THE INFLUENCE OF ACTIVE THYROID HORMONE AND ANTITHYROID DRUGS UPON ELECTROLYTE METABOLISM

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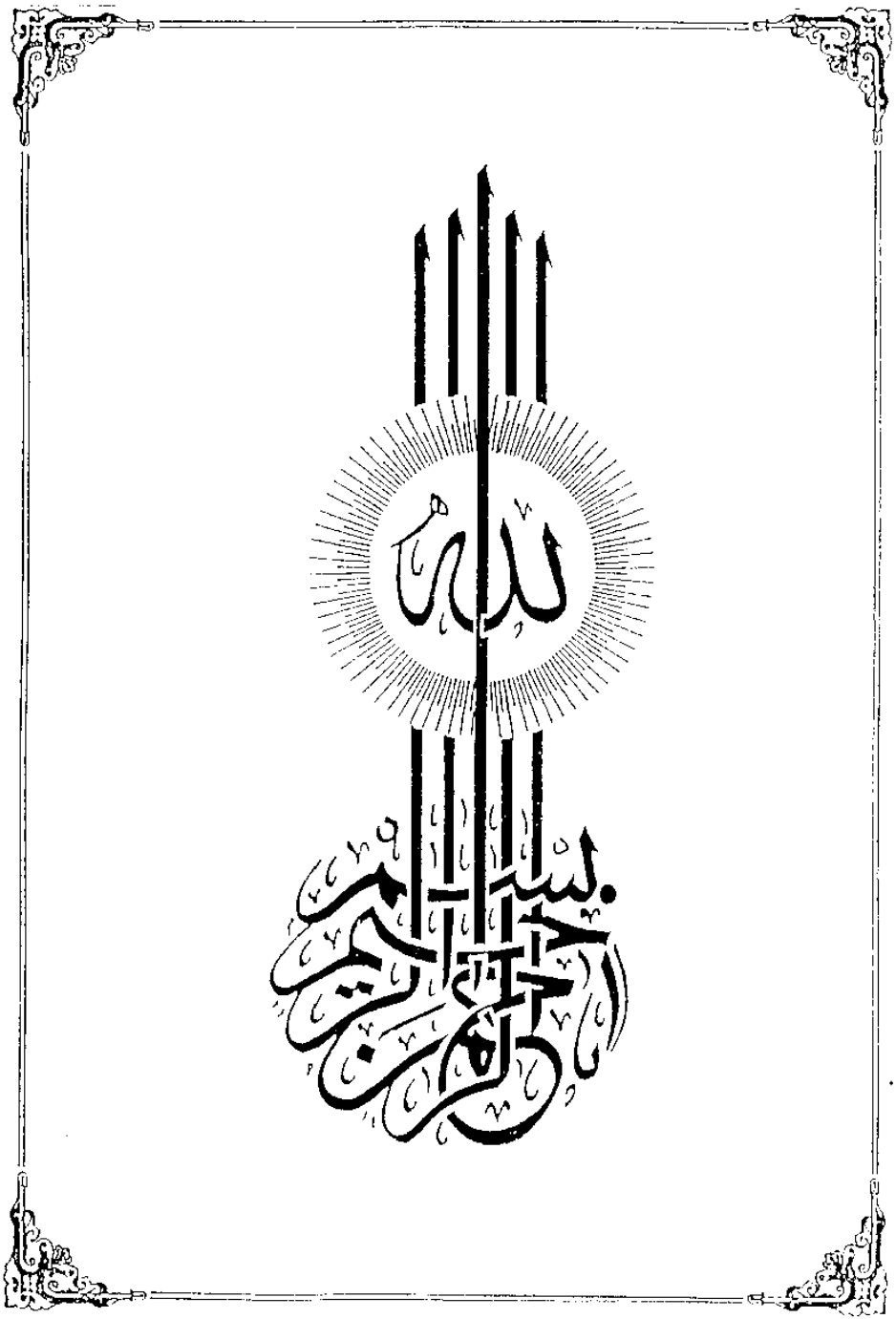

INTRODUCTION

As early as 1827, the relationship between the thyroid and the various body functions was studied by experimental thyroidectomy and the concept of an internal secretion released by the gland was formulated by King 9 years later.

The similarity between myxedema and the clinical picture which developed after successful removal of the thyroid was reported.

Vassale and Generali in 1896 separated the entity of myxedema following thyroidectomy from that of tetany. Murry in 1891 injected a glycerine extract of the thyroid to relieve myxedema. The association of iodine with the thyroid was made in 1896 by Baumann. As early as 1900 Gley and Bourcet identified the presence of organic iodine in plasma in combination with serum proteins. Kendall (1914) on christmas eve, isolated crystalline thyroxine from alkaline hydrolysate of thyroid tissue. Harington (1926), and Harington and Barger (1927) established the chemical structure of thyroxine.

