles, lining cells were seen forming more than one layer thickness Most of the follicles were completely devoid of colloid (Fig 12) Hypertrophied epithelial cells were seen filling the lumen of many of the follicles Some of the follicles showed degeneration and desquamation of epithelial cells and the lumen contained degenerated cells Some of the follicles contained granular eosinophilic material There was small papillary fold of the hyperplastic cells in some of the follicles

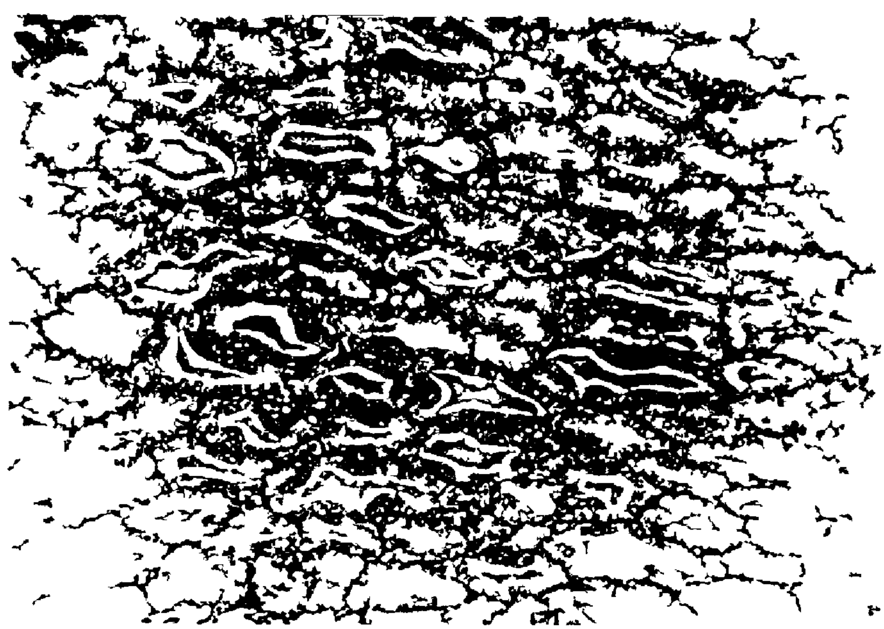
Pituitary

There was diffuse hyperplasia of the basophil cells (Fig 13) Many of the basophil cells showed vacuolisation of the cytoplasm Acidophils were less in number and some of the cells showed vacuolation and degranulation Capillaries were moderately engorged

10 **Photograph** Thyroid - Control group Histology of the normal thyroid gland H & E X 160

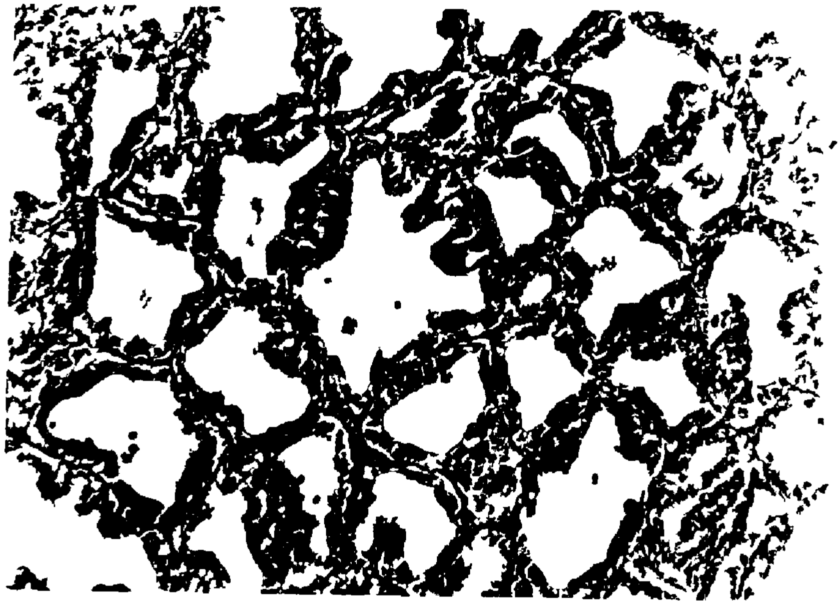
11 **Photograph** Thyroid - Thiourea fed group Numerous, microfollicles lined by tall columnar epithelial cells Follicular lumen is small and is devoid of colloid H & E X 160





