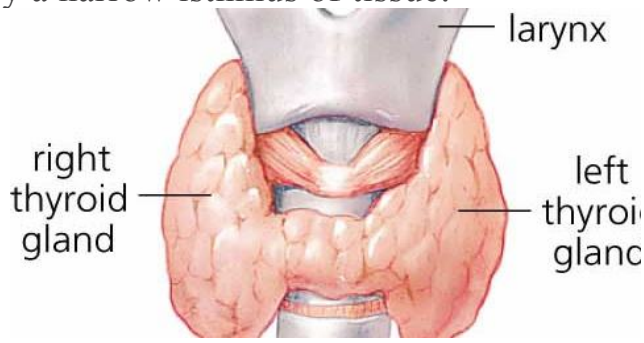
THYROID GLAND

Thyroid gland is the largest organ (weighing about 15-25 gm. in adult human), specialised for endocrine function in human body. This gland is capable of accumulating iodide in great excess and combining it into an organic compound thyroxine, the main hormone of thyroid. This hormone and its precursors are virtually the only iodine compounds in living organisms. The mammalian thyroid also secretes the calcium-lowering hormone calcitonin. Dysfunction and anatomic abnormalities of the thyroid are among the most common diseases of the endocrine glands.

Development of Thyroid Gland:

The thyroid gland is an embryonic derivative of the alimentary tract. A median, unpaired sac-like evagination first appears from the floor of the embryonic pharynx. The distal end of this outgrowth gradually expands and becomes bilobed and the stalked attachment narrows to form the thyroglossal duct.

The duct usually atrophies and two lobes become solid masses of tissue and remain connected to each other by a narrow isthmus of tissue.



Location of Thyroid Gland:

The human thyroid consisting of two lobes, each on either side of the trachea at a position just below the cricoid cartilage. The isthmus that connects two lobes extend over the anterior surface of the trachea. A pyramidal lobe near the isthmus of the thyroid may persist as a remnant of the thyroglossal stalk

Anatomy of Thyroid Gland:

Each lobe of human thyroid in pear-shaped and measures about 2.5-4 cm in length, 1.5-2 cm in width and 1-1.5 cm in thickness. The weight of this labile organ varies with age, reproductive status and diet. However, the normal thyroid of adult weighs 15-25 gm.

The gland is encapsulated by two layers of connective tissues; the outer layer is continuous with the cervical fascia and is loosely connected to the inner capsule that adheres intimately to the surface of the gland.

Post-ganglionic sympathetic fibres from the superior and inferior cervical ganglia and vegal fibres from the superior and inferior laryngeal nerves enter the gland. The gland has a rich vascular supply. The superior and inferior thyroid arteries arise, respectively, from the external carotid and subclavian arteries. The thyroid ima artery arises from the brachiocephalic artery, at the aortic arch.

An important anatomical consideration includes two pairs of parathyroid glands that usually lie behind the upper and middle thyroid lobes

Histology and Cytology of Thyroid Gland:

The thyroid gland is composed of an aggregation of spherical to ovate cyst like follicles of variable size. The thyroid in normal rat contains about 100,000 follicles; the larger follicles generally located near the periphery and the smaller ones in the centre.

The inter-follicular spaces are occupied by highly vascularized network of connective tissue with few lymphocytes and histocytes. Each follicle is lined by a secretory epithelium composed of single layer of cuboidal or low columnar cells.

Surrounded by the epithelium is a closed cavity in each follicle that contains a homogeneous, gelatinous amber-coloured material. This material is called as 'colloid' that gives to the gland its most distinguishing histologic peculiarity (Fig. 7.17).

The follicle cells synthesise thyroglobulin, which is extruded into the lumen of the follicle and remains stored as colloid. Its density varies in different glands and in different follicles of the same gland.