[illegible] by Parry in 1786. [illegible] (1835) established the relation of the ocular complications to the disease. Von Basedow in 1840, popularized the triad of exophthalmos, goiter, and palpitation. Rehn in 1884 performed the first subtotal thyroidectomy. Magnus-Levy (1895) was the first to describe the characteristic elevation of the basal metabolic rate in toxic goiter. Gross and Pitt-Rivers (1952) found a compound with only three iodine atoms (triiodothyronine) in the gland and in plasma. This compound proved to be physiologically more potent and more rapid in onset of action than thyroxine, and was clinically effective in myxedema. These workers speculated that thyroxine is the form in which thyroid hormone is secreted, while triiodothyronine is the form which is active in tissues.

Thyroxine and triiodothyronine are carried in plasma largely bound to protein. Gordon et al (1952) first identified the thyroxine binding globulin (TBG). He described the migration of thyroxine in human serum during electrophoresis in a zone between α_1 and α_2 globulin. Ingbar (1958) noted that thyroxine also

migrated with prealbumen fraction, this fraction was been called thyroxine binding prealbumen (TBPA), also albumen can carry thyroxine. Hollander et al (1962) reported that thryroxine was bound bout 46% by TBG, 30% by TBPA and albumen 20%. The total binding capacity of these proteins are in reverse order, that of TBG was about 25 microgram per 100 ml. of serum, and that ofTBPA 250-300 microgram per 100 ml. The uptake of L-triiodothyronine by TBG is reduced in hyperthyroidism and increased in myxedema (Mitchell et al 1964). The binding of thryoid hormone and serum is a reversible one governed by electrostatic forces. TBG binds thyroxine with such a high affinity that only 1/1000 of the hormone is free. The binding capacity of TBG is very limited because it is present only as a trace protein.

Hershman (1963) and Christensen (1960) reported that salicylate, dinitrophenol, estradiol, as well as thyroxine analogues inhibit the binding of thyroxine to serum proteins in rats.

The difference in potency between thyroxine and triiodothyronine is due to difference in degree of binding to various transport proteins of plasma.

[illegible] the peripheral effect is needed more readily (Greenberg et al 1963).

Free thyroxine in blood indicates the thyroidal state and various methods are suggested for its estimation (Sterling and Hegedus 1962, Ingbar et al 1965, Liewendahl and Lamberg 1965).

Whaley et al (1959) presented evidence that the metabolically active thyroid hormone was triiodothyroacetic acid which is a deaminated triiodothyronine and it produces an immediate increase of oxygen consumption of tissues **in** vitro and in vivo. Triiodothyronine was about 5 times as active as thyroxine and triiodothyroacetic acid was found to be 1/5 potency of thyroxine (Trotter 1957). Gross et al (1957) stated that an unknown metabolite of triiodothyronine found in plasma and bile was triiodothyronine complex readily dissociated by dilute acids, and suggested that thyroxine is metabolised in liver and Kidney to triiodothyronine which is converted into triiodothyronine complex, the latter is secreted into the circulation as a precursor of triiodothyronine

[illegible] in tissues. Trotter (1957) administered iodoacetic acid, triiodothyronine and thyroxine to euthyroid individuals. Each decreased blood cholesterol and depressed the uptake of radio active iodine.

The site of action of the thyroid hormone in accelerating metabolic rate appears to be peripheral. It involves an enzyme level similar to the action of dinitrophenol. Lehninger and his associates (1955) observed marked correlation between mitochondria from different tissues and their increased respiration. Thyroxine produced mitochondrial swelling in liver and kidney but not in spleen brain and testis.

Challoner (1968) showed that thyroxine altered the function and structure of mitochondria in vivo and in vitro. Low concentrations of thyroxine raised oxidative rate and high concentrations lowered phosphorylation i.e. uncoupling mechanism. This can explain myopathy and cardiomyopathy of thyrotoxicosis. The uncoupling action of thyroxine is specifically antagonized by magnessium ions (Neguib, M.A. 1963). Thyroxine may facilitate the transfer of substances involved in energy transfer and respiratory activity through the modified mitochondrial membrane resembling

... acting of insulin in its capacity to pass glucose into the cell.

However Lehninger,A.L. (1962) stated that uncoupling occurs by liberating mitochondrial lipids which are uncoupling agents. This is done by activation of Lipase enzyme via calcium ions.

Dutoit (1952) reported that the incorporation of radio active iodine in protein by liver slices was depressed after thyroidectomy and stimulated by large doses of thyroxine. Sokoloff and Kaufman (1959-1961) demonstrated that L-thyroxine administration either in vivo or in vitro stimulated the rate of amino acid incorporation into liver proteins of normal rats.