12 **Photograph** Thyroid - Thiourea fed group Colloid depleted follicles lined by prominent columnar epithelial cells H & E X 160

13 **Photograph** Pituitary Thiourea fed group Hypertrophy and hyperplasia of basophil cells vacuolar degeneration of hypertrophied basophil cells is evident H & E X 400



Adrenal

Adrenal capsule was moderately thickened Diffuse hyperplasia of the zona fasciculata was evident (Fig 14) Accessory cortical nodule formation characterised by clumps of zona fasciculata cells was evident No pathological changes were seen in the endocrine glands of the control group of animals

Testis

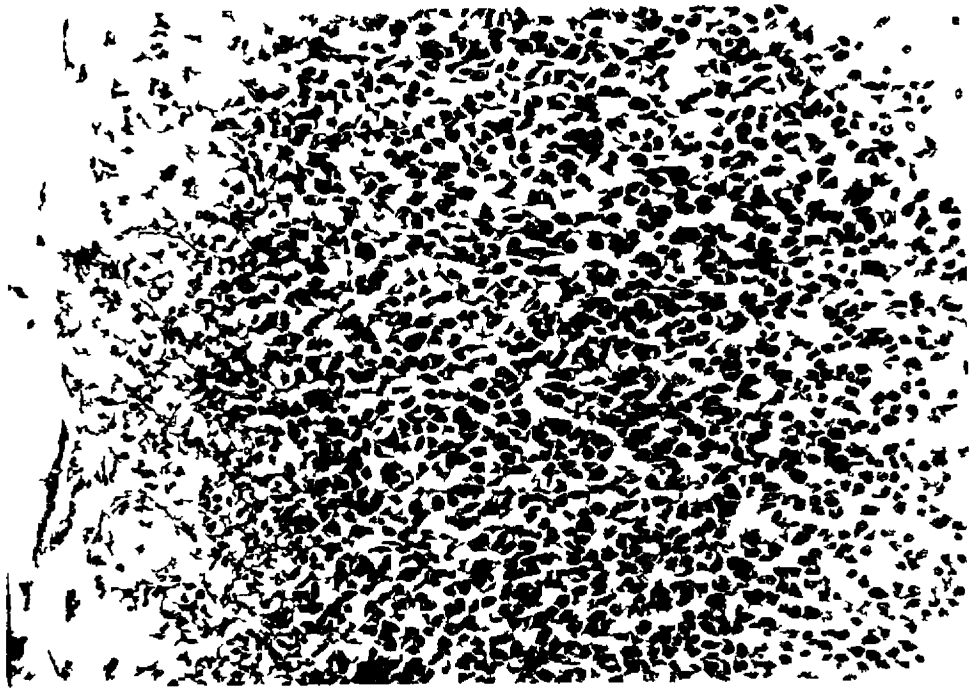
Seminiferous tubules were smaller in size Many of the tubules contained only a few primary and secondary spermatogonial cells In some of the tubules the lumen contained only a net work of fibres and scattered cells (Fig 15) There was moderate degree of interstitial oedema In the control group there was no pathological change in the testis