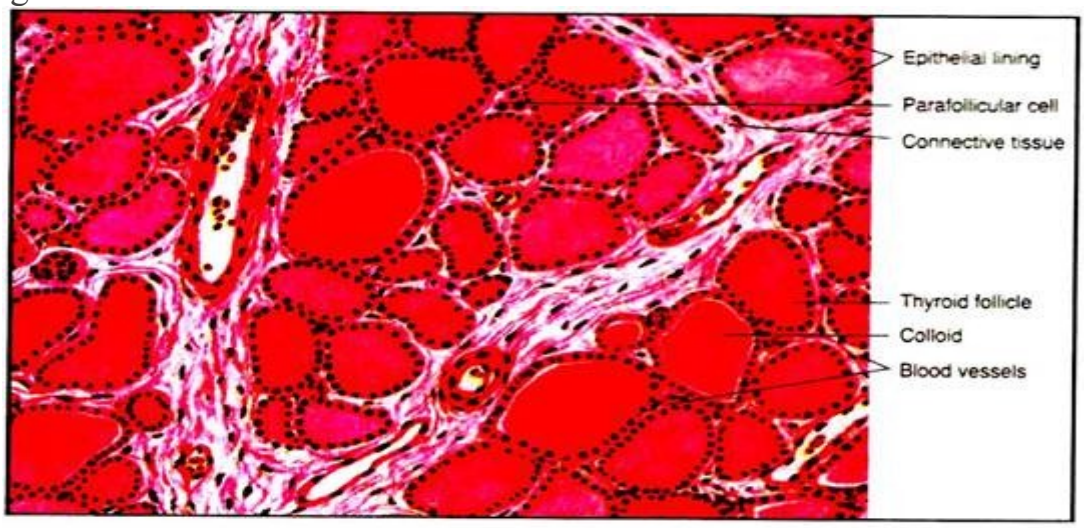


Fig. 7.17 : Histological features of the normal thyroid gland of the rat

When the thyroid is inactive, there is a tendency for colloid to accumulate and for the epithelium to become low cuboidal or squamous. The cells become columnar and plicated, and the colloid stores are depleted when the gland is overactive or stimulated by TSH. There are however, many exceptions, so histological examination alone cannot establish the functional state of the gland.

In the inter-follicular space as well as in the basal region of the follicles, are few ovoid cells with granular cytoplasm and irregularly-shaped nucleus. These are para-follicular cell or C cells (clear cells) of neural crest origin and secreting calcitonin.

Under electron microscope (EM), the cytological features of thyroid follicle cells appear to be similar with many other secretory cells. The cells have extensive endoplasmic reticulum (ER) with dilated cisternae and laden with microsomes. An extensive Golgi apparatus (G) occurs near the apical part of the cell; mitochondria (M) and lysosomes (L) remain scattered throughout the cytoplasm.

The thyroid cytoplasm, in addition to these usual features contains a larger than usual variety of granules of different sizes and densities. The apical surface of the cells have

small thin projections or microvilli (MV) which are increased in number if the gland is stimulated by TSH injection (Fig. 7.18).
Some of the granules may also be present within the microvilli. Release of entire secretion-laden cells (holocrine mode of release) is sometimes found following EM observation.

Biochemistry of Thyroid Hormone:
Thyroid follicular cells synthesise and secrete two iodinated amino acids as hormones, viz., thyroxine or T_4 or 3, 5, 3′, 5′-tetraiodothyronine and T_3 or 3, 5, 3′- triiodothyronine. Instead of these hormones, the C cells of mammalian thyroid secrete a polypeptide hormone calcitonin.

