CHAPTER - I

INTRODUCTION

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The thyroid gland was first described by Wharton in 1656. Wharton thought that the viscous fluid within the follicles lubricated the trachea. He also believed that the gland was larger in women to serve a cosmetic function in giving grace to the contour of the neck. Rush in 1820 described that the large size of the gland in women was "necessary to guard the female system from the influence of the more numerous causes of initiation and vexation of mind to which they are exposed than the male sex" (Harington, 1935).

Originally the theories of thyroid functions were mostly speculative in nature and were based upon little or no experimental evidence. Actually the thyroid gained its importance when its enlargement was thought to be associated with changes in the eyes and functions of the heart. Parry first recorded such a case in 1786 (Parry, 1895) and this was followed by reports of cases from Graves and Basedow in 1835 and in 1840 respectively (Haynes and Murad, 1980). In 1874 Gull described the

atrophy of the gland with characteristic symptoms of the thyroid deficiency (Haynes and Murad, 1980). Four years later Ord reported characteristic thickening of subcutaneous tissue which he thought was due to excess formation of mucous. The term myxedema was coined by him (Ord, 1878).

The credit of earliest treatment of thyroid disorders goes to Marray who in 1891 first treated a case of hypothyroidism by injecting extract of thyroid gland. Later Wowitz, Mackenzie and Fox independently discovered the oral effectiveness of the thyroid tissue (Haynes and Murad, 1980).

In 1895 Magnus-Levy discovered the influence of thyroid secretion on metabolic rate. This observation paved the way for further development of correlative studies of thyroid hormone and metabolism in the following decades.

Thyroid gland is one of the most important endocrine glands concerned with metabolism. It is situated at the root of the throat, having two fairly symmetrical lateral lobes, each measuring about 5x2x2 cm. in human being, one on either side of the trachea, joined by a thin portion of the thyroid tissue called isthmus crossing across in front of the second, third and fourth tracheal rings. From the

isthmus a lobe of variable size may extend upwards in the neck. This is known as pyramidal lobe which becomes clinically predominant in certain thyroid disorder (Nadler, 1974; Halmi, 1986). The thyroid is firmly attached by the pretracheal fascia for which it moves upwards during deglutation. Accessory thyroid gland may be found below the main thyroid gland or along the thyroglossal duct (Ingbar and Woeber, 1981). Weight of the gland in normal person may vary from 20 - 30 g. but it is influenced by age, sex, reproductive state and diet of the individual (Rice, 1938; Ingbar and Woeber, 1981). It is a highly vascular gland supplied by superior thyroid arteries, inferior thyroid arteries and thyroidea ima artery. Total blood flow per minute is about 3.5 - 6 ml/g. of tissue (Romanes, 1972; Feind, 1986).

In the human embryo the thyroid develops from the median diverticulum which appears in the latter half of the fourth week in the furrow immediately caudal to the tuberculum impar. It grows caudally as a tubular duct which bifurcates and subsequently divides into several cellular cords from which subsequently isthmus and portions of the lateral lobes are developed. From fourth pharyngeal pouch an ectodermal diverticulum grows and ultimately fuses with the lateral part of medial thyroid rudiment to form the lateral lobes in adult. The pyramidal lobe is presumed to be a secondary development from the isthmus (Solan, 1962).

There are some lateral anlage of the thyroid gland derived from the ultimo-tracheal portions of the fourth pharyngeal pouch. These appear during the 16-17 day's of gestation and may contribute 10 to 15% of the thyroid tissue (Solan, 1962). These ultimotracheal cells are destined to become calcitonin-secreting cells or parafollicular cells (Pearse and Carvalheira, 1967).

The comparative morphology of the thyroid is essentially almost same in all vertebrates. In vertebrates the follicles form a compact organ enclosed in a connective tissue capsule. Often the organ consists of two bilaterally symmetrical units with or without an isthmus. But in reptile and elasmobrauchs it generally remains as a single median organ (Yammoto, 1960; Werner, 1962). In some animals (Cyclostomus teleosts and unredele amphibians) the capsule is but a remnant or is missing. The follicles are distributed in the lower jaw anterior to the heart. In some fish follicles are much more widely distributed (Baker-Cohen, 1961; Waterman and Gorbman, 1963; Lynn and Zmich, 1967). These morphological variations do not possess any other specific physiological significance. The thyroid cells at both light microscopic and ultramicroscopic levels appear to be similar in fishes, amphibians, reptiles and mammals (Baker-Cohen, 1961; Lynn and Zmich, 1967; Waterman and Gorbman, 1973).