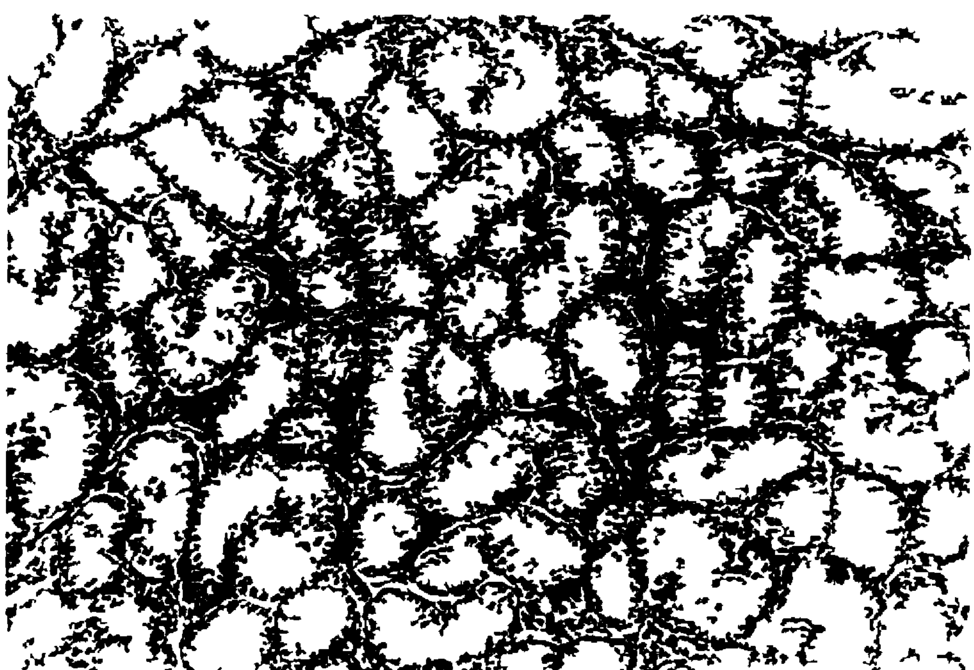
Skin

There was slight but diffuse hyperkeratosis of the epidermal layer Moderate degree of acanthosis and dyskeratosis were evident (Fig 16) Dermal layer showed moderate degree of oedema and scattered mononuclear cell infiltration Some of the hair follicles showed keratinisation and degeneration

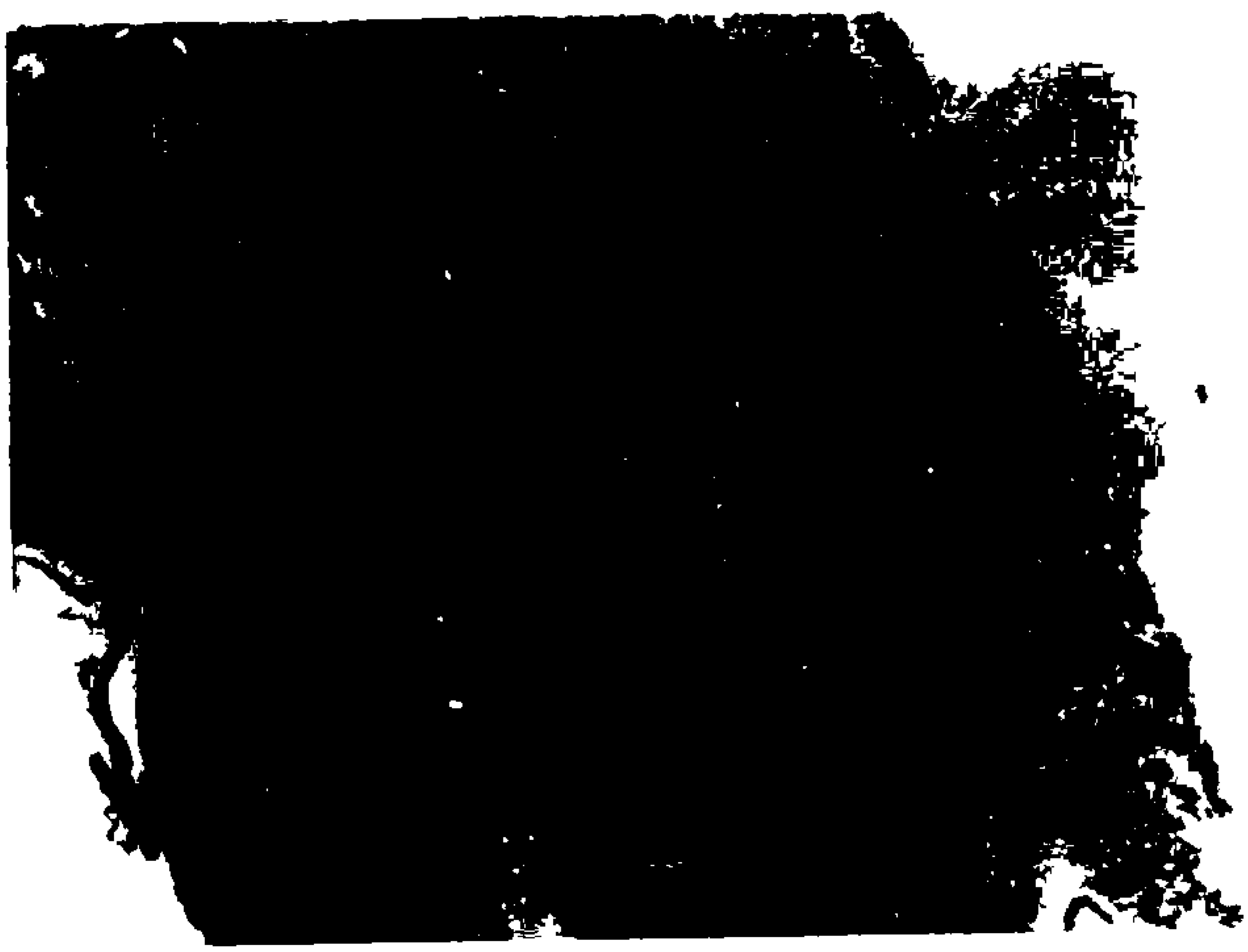
14 **Photograph** Adrenal - Thiourea fed group Hyperplasia zona fasciculata cells is evident The capsule is moderately thickened H & E X 160