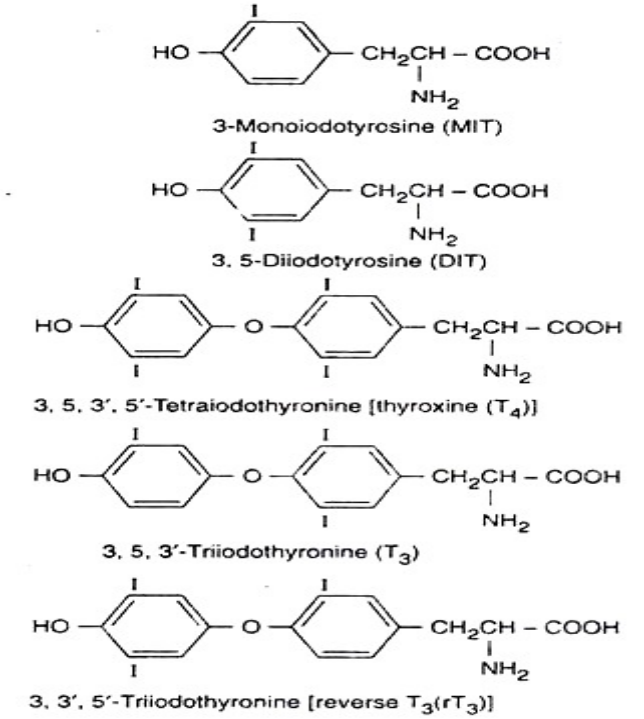


Fig. 7.19 : Structure of thyroid hormones and related compounds

Synthesis of Thyroid Hormone:
The overall synthesis process of thyroid hormones (T_3 and T_4) involves the following major steps:
1. Iodide trap:
Thyroid follicular cells actively collect inorganic iodides (I^-) from the circulation against steep electrochemical gradients with the help of carrier protein, sodium iodide symporter located in the basal plasma membrane in association with Na^+K^+ ATPase. The later provides energy for functioning of iodide symporter which collects about ~33% of the body I^- in the thyroid and concentrate that I^- by 25-50 times the serum I^- concentration.
Such iodide uptake into the thyroid follicle is an example of secondary active transport, sometimes improperly referred to as “iodide pump”. TSH stimulates the iodide transport and this transport is inhibited by some anions, notably perchlorate and thiocyanate.
2. Oxidation of iodide:
A tetrameric heme enzyme, thyroperoxidase of the apical plasma membrane of follicle cells then binds I^-. The enzyme bound I^- is then oxidised to active iodine by H_2O_2, generated by

an NADPH dependent enzyme system in presence of Ca^{2+}. The active iodine may be iodinium ion (I^+), hypo-iodate (IO^-) or free iodine radical (I).

3. Iodination of tyrosyl in thyroglobulin:

The thyroperoxidase enzyme then incorporates active iodine into C^3 and C^5 of some tyrosyl groups of thyroglobulin (TG) and form monoiodotyrosine (MIT) and diiodotyrosine (DIT) residues, respectively.

4. Coupling of iodotyrosines in thyroglobulin:

The coupling of iodo-tyrosyl residues in thyroglobulin is again catalysed by thyroperoxidase. It is probably an intra-molecular process that involves:

(i) Oxidation of iodo-tyrosine to an active form by thyroperoxidase,

(ii) Coupling of activated iodo-tyrosyl residues within the same thyroglobulin molecule to form a quinol ether intermediate and

(iii) Spliting of the quinol ether to form iodothyronine with conversion of the alanine side chain of the donor iodo-tyrosine to dehydroalanine (Fig. 7.20). Dimeric structure of thyroglobulin actually helps this process. Within it, two molecules of DIT may couple to form T_4, and an MIT and a DIT molecule may couple to form T_3.

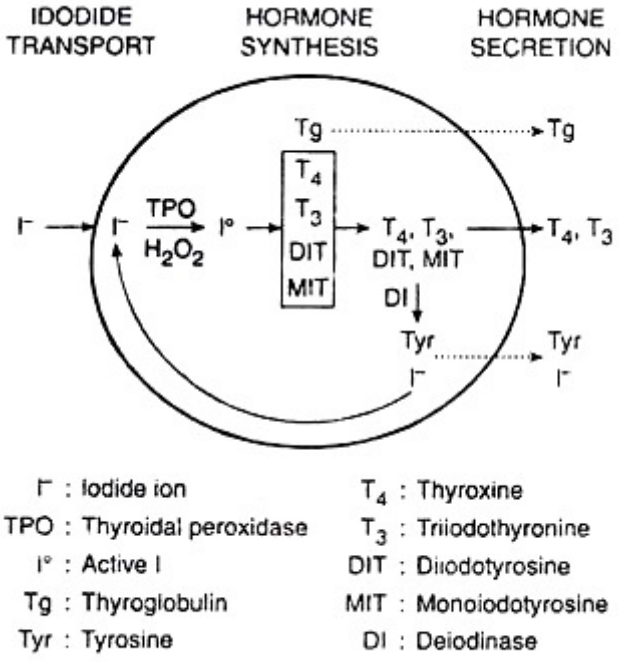


Fig. 7.20 : Thyroid hormone synthesis in a thyroid follicle

Thyroglobulin:

The main intra-thyroidal storage form of thyroid hormone is thyroglobulin which is a large glycoprotein molecule containing 5,496 amino acids, with a molecular weight of about 660,000. In thyroglobulin containing 0.5% iodine, there would be 5 molecules of MIT, 4.5 molecules of DIT, 2.5 molecules of thyroxine (T_4) and 0.7 molecules of triiodothyronine (T_3).

