STUDY OF THYROID ANTIBODIES IN THYROTOXICOSIS BEFORE AND AFTER MEDICAL CONTROL

THESIS

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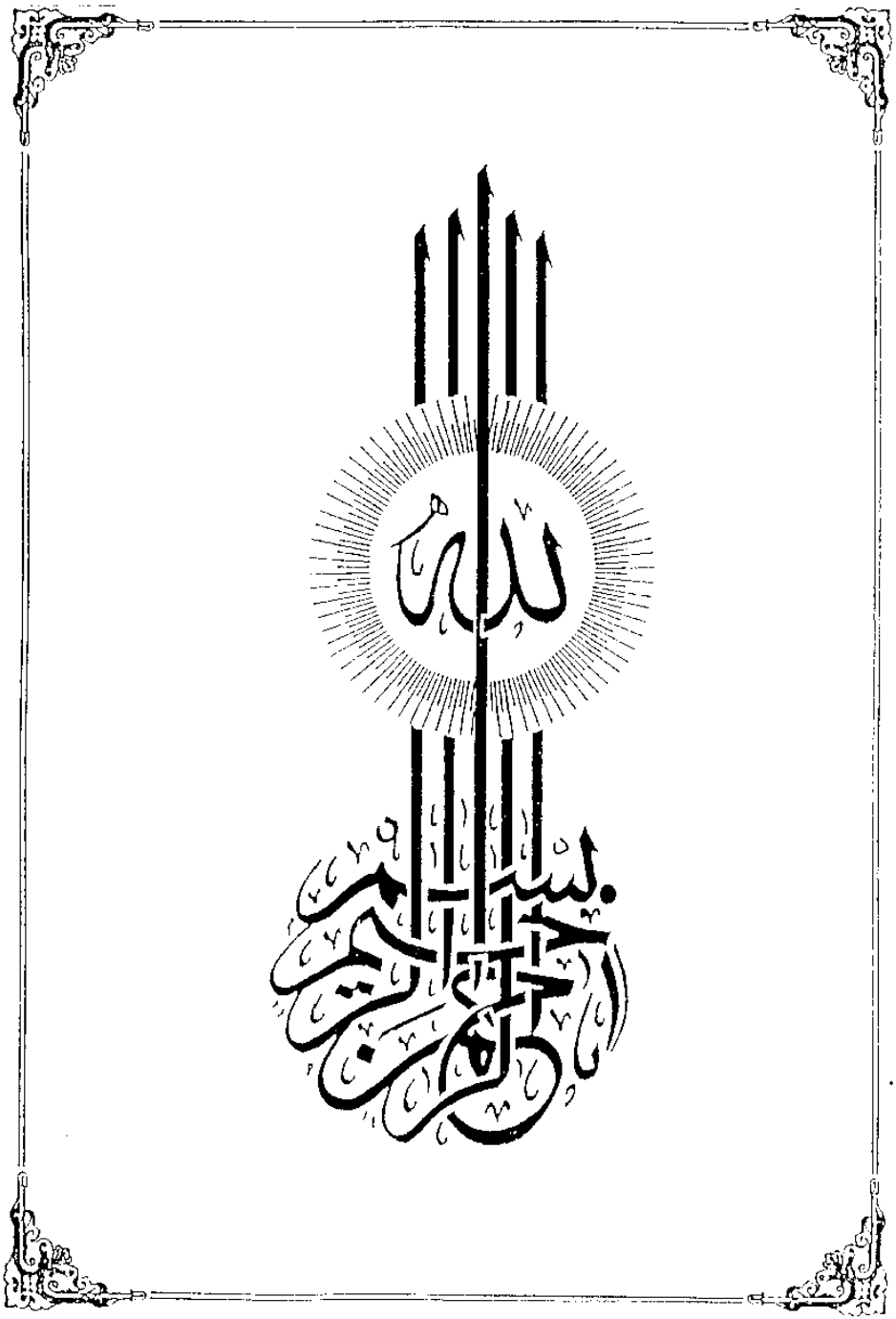
To my family



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Introduction and Aim of the work

Introduction:-

Hyperthyroidism may be due to diffuse hyperplasia (diffuse toxic goiter or Graves' disease), Toxic nodular goiter or localized autonomous adenoma.

Study of the involvement of autoimmunity in hyperthyroidism is hampered by the lack of a well defined experimental model.

The theory of an immunologic origin of hyperthyroidism rests on the demonstration of Long - acting thyroid stimulator (LATS) as a stimulating autoantibody.

It is possible that other thyroid autoantibodies may have a stimulatory effect. For example, complement - fixing antibodies to thyroid microsomes are relatively prominent in hyperthyroidism - In small amounts, these antibodies may increase the function of thyroid cells. Immune complexes formed in certain ratios of thyroglobulin to its respective antibody may also exert stimulatory effects. Cell-mediated immunity to thyroid microsomes has been demonstrated in most hyperthyroid patients. T-lymphocytes within the thyroid gland may directly stimulate thyroid cells (Rose, 1978).