15 **Photograph** Testis - Thiourea fed group Small seminiferous tubules Number of spermatogonal cells are very few H & E X 160





16 **Photograph** Skin - Thiourea fed group Acanthosis dyskeratosis and keratinisation of hair follicles evident H & E X 160



Heart

Interstitial oedema was evident between the cardiac muscle fibres Some of the muscle fibres showed focal areas of degeneration and hyalinisation

Liver

Hepatic cells showed diffuse vacuolar degeneration Degenerative and necrotic areas were seen scattered in the parenchyma

Kidney

Renal tubular epithelium showed degeneration and desquamation of epithelial cells There was diffuse haemorrhage and moderate degree of congestion of capillaries

Brain

There was slight perineuronal oedema Blood vessels showed moderate degree of congestion

The skin heart liver kidney and brain of the control group of animals did not show any histological change

Survey Study

In order to assess the functional status of the thyroid in pigs a field survey study was conducted using T_4 as the marker The results are presented in the Table 13 and 14 There was no significant variation in the thyroxine level and in all of the pigs the values fell with in the normal range

Table 13 Serum thyroxine level of pigs collected from Meat Products of India, Koothattukulam

Case No	Serum thyroxine level micro g/dl	Case No	Serum thyroxine level micro g/dl
1	4 50	26	1 30
2	3 60	27	1 20
3	3 40	28	4 50
4	3 50	29	6 00
5	3 90	30	1 20
6	2 30	31	4 50
7	3 40	32	6 00
8	3 70	33	6 20
9	3 50	34	6 40
10	3 40	35	4 70
11	2 80	36	2 82
12	2 70	37	5 90
13	4 80	38	2 50
14	4 40	39	1 80
15	3 40	40	1 80
16	3 00	41	1 00
17	3 40	42	5 80
18	6 40	43	4 70
19	5 00	44	3 40
20	4 70	45	4 80
21	6 10	46	4 40
22	6 20	47	3 40
23	5 90	48	3 80
24	4 40	49	4 70
25	5 50	50	4 70

Mean 4 028±0 210

Table 14 Serum thyroxine level of pigs collected from University Pig Farm, Mannuthy

Case No	Serum thyroxine level micro g/dl
1	4 00
2	4 80
3	6 10
4	2 00
5	1 00
6	4 50
7	6 80
8	3 50
9	4 50
10	4 60
11	4 50
12	4 10
13	4 80
14	2 20
15	2 40
16	5 90
17	4 70
18	6 40
19	6 20
20	5 90
21	4 80
22	4 00
23	4 20
24	8 00
25	5 80