There are four tyrosyl sites for hormonogenesis on the thyroglobulin molecule; one site is located at the amino-terminal end of the molecule, and the other three are located in a sequence of 600 amino acids at the carboxyl terminal end.

In the Golgi apparatus of follicle cells, the thyroglobulin dimers are incorporated into exocytotic vesicles that fuse with the basement membrane and release the thyroglobulin into the follicular lumen. There, at the apical colloid border, thyroglobulin is iodinated and are stored in colloid (Fig. 7.21).

Storage, Release and Transport:

The thyroid hormones (T_4 and T_3) formed within the thyroglobulin molecules at the apical colloid border remain stored in the colloid. During release, at the cell-colloid interface, colloid is engulfed into colloid vesicles by the process of macro-pinocytosis or micro-pinocytosis and is absorbed into the thyroid cell.

The cellular lysosome containing proteases, endo-peptidases, glycoside hydrolyase, then fuse with colloid vesicles. In the fused vesicles, hydrolysis of thyroglobulin occurs, releasing T_4, T_3, DIT MIT, peptide fragments and amino acids.

T_3 and T_4 pass into blood across the basal cell membrane. DIT and MIT are de-iodinated by NADPH dependent microsomal deiodinase and the released iodine is recycled into tyrosyl iodination. Thyroid hormone secretion is stimulated by TSH. Thyroglobulin proteolysis is inhibited by excess iodide and by lithium.

In blood, little amount of T_4 and T_3 are carried as free T_4 and T_3, while the maximum amount of both hormones are carried as bound form with thyroid binding globulin (TBG). Some amount of T_4 also remains bound to thyroxine binding pre-albumin (TBPA) and serum albumin.

Secretion of Thyroid Hormone:

The secretion of thyroid hormone is regulated by thyroid stimulating hormone (TSH) from the pituitary gland that in turn is regulated by thyrotropin releasing hormone (TRH) of hypothalamus. Thyroid hormones feed back at the pituitary and hypothalamic levels to inhibit TSH secretion (Fig. 7.22).

TSH secretion is inhibited by stress in a number of species. Recent experimental evidences suggest that acute neuroendocrine reflex exists for TSH as well as TRH release.

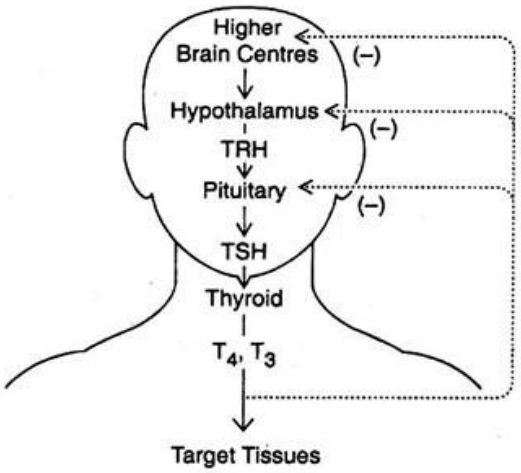


Fig. 7.22 : Control of thyroid hormone secretion

High level of plasma T_4 exerts .negative feedback action on pituitary TSH production. T_4 also controls TRH synthesis by regulating gene expression of the TRH pro-hormone in the thyrotrophic area of the hypothalamus.

The functions of thyroxine (T_4) and tri-iodothyronine (T_3) are as follows.

(a) They regulate the metabolic rate of the body and thus maintain basal metabolic rate (BMR).

(b) They stimulate protein synthesis and, therefore, promote growth of the body tissues.

(c) They regulate the development of mental faculties.

(d) As they increase heat production, thus they maintain body temperature.

(e) They help in metamorphosis of tadpole into adult frog. If thyroid gland of the tadpole (larva) is removed, the larva fails to change into an adult.

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(f) They increase action of neurotransmitters like adrenaline and noradrenaline.

(ii) Thyrocalcitonin (TCT):

It is secreted when calcium level is high in the blood. It then lowers the calcium level by suppressing release of calcium ions from the bones. Thus calciton has an action opposite to that of the parathyroid hormone on calcium metabolism. Calcitonin is a peptide which contains 32 amino acids.