The parafollicular cells are normally absent in pisces; they are occassionally found in amphibian thyroids (Copp, 1969).

Iodine is an essential mineral for the synthesis of thyroid hormones. Sea fish is the richest source of dietary iodine but it also occurs in milk, vegetables and bread. Drinking water also contains small amount of iodine. The normal dietary intake of iodine is 100-200 μg daily. Iodine deficiency may result from continuous intake of less than 50μg of iodine daily for a prolonged period. Some Japanese people in the sea coast region consume a great quantity of iodine with sea fish. It has been found that within the range of 50μg to several mg of daily iodine intake, body can adopt thyroid hormone production to such a level as to maintain a euthyroid state (Keele, Neil and Joels, 1983).

Iodine is absorbed in the small intestine and passes through the liver. When the organic form of iodine is ingested a variable portions of the molecule undergo hepatic deiodination. It then circulates in the blood and enters the thyroid gland. The major sites of metabolism of iodine are kidney and liver. The iodine lost in the urine

is present almost entirely in inorganic form, while the loss in the feces is almost entirely in organically bound form (Ingber and Waeber, 1981; Greer and Solomon, 1974).

The thyroid gland is composed of large number of closed follicles lined with cuboidal epithelial cells (150 - 300 micron in diameter). The acini filled with secretary substance called colloid and the acinus cells secrete colloidal substance into the interior of the follicles. The major constituents of the colloid are the large protein, thyroglobulin, which contains the thyroid hormones, thyroxine and triiodothyronine (T_4 and T_3). There is another variety of cells, in between the follicular cells, which are known as parafollicular cells or 'C' cell responsible for the secretion of thyrocalcitonin (Pearse, 1966; Guyton, 1976).

Thyroid gland secretes following three hormones :

1. Thyroxine or Tetraiodothyronine or T_4
2. Triiodothyronine or T_3 and
3. Thyrocalcitonin.

Besides these, large number of closely related iodinated hormones are secreted by the thyroid gland. It has been found that these hormones have a prolonged effect on the metabolic rate of the body. But these are present in very minute quantity (Guyton, 1976).

The cell membranes of thyroid gland have a specific ability to transport iodides actively to the interior of the follicles by iodide pump or iodide-trapping mechanism. In normal individual thyroid pump can concentrate the iodide about 25 times. This concentration may be increased to 350 times in vary hyperactive condition of the gland (Robbins and Rall, 1960).

The thyroid cells synthesize and secrete into follicles a large glycoprotein molecule called thyroglobulin with a molecular weight of 660,000 Daltons. Each thyroglobulin molecule contains 25 tyrosine amino acids and these are the major substrate that combines with iodine to form thyroid hormones (T_3 and T_4). These hormones are formed within the thyroglobulin molecule. In addition to secreting the thyroglobulin the glandular cells secretes iodine, enzymes and other substrates necessary for the thyroid hormone synthesis (Taurog, 1970).

The first stage of the formation of thyroid hormones is believed to be initiated by the formation of elemental iodine from iodide by the enzyme peroxidase abundantly present in the thyroid tissue (Nunez and Prommier, 1968). In the absence of this enzyme formation of the thyroid hormones is greatly reduced. Tyrosine is first iodized to monoiodotyrosine and then to diiodotyrosine. One molecule of monoiodotyrosine

and one molecule of diiodotyrosine couple to form triiodothyronine with the elimination of one alanine molecule. Again two molecules of diiodotyrosine couples to form thyroxine with the elimination of one molecule of alanine. After production of thyroid hormones, they are stored in thyroglobulin. Thyroglobulin being a macromolecule cannot enter into the circulation, rather thyroxine and triiodothyronine are first cleaved from the thyroglobulin molecule then these free hormones are released (Blasi et al, 1969; Taurog, 1970). The proteinases amongst other digestive enzymes digest the thyroglobulin molecules and release the hormones when they defuse through the base of the thyroid cells; through the basement membrane and finally into the surrounding capillaries (Maayan, 1964; Schneider, 1970).

About 90% of the iodohormones released from thyroid is thyroxine (T_4) and rest is triiodothyronine (T_3). But in circulation thyroxine is slowly deiodinated to form some amount of additional triiodothyronine. However functionally the triiodothyronine is four times more potent than the hormone, thyroxine (Oppenheimer et al, 1970).

Deficiency of calcitonin or hyperacting parafollicular cells rarely produce a clearcut clinical picture which can be

attributable to 'C' cell activity (Aurbach et al, 1981).