Mean 4 628±0 322

Discussion

DISCUSSION

Hypothyroidism was experimentally induced in piglets feeding thiourea as a goitrogen The study has yielded valuable information on the manner in which piglets are affected by hypothyroidism Thiourea and related compounds have been used to induce experimental hypothyroidism in different species of animals The observations made during this study have clearly shown that thiourea at low dose level could be used as an experimental goitrogen in piglets also without any side effects

Clinically hypothyroidism was characterised by disturbance in growth and weight loss in the experimental group of animals dosed with thiourea Lombardi et al (1962) did not observe any deleterious effect on the growth of dogs dosed with thiouracil This was attributed to the fact that the metabolic process in the dog is less dependent on the production of thyroid hormone Studies conducted by Sreekumaran (1976) and Reddy (1982) in goats indicated that goats are more dependent on thyroxine for their growth than dogs Similar observations were noticed by Abraham (1986) in cattle and Ratnakumar (1989) in rabbits in which thiourea and propyl thiouracil were fed as giotrogens respectively From the observations made in this study it would appear that pigs are very much dependent on thyroxine for their metabolic activity

The piglets dosed with thiourea recorded gradual increase in the body weight during the first month Subsequently there was a gradual and progressive reduction in the body weight Goitrogens have been found to retard growth rate in sheep (Lascelles and Setchell 1959) and in poultry (Singh et al 1968) Retardation of growth in hypothyroidism has been attributed to defective synthesis of new protein (Metzger and Freinkel 1971) Kimberg (1971) reported diminution of absorption of nutrients in human beings in the absence of thyroxine and this was explained as the reason for reduction in weight

The weight gain in the first one month suggested that there has been some anabolic effect at lower dose level of thiourea The slow onset of hypothyroidism lowers the BMR and causes reduction in the catabolism of protein and utilisation of energy for body functions and this leads to a transient positive anabolic effect causing a gain in weight Thus it would appear that low doses of thiourea have transient beneficial effect in increasing body weight when given for shorter periods Pearson et al (1966) reported that thiourea in low doses in pigs has been used for fattening

A progressive reduction in growth and weight was appreciable in experimental animals But the clinical symptoms were not so pronounced and in field condition hypothyroidism as the cause for stunted growth and reduction in growth rate of animals is likely to be overlooked Therefore of the several factors responsible for reduction in weight gain in field situations the role of hypothyroidism in inducing stunted growth and lowered production should be viewed seriously particularly when the piglets are fed with compounded feeds containing goitrogenic substances

The hair coat of the experimental animals was rough and matted There was moderate degree of alopecia Freedberg (1971) reported that epidermal layer is an important target organ to the action of thyroxine This is supported by the histopathological findings in the skin where there was hyperkeratosis, acanthosis and diffuse oedema in the epidermis and dermis

The serum cholesterol level was significantly higher in all the piglets dosed with thiourea Increase in serum cholesterol level has been observed as a more specific change in lipid metabolism by Peters and Man (1950) in human myxoedema Fletcher and Myant (1958) indicated that in hypothyroid rats the hepatic synthesis and release of cholesterol from acetate was subnormal but the peripheral breakdown and biliary execretion is lowered and this they ascribed as the reason for increase in the serum cholesterol level

Increased level of serum cholesterol was observed in sheep in experimental hypothyrodism by Lascelles and Setchell, 1959 Belonji , 1967) in goats by Sreekumaran (1976) and Reddy (1982) in cattle by Abraham (1986) and in rabbits by Ratnakumr (1989)

Hypothyroid state in piglets dosed with thiourea was also associated with moderate increase in total plasma protein level Crispell and Wilson (1964) documented reduction in both anabolism and catabolism of protein, the latter being more reduced than anabolism of protein in hypothyroidism This would account for the rise in plasma protein level Similar observation was reported in hypothyroidism in human beings (Lamberg and Grasbeck 1955) and in poultry (Nangia et al 1975) Sreekumaran (1976) and Reddy (1982) reported increased total plasma protein level in experimental hypothyroidism in goats This observation was in agreement with the findings of Abraham (1986) in cattle and Ratnakumar (1989) in rabbits in experimentally induced hypothyroidism