Actions of the Thyroid Gland:

1. Calorigenic Action:

It increases the oxygen consumption in almost all the tissues of the body except adult brain, gonads, lymphoid tissue. Increased metabolic rate increases the heat production in the body. The unit to measure heat energy is calorie .

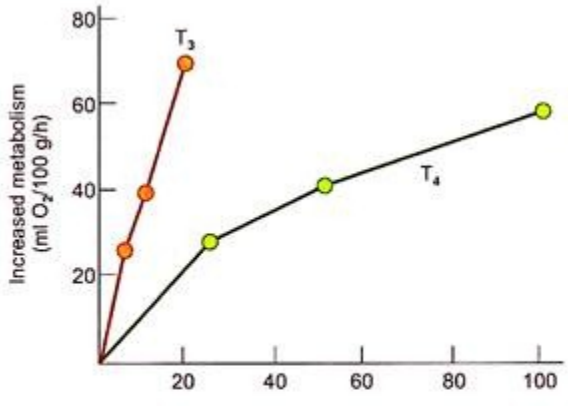

Fig. 6.34: Graph comparing the metabolic rate action of triiodothyronine and thryoxine

In normal adult male, the basal metabolic rate (BMR) is about 40 Kcal/sq m BSA/Hr ±15%.

In hyperthyroidism, it can be as much as + 60 to 100%.

In hypothyroidism, it can fall by -40 to -60%. Hence estimation of BMR forms one of the thyroid function tests.

2. Nervous System:

For the growth of the nervous system in the first three years of even during the postnatal period, the action of the thyroxine on brain is essential. The growth of the brain occurs only during this phase after birth.

The growth of the brain includes:

i. Formation of the synapses.
ii. Growth of axon and dendrites and arborization of these processes.
iii. Increase in the number of glial cells.
iv. Myelination of nerve fibers.

In cretin (when thyroxine is deficient from childhood):

1. The brain remains smaller than normal.
2 Number and size of the nerve cells reduced.
3. Arborization of the dendrites is less profuse.
4. Net effect in the child will be marked decrease in IQ.
5. Myelination will be defective.
6. CSF protein content is increased.

Because of these reasons, the action of hormone on the brain is very crucial in the first two to three years of postnatal life. If there is deficiency of the hormone during this period, it can lead to mental retardation. This is associated with delayed milestones during the growth of the infant.

3. On Growth and Development:

It affects the growth and development of other parts of body as well.

The general growth is influenced by the growth hormone of the anterior pituitary gland but thyroxine potentiates the action of the growth hormone and hence the summated effect of these hormones is very much for the linear growth of the body and the growth of other organs.

It also affects the growth of reproductive organs and lack of the hormone may lead to sterility, infantile sex organs in adults and in adult females menstrual problems.

4. Metabolic Actions:

Apart from its action on the oxygen consumption by the tissues, it also influences the metabolism of carbohydrate, fats and proteins.

a. Carbohydrate metabolism:

It acts as a hyperglycemic agent. It increases the blood glucose level by increasing gluconeogenesis and glycogenolysis in the liver. It also enhances the peripheral utilization of glucose.

b. Protein metabolism:

It has both anabolic and catabolic effects. Excess of hormonal level in circulation, catabolism predominates and leads to loss of body weight and muscular weakness. In hypothyroidism, the anabolism suffers and again leads to muscular weakness.

c. Fat metabolism:

It increases lipolysis. Cholesterol synthesis and degradation are both affected by this hormone. The degradation is more dependent on thyroxine than synthesis and hence in hypothyroidism the serum cholesterol level is increased.

d. On mucopolysaccharides:

The excretion of substances, like hyaluronic acid and chondroitin sulphate, is affected by the action of this hormone. Hence, in hypothyroidism, they get deposited in the subcutaneous region giving rise to myxedema.

5. On Systems:

The hormone affects functioning of the different systems of the body.

Some of the systems on which the actions are more pronounced are:

a. CVS:

It increases both the heart rate and force of contraction. It increases the number of beta receptors and affinity of the beta receptors for catecholamine. Hence, the resting heart rate will be more in hyperthyroid subjects. The increase in cardiac output leads to increase of systolic blood pressure (systolic hypertension).