The stimulation of protein synthesis involved the transfer of soluble RNA-bound amino acids to microsomal protein (Stein and Gross 1962). The effect on protein is dependent upon the presence of mitochondria and an oxidizable substrate (Brown 1966). Blockade of protein synthesis, and therefore also thyroxine effect by puromycin restored the increased metabolic rate of thyroxine treated rats to normal (Weiss and Sokoloff 1963, and Tata 1963). It was

found that phenylbutazone and oxyphenbutazone inhibit the action of cyclic AMP (Michels et al. 1963).

Long Acting Thyroid Stimulator (LATS):

Adams and Purves (1956) observed that the thyroid stimulating activity of the blood of thyrotoxic patient is not due to thyroid stimulating hormone (TSH) and noted that when the serum of thyrotoxic patients was injected into a guinea pig previously given radio active iodine, the discharge of iodine from the gland was prolonged. This is quite unlike the short-lived response to TSH. These findings were confirmed by McKenzie (1958) and Munro (1959). The newly discovered thyroid stimulator was called long acting thyroid stimulator (LATS).

Major and Munro (1960 and 1962) attributed the more prolonged activity of LATS due to its slower disappearance from the serum. Also McKenzie (1961) reported that its half life is 30 times that of TSH. Another difference between LATS and TSH is that, unlike TSH, LATS does not reside in the pituitary gland. (Major and Munro, 1962) and this correlates with clinical evidence that hyperthryoidism may occur after hypophysectomy. Fajans (1958) and Wane et al

[illegible] differentiation of LATS. Adams (1960), and Dorrington and Munro (1965) could demonstrate chemical and immunological differences between LATS and TSH.

Dorrington et al (1966) stated that LATS being an immuno globulin belonging to the 7 S gamma globulin, it would be expected to arise from antigenic stimulus which probably resides in the microsomes of thyroid epithelial cells.

Kriss et al (1964) had suggested that LATS is causally related to development of infiltrative ophthalmopathy and dermopathy (localised pretibial oedema). However Noguchi (1964), Pinchera (1965) and McKenzie (1965) found LATS in the absence of particular clinical feature. Beall (1966) and Kriss (1964) stated that LATS disappeared from the serum of some patients when they became cured from Graves' disease.

Adams and Kennedy (1967) discovered a circulating gammaglobulin and it has no metabolic activity, but protects LATS from neutralization by extracts of thyroid cells and named it LATS protector.

The Thyroid and Electrolytes:-

Studies on Calcium:

As regards the relation of the thyroid on electrolyte metabolism, Koeppen as early as 1892 reported that, there appeared to be connection between exophthalmic goiter, osteomalacia and other bone diseases. Pierallini in 1906 investigated the possibility of an intimate relation between thyroid function and the metabolism of calcium and phosphorus (Phosphate as a passive partner of calcium). In his experiment, urinary calcium only was determined. The calcium intake was unknown and unrestricted because he assumed that the urinary calcium content is an index of endogenous calcium metabolism. His figures showed the calcium and phosphorus excretion to be normal in Basedow's disease. However, his results were of limited value.

Scholz in 1906, stated that the untreated crotin was found to retain phosphorus and to excrete an abnormally large amounts of calcium. Administration of thyroid preparation exerted no marked effect on the phosphorus metabolism, but reduced the urinary excretion of alkaline earths particularly calcium.

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A year later, Silvestri and Rossetti reported the effect of administration of thyroid extract on the calcium exchange in various diseases and found that daily ingestion of one tablet of thryoid favoured retention of calcium and their results can be explained by insufficient dosage of thyroid and inadequate duration of observation.

In referring to the work done with Bolaffio and tedesco, Fulta in 1909 mentioned experiments in which administration of thyroid increased the ratio of nitrogen to phosphate in urine and increased the phosphate in stools. He concluded that, there must be an increase in foecal excretion of calcium to account for the augmented phosphorus output in stools.

Another series of observation was made by Parhon in 1912, the calcium exchange of 9 rabbits was determined both before and after administration of thyroid, and indicated that thyroid does exert stimulating influence on calcium excretion.

Kojima in 1917, approached the problem from a different angle. He removed the thyroid gland and the parathyroid from rats, and then replaced the

Kummer, determined the nitrogen and calcium excretion and found that both has been diminished. He could not, however demonstrate in these experiments that administration of thyroid affected the calcium metabolism. The reduced calcium excretion after thyroidectomy might be explained by parathyroid defeciency. Kummer in the same year published data obtained from patients with exophthalmic goiter receiving 2.5 liters of milk daily (about 5 gm calcium per day) and concluded that the mineral excretion was high but very irregular, and because of urine calcium was normal and foecal calcium was high, Kummer attributed high foecal calcium in Basedow's disease to a difficulty in absorption rather than an abnormal excretion. Vines (1924) stated that calcium is lost from the body during diabetes mellitus and Graves' disease, and retained in myxedematous individuals.

In 1929, Aub and his associates established that hyperfunction of the thyroid gland is associated with increased excretion of calcium and phosphorus, and so may result in hypercalcuria and negative phosphate balance.