The serum thyroxine level was studied in this experiment All the piglets dosed with thiourea recorded significant decrease in the thyroxine level Feeding thiourea leads to hypothyroidism by inhibiting organification of iodide and the subsequent formation of iodothyronines (Mayberry and Astwood 1961) The inorganic iodide content of the thyroid was also diminished and there was slight inhibitory effect on iodide pump (Danowski 1962) This observation is in agreement with the observation of Nasseri et al (1987) that serum thyroxine reduced significantly in ewes fed thiourea Gillen (1987) reported hypothyroidism in a cat which was associated with subnormal T_4 and T_3 levels Ratnakumar (1989) found marked decrease in the serum thyroxine level in rabbits in experimental hypothyroidism using propyl thiouracil From the observation made during the course of this investigation it is reasonable to conclude that the serum thyroxine level along with serum cholesterol level could be used as a reliable marker to screen the existence of hypothyroid state in piglets in field conditions

The haematological observation indicated that there was decrease in the total erythrocyte count haemoglobin value and packed cell volume in animals dosed with thiourea Rivlin (1971) observed that the most significant effect of hypothyroidism in man is the reduction of intestinal absorption of Vitamin B_{12} Adamson and Finch (1966) have demonstrated decreased production of erythropoietin in hypothyroidism The normocytic hypochromic anaemia in experimental hypothyroidism was reported by Sreekumaran (1976) and Reddy (1982) in goats Abraham (1986) in cattle and Ratnakumar (1989) in rabbits

There was significant increase in the relative weight of the thyroid gland in piglets dosed with thiourea This observation shows that there has been reactive hyperplastic response in the thyroid under the influence of TSH The increase in thyroid weight can be explained as a consequence to compensatory hyperplastic response mediated through pituitary under the influence of lowered thyroxine level Thyroid enlargement has been reported in experimental hypothyroidism in different species of animals (Kennedy, 1942 Jones et al 1946 Harkness et al 1954 Goldberg et al 1957 Lascelles and Setchell 1959 Lazo-wasem 1960) and in spontaneous hypothyroidism (Southcott 1945 Lall, 1952 Dutt and Kehar 1959). Sreekumaran (1976) and Reddy (1982) made similar observations in goats Abraham (1986) in cattle and Ratnakumar (1989) in rabbits

There was a significant increase in the relative weight of the adrenal gland in the experimental animals fed thiourea This observation is in contrast to the reports of atrophy of adrenal glands in laboratory animals and pigs dosed with thiouracil and allied compounds by Baumann and Marine (1945) Zarrow and Money (1949) and Mc Carthy et al (1959) However the present observation is in agreement with the findings of Durlach et al (1954) who have reported an increase in the adrenal weight in guinea pigs dosed with propyl thiouracil Similar observations were reported by

Sreekumaran (1976) Reddy (1982) in goats and Abraham (1986) in cattle The animals with induced hypothyroid state with thiourea were under the influence of stress and this might have been responsible for the enlargement of adrenal glands This is supported by the histological findings in the adrenal where there was diffuse hyperplasia of the zona fasciculata and formation of accessory cortical nodules

Consistently there was increase in the relative weight of the pituitry gland in thiourea fed animals Similar observation was reported in experimental hypothyroidism in laboratory animals (Kennedy and Purves 1941 Griesbach et al 1941 Goldberg et al 1957 Lazo Wasem 1960) in goats (Sreekumaran 1976 and Reddy 1982) in cattle (Abraham 1986) and in rabbits (Ratnakumar 1989) Similar documentation was reported in spontaneous hypothyriodism in goats (Lall 1952) The high levels of thiourea interfered with organic binding of iodine and acute deficiency of thyroxine stimulated basophil cells to undergo hypertrophy with concomitant increase in the number in order to meet the increased demand for TSH

The piglets dosed with thiourea were in poor condition and there was gelatinisation of body fat This might have been due to reduced feed consumption and feed conversion in the absence of thyroxine Russel (1943) indicated that most energy demands are being met from preformed lipid in the hypothyroid rat Therefore gelatinisation of body fat might be due to utilization of fat for body vital functions and energy requirement for the animal

