Chapter 67

Thyroid Gland

INTRODUCTION

Thyroid is an endocrine gland situated at the root of the neck on either side of the trachea. It has two **lobes,** which are connected in the middle by an **isthmus** (Fig. 67.1). It weighs about 20 to 40 g in adults. Thyroid is larger in females than in males. The structure and the function of the thyroid gland change in different stages of the sexual cycle in females. Its function increases slightly during pregnancy and lactation and decreases during menopause.

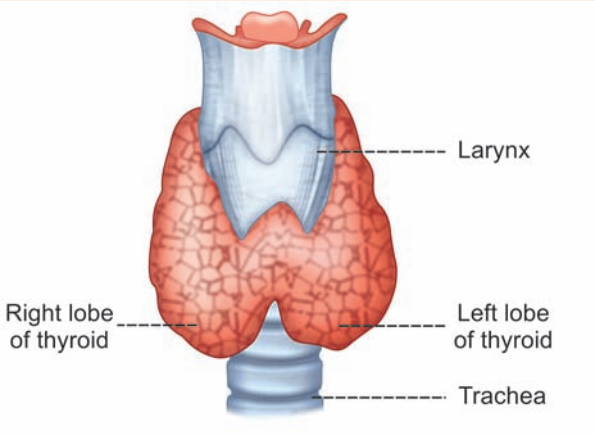

FIGURE 67.1: Thyroid gland

HISTOLOGY OF THYROID GLAND

Thyroid gland is composed of large number of closed **follicles.** These follicles are lined with cuboidal epithelial cells, which are called the **follicular cells.** Follicular cavity is filled with a colloidal substance known as **thyroglobulin,** which is secreted by the follicular cells. Follicular cells also secrete tetraiodothyronine (T_4 or thyroxine) and tri-iodothyronine (T_3). In between the follicles, the **parafollicular cells** are present (Fig. 67.2). These cells secrete calcitonin.

HORMONES OF THYROID GLAND

Thyroid gland secretes three hormones:

1. Tetraiodothyronine or T_4 (thyroxine)
2. Tri-iodothyronine or T_3
3. Calcitonin.

T_4 is otherwise known as **thyroxine** and it forms about 90% of the total secretion, whereas T_3 is only 9% to 10%. Details of calcitonin are given in next chapter.

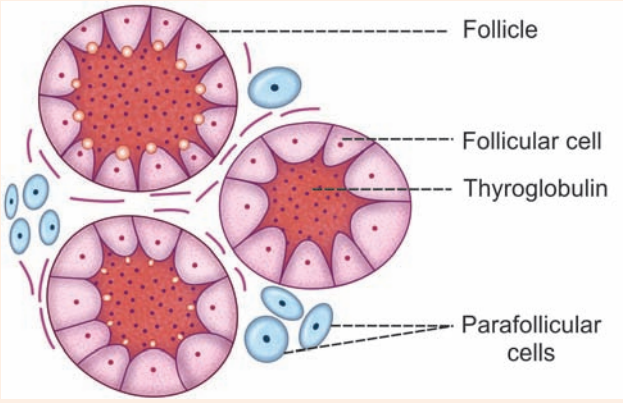

FIGURE 67.2: Histology of thyroid gland

Chemistry

Both T_4 and T_3 are iodine-containing derivatives of amino acid **tyrosine.**

Potency and Duration of Action

The potency of T_3 is four times more than that of T_4. T_4 acts for longer period than T_3. Duration of T_4 action is four times more than T_3 action. This is because of the difference in the affinity of these hormones to plasma proteins. T_3 has less affinity for plasma proteins and combines loosely with them, so that it is released quickly. T_4 has more affinity and strongly binds with plasma proteins, so that it is released slowly. Therefore, T_3 acts on the target cells immediately and T_4 acts slowly.

Half-life

Thyroid hormones have long half-life. T_4 has a long half-life of 7 days. Half-life of T_3 is varying between 10 and 24 hours.