But dysfunction of thyroid gland due to inadequate secretion of excess production of T_3 and or T_4 is frequently met with as hypothyroidism which may be thyroprivic, goitrous and trophoprivic in nature and as hyperthyroidism otherwise known as Grave's disease or Basedow's disease (Ingbar, 1983).

Hypothyroidism :

Irrespective of the cause of hypothyroidism several changes are manifested in human beings. The diminution of mental growth and functions, stunted skeletal and visceral growth, delayed milestones of life and less calorific requirements are the principal clinical features in infancy and childhood (Guyton, 1976; Ingbar and Weeber, 1981).

Dry coarse skin, cold intolerance, depressed perspiration, yellowish skin, pallor, hair lossness, fatigue, marked lethargy, slow speech, horseness of voice, thick tongue, constipations, somnolence, impairment of memory, reduced BMR (by 20%), myxoedema and hypercholesterolaemia are some of the salient features of hypothyroidism in adult (Hoch, 1968).

Hyperthyroidism :

Hyperthyroidism rarely occurs in childhood. In adult increased perspiration, heat intolerance, goiter, tremor, nervousness, weight loss, palpitation, proptosis, brisk reflexes, elevated BMR (by 20%), a low cholesterol level in blood are common clinical features in hyperthyroidism. Dermopathy is almost never seen, the skin remains smooth, soft, wet and retains its lustre (Hoch, 1974).

Thyroid hormones are involved in cellular production of heat and are also involved in regulation of body temperature. The role of thyroid hormones in the adaptation of low temperatures is a controversial issue because animals kept under natural winter conditions, or natural wild animals or humans do not respond by a rapid increase of the BMR as do mice and rats (Hoch, 1974).

During cold adaptation, however, the thyroid hormone secretion is increased presumably through the hypothalamic thyrotrophin releasing factor. When the animals are exposed to 10 - 20^{o}C environments or when humans are under hypothermia during surgery there is release of thyrotrophin which reach the peak level in less than an hour and persists for 2 - 3 hours (Itoh et al, 1966; Wilber and Baurn, 1970).

Further it has been found that the hormones (T_3 and T_4) reaches the mitochondria of the liver and other tissues rapidly in rats (Tonone and Metsumoto, 1961; Albright et al, 1965).

Mechanism of thyroid actions :

Like most of the other hormones, thyroid hormones have multiple biological actions. These can be broadly classified into two groups: One group controlling growth and development and the other group regulating metabolic activity both during and after development.

Investigators have observed that thyroid hormones increase the rate of growth, enhance maturation of central nervous system, accelerate the metamorphosis of amphibians, stimulate the mitocondrial respiratory enzymes and structural elements (Pitt-Rivers and Tata, 1959; Tata, 1964).

The early stimulatory effect of thyroid hormones on nuclear RNA synthesis has been demonstrated both as rapidly labeled RNA synthesis in vivo and as RNA polymerase activity in isolated nuclei. A careful analysis of the results reveals that it was the changes in the rates of ribosomal RNA synthesis that were most significant during the early phase of hormone actions (Tata and Windell, 1966; Tata, 1967).

Besides the increased synthesis of RNA by the thyroid hormones, there are increased rates of production of RNA polymerase, amino acid incorporation into protein by mitochondria and microsomes, microsomal phospholipids, microsomal membrane enzymes, mitochondrial respiratory enzymes, serum albumin, adult haemoglobin and urea cycle enzymes (Tata, 1966; Tata and Widnell, 1966; Tata, 1967 and Wyatt and Tata, 1968).

Butcher et al (1968) described that the thyroid hormones do not control metabolic activity through the production of cyclic AMP and none of the actions of thyroid hormones can be mimicked by cyclic nucleotide. On the contrary, recently it has been reported that T_3 increases cellular cyclic AMP within few minutes after addition of T_3 to the culture media (Ingbar and Woeber, 1981).

Interrelation of thyroid hormones with other endocrine glands :

The documentation of most important interrelation of thyroid hormones is alteration of certain responses to catecholamines without influencing others. It is an important finding in understanding of thyroid hormonal action (Ellis, 1956; Bray, 1968). The calorigenic effects of epinephrine are almost completely abolished in the absence of thyroid gland and are potentiated by the administration of thyroxine

(Swamson, 1956), and also treatment with triiodothyronine enhances the sensitivity of adipose tissue to the lipolytic effects of catecholamines within 3 hours (Vaughan, 1967; Challoner, 1969). These observations have been questioned by some investigators who failed to obtain any effect of thyroid on the catecholamine response (Bray, 1968). Further studies have shown that concentration of epinephrine in medullary tissue of rats, sheeps and guineapigs is significantly reduced by treatment with the thyroid hormone (Leak, 1970 and in hypothyroidism medullary epinephrine and non-epinephrine are increased (Hokfelt, 1951) while blood level of epinephrine remains unchanged (Hoggendal and Svedmyr, 1966).