It also increases the blood flow to the skin in order to facilitate the heat loss from the body. It is essential as the hormone increases basal metabolic rate and hence increased heat production. As a result of this cutaneous vasodilatation, the peripheral resistance decreases which will result in fall in diastolic BP.

b. GIT:

Hormone is required for normal secretory aspects and movements of gastrointestinal tract. In hyperthyroidism, the patients suffer from diarrhea and in hypothyroidism the patient may develop constipation.

c. Nervous system:

In adult, it affects the velocity of impulse conduction in the nerve fibers. In hyposecretion state, it results in increased reflex time and vice versa in hyperthyroidism.

Regulation of Thyroid Hormone:

It is brought about by the negative feedback mechanism. There is involvement of hypothalamo-pituitary-thyroid axis .

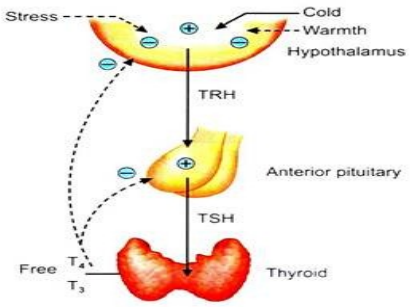

Fig. 6.35: Regulation of secretion of thyroxine (by negative feedback mechanism)

Increase in free form of hormone in circulation acts on hypothalamus and anterior pituitary gland. Acting on hypothalamus, it decreases the secretion of thyrotropin-releasing hormone (TRF/TRH) and this acts on anterior pituitary decreases secretion of TSH.
Net effect will be decreased TSH from anterior pituitary gland. This decreases the secretion of thyroid hormones from the gland.
Many of the other chemical influences acting on TRH-TSH-Thyroxine (hypothalamo-pituitary-thyroid axis) secretions have been shown in Table 6.7.

Table 6.7: Thyroid hormone feedback

Hypothalamus	*Stimulatory*	*Inhibitory*
Decreased TRH	Alpha adrenergic agonists	Alpha adrenergic blockers
		Tumors
Anterior pituitary	*TRH*	*Somatostatin*
Decreased TSH	Estrogen	Dopamine
		Glucocorticoids
		Chronic illness
Thyroid gland	*TSH*	*TSH receptor blocking antibody*
Decreased T_3 and T_4	TSH receptor stimulating antibody	Iodine, lithium

Alteration in the temperature can directly act on the hypothalamus to alter the secretion of the hormone.

Thyroid Function Tests:

1. Determination of BMR.
2. Blood cholesterol level.
3. Estimation of protein bound iron (PBI)
4. ^{131}I uptake studies (Figs 6.36, 6.37)
5. Estimation of free T_3, T_4 and TSH in plasma.

Thyroid Disorders:

(A) Hyperthyroidism (Hyper secretion of thyroid hormone).

Exophthalmic goitre or Graves' disease or Basedow's disease or Parry's disease:

It is a thyroid enlargement (goitre) in which the thyroid secretes excessive amount of thyroid hormone. It is characterised by exophthalmia (protrusion of eye balls because of fluid accumulation behind them), loss of weight, slightly rise in the body temperature, excitability, rapid heartbeat, nervousness and restlessness.

(B) Hypothyroidism (Hypo secretion of thyroid hormone):

(a) Cretinism:

This disorder is caused by deficiency of thyroid hormone in infants. A cretin has slow body growth and mental development of reduced metabolic rate.
Other symptoms of this disorder are slow heart beat, lower blood pressure, decrease in temperature, stunted growth, pot-belly, pigeon chest and protruding tongue and retarded sexual development. This disease can be treated by an early administration of thyroid hormones.

Fig. 22.5. Cretinism.

(b) Myxoedema or Gull's disease:

It is caused by deficiency of thyroid hormone in adults. This disease is characterized by puffy appearance due to accumulation of fat in the subcutaneous tissue because of low metabolic rate. The patient lacks alertness, intelligence and initiative. He also suffers from slow heart beat, low body temperature and regarded sexual development. This disease can be treated by administration of thyroid hormones.

Fig. 22.6. Myxoedema.

(c) Simple Goitre:

It is caused by deficiency of iodine in diet because iodine is needed for the synthesis of thyroid hormone. It causes thyroid enlargement. It may lead to cretinism or myxoedema. This disease is common in hilly areas. Addition of iodine to the table salt prevents this disease.

Fig. 22.7. Simple goitre.

(d) Hashimoto's disease:

In this disease all the aspects of thyroid function are impaired. It is an autoimmune disease in which the thyroid gland is destroyed by autoimmunity.