There was moderate degree of hydrothorax and dilatation of the right ventricles in animals dosed with thiourea Similar findings have been reported in human beings in myxoedema (Zondek 1918) Hydrothorax might have been due to increased capillary permeability Cardiac dilatation could be considered as a pathological change resulting from the effort on the part of heart to compensate the function in the face of reduced cardiac output and decreased velocity of blood flow in hypothyroidism Similar observation has been reported in experimental hypothyroidism in goats (Sreekumaran, 1976 and Reddy, 1982) and in cattle (Abraham 1986)

Reactive hyperplasia was the characteristic histologic picture observed in the thyroid gland This is an expected pathological change in hypothyroid state This is a direct histological evidence which shows that thiourea has caused lowered thyroxine production and pituitary mediated compensatory thyroid hyperplasia Thyroid hyperplasia has been reported in spontaneous hypothyroidism in sheep (Growth 1962 Wallach 1965 George et al 1966) in goats (Lall 1952 Dutt and Kehar 1959 Roy et al 1964) and in experimental hypothyroidism in laboratory animals (Jones, et al 1946 D Angelo et al 1951 Durlach et al 1954 Goldberg et al 1957) in goats (Sreekumaran 1976 and Reddy 1982) in cattle (Abraham 1986) and in rabbits (Ratnakumar, 1989)

The most important histological observation was the complete absence of colloid in many of the thyroid follicles This would suggest that although there had been stimulation by TSH and hyperplasia of thyroid epithelium there has been no synthesis of thyroglobulin due to the non-availability of iodine in the presence of thiourea This would support the observation that thiourea has effectively blocked the thyroglobulin production and has lowered serum thyroxine level The unsuccessful severe hyperplastic reaction also resulted in degeneration and desquamation of many lining cells and the granualr PAS negative material seen in the follicles might have been the degenerated cells Since the stimulation of the thyroid gland was low and continuous this resulted in follicles with well formed multilayered epithelial cells and scanty colloid Formation of new small follicles without having colloid would suggest that TSH stimulation was very severe and blocking of iodide has been very effective

In the pituitary gland there was diffuse hyperplasia of basophil cells Pituitary basophil hyperplasia is an observation which would support the conclusion that thyroid activity has been diminished by thiourea administration in piglets There was loss of granules in many cells and complete degranulation and vacuolation of basophil cells These vacuolated basophil cells have been described in rats as thyroidectomy cells (Zeckwer et al 1935) These changes have been described in experimental hypothyroidism in dogs (Lippincott et al 1957) in rats (Goldberg and Chaikoff, 1951) in goats (Sreekumaran, 1976 and Reddy, 1982) in cattle (Abraham, 1986) and in rabbit (Ratnakumar, 1989) The basophil hypertrophy has been reported in spontaneous hypothyroidism in sheep and goat (Lall, 1952, Dutt and Vasudeva, 1963)

Degranulation of acidophils was observed in the pituitary This might be due to a feed back inhibition of the acidophils resulting from inefficient utilisation of growth hormone produced by the pituitary in the absence of thyroxine Similar pathological changes were reported in hypothyroidism induced by thyroidectomy and goitrogens in laboratory animals (Zeckwer et al 1935, Goldberg et al 1957, Contopoulos et al 1958) in goats (Sreekumaran, 1976 and Reddy , 1982) in cattle (Abraham, 1982) and in rabbits (Ratnakumar 1989)

The histologic picture of the heart was characterised by interstitial oedema and separation of myocardial fibres Myocardial fatty change was reported in hypothyroidism induced by thyroidectomy in the dog (Lippincott et al , 1957) and goats (Sreekumaran, 1976 and Reddy, 1982)

No significant pathological changes were seen in the kidney and spleen Bradely (1971) observed that hypothyroidism is not usually associated with any serious effect in the renal function in human beings

In the testis, the seminiferous tubules were smaller in size and the tubules were lined by a single layer of epithelium and there was no spermatogenesis Some of the tubules showed degenerative changes and slight degree of interstitial oedema The testicular degeneration in experimental hypothyroidism was reported by Sreekumaran (1976) and Reddy (1982) in goats, Abraham (1986) in cattle and Ratnakumar (1989) in rabbits Sharma and Singh (1971) reported compact and highly coiled arrangement of seminiferous tubules in chicks fed with propyl thiouracil It is relevant to mention here that studies on the reproductive organs in different species of animals in hydpothyroidism had varying results (Werner, 1971)