Rate of Secretion

Thyroxine	=	80	to	90	µg/day
Tri-iodothyronine	=	4	to	5	µg/day
Reverse T_3	=	1	to	2	µg/day.

Plasma Level

Total T_3	=	0.12 µg/dL
Total T_4	=	8 µg/dL.

Metabolism of Thyroid Hormones

Degradation of thyroid hormones occurs in muscles, liver and kidney.

■ SYNTHESIS OF THYROID HORMONES

Synthesis of thyroid hormones takes place in thyroglobulin, present in follicular cavity. Iodine and tyrosine are essential for the formation of thyroid hormones. Iodine is consumed through diet. It is converted into iodide and absorbed from GI tract. Tyrosine is also consumed through diet and is absorbed from the GI tract.

For the synthesis of normal quantities of thyroid hormones, approximately 1 mg of iodine is required per week or about 50 mg per year. To prevent iodine deficiency, common table salt is iodized with one part of sodium iodide to every 100,000 parts of sodium chloride.

■ STAGES OF SYNTHESIS OF THYROID HORMONES

Synthesis of thyroid hormones occurs in five stages:

1. Thyroglobulin synthesis
2. Iodide trapping
3. Oxidation of iodide
4. Transport of iodine into follicular cavity
5. Iodination of tyrosine
6. Coupling reactions.

1. *Thyroglobulin Synthesis*

Endoplasmic reticulum and Golgi apparatus in the follicular cells of thyroid gland synthesize and secrete thyroglobulin continuously. Thyroglobulin molecule is a large glycoprotein containing 140 molecules of amino acid tyrosine. After synthesis, thyroglobulin is stored in the follicle.

2. *Iodide Trapping*

Iodide is actively transported from blood into follicular cell, against electrochemical gradient. This process is called iodide trapping.

Iodide is transported into the follicular cell along with sodium by sodium-iodide symport pump, which is also called iodide pump. Normally, iodide is 30 times more concentrated in the thyroid gland than in the blood. However, during hyperactivity of the thyroid gland, the concentration of iodide increases 200 times more.

3. *Oxidation of Iodide*

Iodide must be oxidized to elementary iodine, because only iodine is capable of combining with tyrosine to form thyroid hormones. The oxidation of iodide into iodine occurs inside the follicular cells in the presence of thyroid peroxidase. Absence or inactivity of this enzyme stops the synthesis of thyroid hormones.

4. *Transport of Iodine into Follicular Cavity*

From the follicular cells, iodine is transported into the follicular cavity by an **iodide-chloride pump** called **pendrin.**

5. *Iodination of Tyrosine*

Combination of iodine with tyrosine is known as iodination. It takes place in thyroglobulin. First, iodine is transported from follicular cells into the follicular cavity, where it binds with thyroglobulin. This process is called **organification** of thyroglobulin. Then, iodine (I) combines with tyrosine, which is already present in thyroglobulin (Fig. 67.3). Iodination process is accelerated by the enzyme iodinase, which is secreted by follicular cells.

Iodination of tyrosine occurs in several stages. Tyrosine is iodized first into monoiodotyrosine (MIT) and later into di-iodotyrosine (DIT). MIT and DIT are called the iodotyrosine residues.

6. *Coupling Reactions*

Iodotyrosine residues get coupled with one another. The coupling occurs in different configurations, to give rise to different thyroid hormones.

Coupling reactions are:

i. One molecule of DIT and one molecule of MIT combine to form tri-iodothyronine (T_3)

ii. Sometimes one molecule of MIT and one molecule of DIT combine to produce another form of T_3 called reverse T_3 or rT_3. Reverse T_3 is only 1% of thyroid output

iii. Two molecules of DIT combine to form tetraiodothyronine (T_4), which is thyroxine.