Aim of the work:-

Untreated hyperthyroidism can produce irreversible problems in several organ systems. There may be gradual

deterioration of the cardiovascular system leading to congestive heart failure. Stressfull situations, including infection, may precipitate thyrotoxic crisis or "storm"

All three major forms of therapy (Radioactive iodide, Anti - thyroid drugs, surgery) should result in relatively prompt control of hyperthyroidism and most patients subsequently lead a normal life. It is interesting to note that none of these lines of treatment is directed towards the etiology of the illness.

There is a tendency for patients who respond to antithyroid drugs (Less so to surgery) to have recurrence of illness years later.

This work is intended to study thyroid antibodies before and after medical control of thyrotoxicosis to provide immunological screening for diagnosis, assessment of medical control and to determine incidence of relapse of thyrotoxicosis after such control.

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PART I

Review of Literature

Anatomy

Embryologically, the thyroid gland appears in about the third week, when the embryo is only 3.5 To 4.0 mm. long. It begins as a proliferation of epithelial cells in the floor of the developing pharynx at apoint indicated by the foramen cecum, a dimple - like depression of the base of the tongue.

As the thyroid primordium descends, it acquires mesodermal contribution which will develop the parafollicular C cells, that secrete calcitonin. The thyroid then emerges as a bilobed diverticulum connected to the pharynx by the thyroglossal duct, which usually obliterates. With further descent, the thyroid gland eventually reaches its definitive location in front of the hyoid bone and the laryngeal cartilages and assumes its fully developed configuration of two lateral lobes usually joined by a median isthmus. At the end of the third month of fetal development, follicles containing colloid become visible, and its probable that the gland begins to release thyroid hormone at this time.

The normal thyroid weighs about 20gm, and is attached to the anterior and lateral aspects of the trachea by loose connective tissue.

The isthmus joins the two lobes, and its upper margin lies just below the cricoid cartilage. The two thyroid lobes are found along the lower half of lateral margins of the thyroid cartilage. The thyroid is surrounded by a thin fibrous capsule that penetrates the gland, forming pseudolobules.

Migration of the thyroid tissue into the anterior mediastinum is frequent. Substernal goitre may develop in this location and often is continuous with the cervical thyroid. Rarely, posterior mediastinal thyroid tissue is found, and from it may arise large goitres of posterior mediastinum that are usually not continuous with the cervical thyroid gland. Occasionally, fully developed children or adult may have a sublingual thyroid that represents the only thyroid tissue and can be confirmed by iodine 131 Scan.

The blood supply of the thyroid is primarily through the inferior thyroid artery, a branch of the subclavian, and superior thyroid artery, arising from the external carotid. The thyroidea ima artery may also be present, varying in size, and arising from either the innominate artery or the aortic arch and coursing upward anterior to the trachea to the inferior border of the thyroid. The excellent blood flow of the thyroid, is in the range of 4 to 6 ml. per gram per minute, or approximately 50 times as much blood per gram as in the body as a whole. (Harrison, 1981).

The venous return from the upper pole follows the superior thyroid artery. This vein, the superior thyroid vein enters either the internal jugular or common facial vein in about equal proportions. The middle thyroid vein, short and wide, is usually present. It passes from the middle of the lobe, directly into the internal jugular vein. From the isthmus and lower poles, the inferior thyroid veins form

a plexus that lies the pretracheal fascia, in front of the cervical part of the trachea. The plexus drains into the brachic - cephalic veins, most of it into the left one.

The lymphatics follow the arteries. From the upper pole they enter the antero - superior group of deep cervical lymph nodes. From the lower pole they pass with the inferior thyroid artery back to its point of origin from the subclavian behind the carotid sheath into the postero - inferior group.A few pass downwards into pretracheal nodes, following the course of thyroidea ima artery.

Nerve supply of the thyroid gland: The bulk of the sympathetic supply is derived from the middle cervical ganglion and enters the gland on the inferior thyroid artery. Some fibres from superior cervical ganglion travel with the superior thyroid artery. The sympathetic fibres are vaso - constrictor. Vagus nerve filaments are traceable to the gland, their purpose is unknown. (Last, 1977).

The microscopic appearance of the thyroid shows numerous follicles (acini) filled with proteinaceous colloid. The wall of the acinus is composed of a single layer of cuboidal cells resting on a basement membrane that is richly supplied with capillaries. The acini are arranged in subunits of 20 - 40, which are demarcated by connective tissue to form lobules, each supplied by an individual artery. The height of the epithelial cell lining the follicles varies with the state of functional activity but normally is about 15μ. The size

of the follicles also varies but approximates 200μ in diameter. In any microscopic slide, the follicles vary widely in size since they are cut at different planes in the section. (Harrison, 1981).

When the gland is inactive, the colloid is abundant, the follicles are large, and the cells lining them are flat. When, the gland is active, the follicles are small, the cells are cuboidal or columner, and the edge of the colloid is scalloped, forming many small "reabsorption lacunae" (Figure 1). Microvilli project into the colloid from the apexes of the thyroid cells, and canaliculi extend into them. There is a prominent endoplasmic reticulum, a feature common to most glandular cells, and secretory droplets of thyroglobulin are seen (Figure 2).