A random survey study was conducted in pigs for assessing the thyroid status using T_4 as a marker the mean value of T_4 in clinically healthy pigs brought for slaughter to MPI, Koothattukulam was found to be 4 028$\pm$0 210 ug/dl

The mean value of T_4 recorded in pigs reared in University Pig Farm Mannuthy was 4 628±0 322 ug/dl Both these values are in the normal range of serum thyroxine level in pigs (Reap et al 1978)

Summary

SUMMARY

Employing thiourea at the rate of 50 mg/kg body weight hypothyroidism was induced experimentally in piglets with the objective of studying the sequence of clinico-pathological changes in subclinical hypothyroidism

Clinically all the experimental animals revealed progressive weakness stunted growth and reduction in weight when compared to the control animals

The hypothyroid piglets had high blood cholesterol values and plasma protein levels when compared to euthyroid controls

A significant decrease in the serum thyroxine was recorded in animals dosed with thiourea This study indicated that estimation of serum cholesterol level and serum thyroxine level could be used as reliable markers for detecting hypothyroidism in pigs

The haemogram in hypothyroid piglets revealed a normocytic hypochromic anaemia

An increase in the relative weight of the thyroid was consistently observed The increase in weight was found to be due to compensatory thyroid hyperplasia

There was increase in the relative weight of the pituitary and adrenal glands in animals dosed with thiourea

Hydrothorax and cardiac dilatation were observed in hypothyroid piglets

Histologically the thyroid gland exhibited varying degree of hyperplastic changes Hyperplasia was characterised by formation of colloid depleted follicles Lining cells were hyperplastic and concomitant degenerative changes were also observed

Predominant histological picture in the pituitary was hyperplasia and hypertrophy of basophils and vacuolar degeneration of hypertrophied basophils

Pathological changes in the adrenal glands were characterised by hyperplasia of zona fasciculata mild degree of degeneration and formation of accessory cortical nodules

In the testis there was degeneration of the seminiferous tubules Histological picture in the liver showed degeneration and necrosis In the heart there was diffuse interstitial oedema Skin revealed hyper-keratosis, acanthosis and dermal oedema

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PATHOLOGY OF HYPOTHYROIDISM IN PIGS

By

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ABSTRACT OF A THESIS

Submitted in partial fulfilment of the requirement for the degree of

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ABSTRACT

An experimental model of hypothyroid state was induced in piglets using thiourea with the objective of studying the sequence of clinico pathological changes and its influence on the animal health and growth

Tweleve Large White Yorkshire male piglets of 2 3 months age were selected for the study The animals were divided into control group of six animals and experimental group of six animals Experimental hypothyroidism was induced by feeding thiourea daily for a period of three months at the dose level of 50 mg per kg body weight Haemogram body weight plasma proteins serum chloesterol and serum thyroxine values were estimated at periodic intervals The piglets were subjected to detailed autopsy after sacrifice Gross lesions were recorded and detailed histopathological examination of tissues was carried out

During the course of experiment all the experimental animals recorded stunted growth and appreciable reduction in feed intake and alopecia of neck and shoulder regions

There was significant increase in blood cholesterol values and plasma protein level in thiourea fed group A

significant reduction in serum thyroxine level was also recorded There was significant increase in the relative weight of thyroid adrenal and pituitary glands of experimental animals Gelatinisation of subcutaneous fat and dilatation of right ventricles were common findings at autopsy Histologically the thyroid glands exhibited varying degree of hyperplastic changes and depletion of colloid in the follicles Hyperplasia and hypertrophy of the lining epitheluim was also observed Predominant histological changes in the pituitary was hyperplasia and hypertrophy of the basophil cells and degranulation of the acidophil cells Adrenal glands showed diffuse hyperplasia of zonafasiculata and accessory cortical nodule formation Skin revealed acanthosis hyperkeratosis and keratini sation of harifollicles In all the hypothyroid animals testis showed varying degree of tubular degeneration

A random survey study was conducted to assess the thyroid status of pigs from different parts of Kerala using serum thyroxine as the marker This concluded that most of the animals had the normal range of serum thyroxine levels