Scientific data have accumulated over more than forty years showing that thyroid hormones can modify the secretion and turn-out rate of insulin. Earlier Houssay showed that thyroid treated dogs became parmanently diabetic when two-third or more of the pancreas was removed (Houssay, 1944). Small doses of thyroid hormone can produce diabetes in animals which could not be made diabetic after administration of regulated small doses of alloxan (Mallander and Kirschbaum, 1949). Later, it has been observed that thyroid hormones also increase the turnover rate and metabolism of insulin. Degradation of insulin is slower in hypothyroid subjects and increased in hyperthyroidism (Vince et al, 1970).

Adams et al (1967) reported that hyperthyroidism is often associated with profound influence on the metabolism of calcium; the turnover of calcium exceeds intake . Concentration of calcium in the serum in some cases of hyperthyroidism has been found to be elevated for which no explanation could be furnished (Parfit and Daut, 1970).

In the last century Niepce (1851) observed degranulation, hypertrophy and hyperplasia of hypophysial cells in hypothyroidism in man and this has been substantiated by the observations of Furth and Clifton in 1966. It has been reported that the normal growth rate of thyroidectomized rats treated with thyroxine requires the presence of pituitary, and the administration of thyroxine alone becomes ineffective in hypophysectomized, thyroidectomized animals (Eartly and Leblond, 1954). Further studies have shown that thyroidectomy causes significant reduction of acidophil cells of adenohypothysis which are regarded as cellular source of growth hormones (Schooley et al, 1966).

After experimental thyroidectomy in rats the plasma level of ACTH, glucocorticoids and adrenal weight decline and these are increased in hyperthyroidism. But no such significant change has been reported in man (Fortier et al, 1970).

It is commonly observed that altered thyroid activity impairs the fertility of women which might be due to deranged cyclical ovarian functions. However it is not clear at which points the thyroid hormones influence the complex physiological mechanism of ovulation (Bray and Jacob, 1974). Secondary sexual characters are poorly developed in the absence of thyroid hormones (Cowie, 1966).

Vitamin A and allied compounds :

Vitamin A or retinol is available from vegetable and animal sources. The animal sources are fish oil, liver, milk and butter. Vegetable source include carrot, spinach, green leaves, yellow coloured fruits e.g., tomatoes, magnoes etc. The vitamin exists in carrots and in all vegetables as carotene. Vitamin A can be synthesised in the body by the liver from carotene (Davidson et al, 1975).

It has also been conclusively proved that retinoic acid is a retinol derivative. In vitamin A deprived animals fed with retinoic acid, it has been found that certain tissues functions well, growth and development is not affected but vision fails and spermatogenesis does not occur (Dowling and Wald, 1960).

Aims and Objects

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Vitamin A, a fat soluble vitamin, is essential for the epithelial cells particularly of the skin, eye, respiratory tract and urinary tract. Hyperkeratosis of the hair follicles, specially on the extensor surface of the limb producing the so called phrynoderma or toad skin occurs in hypovitaminosis A. But it is not absolutely certain that phrynoderma is entirely due to the deficiency of vitamin A. It could not be produced in experimental vitamin A deficiency when this was studied (Smart, 1974).

In hypothyroidism the skin feels dry and coarse with roughness and scaling particularly over the extensor surface of the limbs; it is thickened by mucinous infiltration. Sweating is absent. Body hair is short and sparse. The loss of hair from the temporal aspect of eyebrow is more common. There is intolerance to cold (Ingbar and Waeber, 1987).

Both the thyroid hormones and vitamin A appear to affect the metabolism of dermal mucopolysaccharide (Dingle and Lucy, 1965).

These skin manifestations of vitamin A deficiency simulate those of the thyroid deficiency (T_3 and T_4). But scientific literature regarding the physiological correlation between thyroid hormones and vitamin A are meagre to find out such correlations.

Further, in the present study an attempt has been made to show wheather retinoic acid alone can substitute for

thyroxin, because it has already been found that retinoic acid can act as a substitute for retinol in growth and development (Dowling and Wald, 1960) and in hypothyroid the growth and development are affected (Ingbar and Woeber, 1981). Naturally it seems that there may be some relation between retinoic acid (which is derived from retinol or other form of vitamin A) and the thyroid hormones.