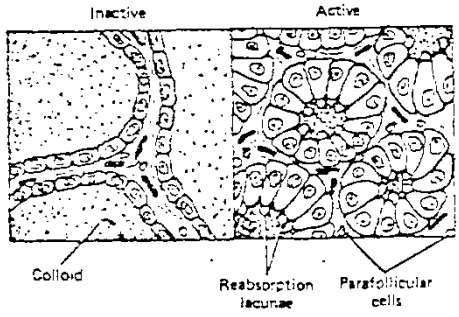

Figure (1) Thyroid histology. Note the small, punched-out "reabsorption lacunae" in the colloid next to the cells in the active gland.

After Ganong, (1985)

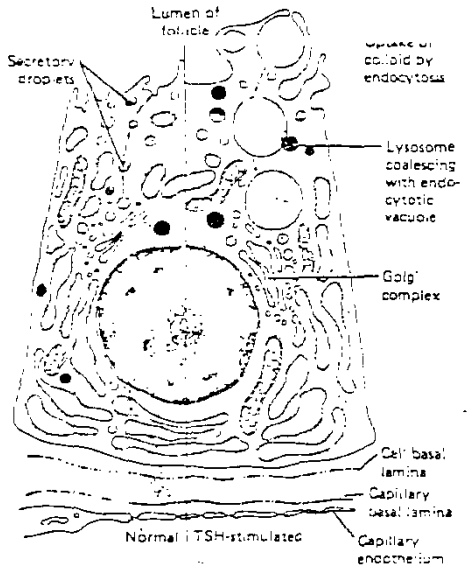

Figure (2) Thyroid cell. *Left*: Normal pattern. *Right*: After marked TSH stimulation. The arrows on the left show the secretion of thyroglobulin into colloid. On the right, endocytosis of the colloid and merging of a colloid-containing vacuole with a lysosome are shown. The cell rests on a capillary with gaps (fenestrations) in the endothelial wall. (Modified and reproduced, with permission, from Fawcett DW, Long JA, Jones AL. The ultrastructure of endocrine glands. *Recent Prog Horm Res* 1969; 25:315.)

After Ganong, (1985)

The individual thyroid cells rest on a basal lamina that separates them from the adjacent capillaries. the endothelial cells are attenuated at places, forming gaps (fenestrations) in the walls of the capillaries (Figure 2). This fenestration of the capillary walls also occurs in most other endocrine organs. (Ganong, 1985).

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Physiology

Thyroid Hormone Formation:

The general scheme of thyroid hormone biosynthesis is depicted in (Fig. 3)

Thyroid Hormone Formation

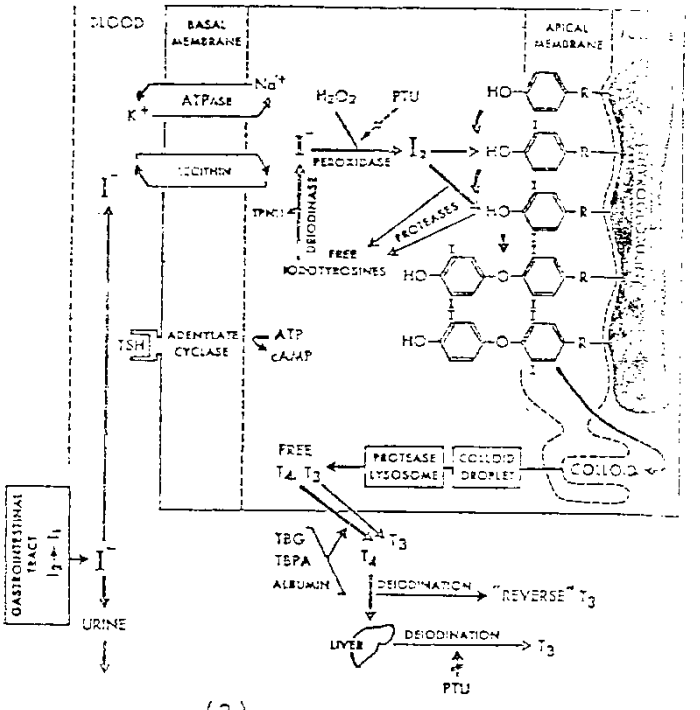

FIG. (3) Biosynthesis of thyroid hormones.

After Berkow, (1982).

Iodide, ingested in food and water, is actively concentrated by the thyroid gland, converted to organic iodine by peroxidase, and incorporated into tyrosine in thyroglobulin. The tyrosines are iodinated at either one (monoiodotyrosine, MIT) or two (diiodotyrosine, DIT) sites and then coupled to form the active hormones (diiodotyrosine + diiodotyrosine ⟶ tetraiodothyronine (Thyroxine, T_4); diiodotyrosine + monoiodotyrosine ⟶ Triiodothyronine (T_3). Throglobulin, a glycoprotein containing T_3 and T_4 within its matrix, is taken