Tyrosine + I = Monoiodotyrosine (MIT)
MIT + I = Di-iodotyrosine (DIT)
DIT + MIT = Tri-iodothyronine (T_3)
MIT + DIT = Reverse T_3
DIT + DIT = Tetraiodothyronine or Thyroxine (T_4)

■ STORAGE OF THYROID HORMONES

After synthesis, the thyroid hormones remain in the form of vesicles within thyroglobulin and are stored for long period. Each thyroglobulin molecule contains 5 or 6 molecules of thyroxine. There is also an average of 1 tri-iodothyronine molecule for every 10 molecules of thyroxine.

In combination with thyroglobulin, the thyroid hormones can be stored for **several months.** Thyroid gland is unique in this, as it is the only endocrine gland that can store its hormones for a long period of about 4 months. So, when the synthesis of thyroid hormone stops, the signs and symptoms of deficiency do not appear for about 4 months.

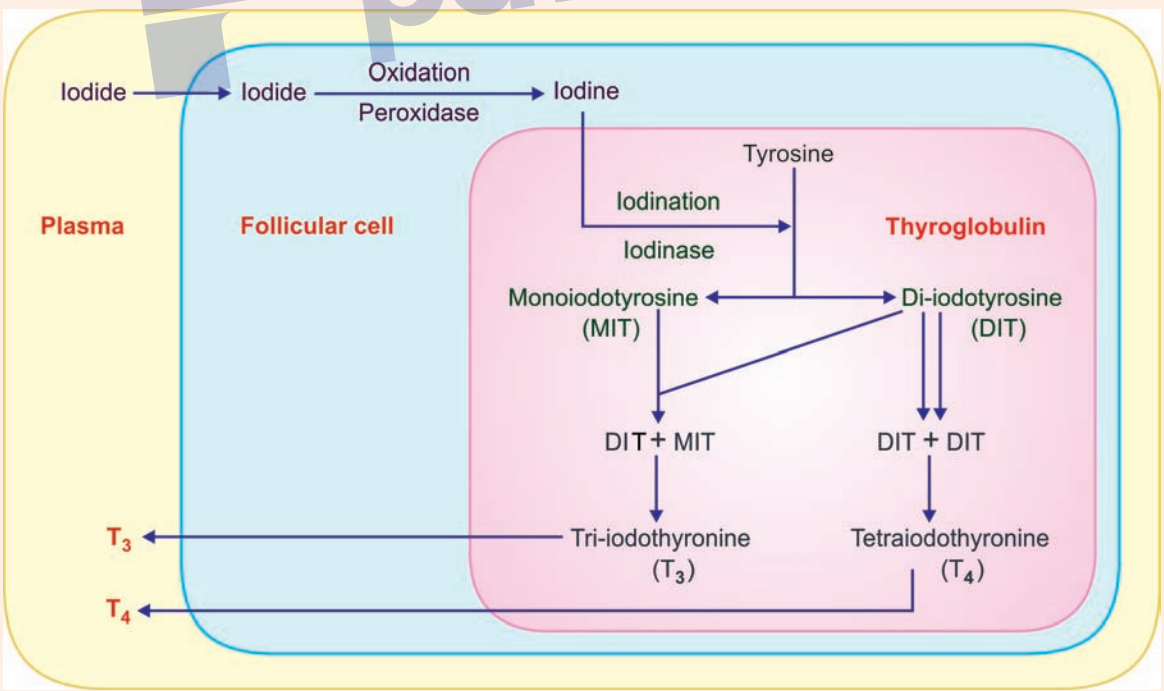

FIGURE 67.3: Synthesis of thyroid hormones

RELEASE OF THYROID HORMONES FROM THE THYROID GLAND

Thyroglobulin itself is not released into the bloodstream. On the other hand, the hormones are first cleaved from thyroglobulin and released into the blood.

Sequence of Events

1. Follicular cell sends foot-like extensions called **pseudopods,** which close around the thyroglobulin-hormone complex. This process is mediated by a receptor-like substance called **megalin,** which is present in the membrane of follicular cell
2. Pseudopods convert thyroglobulin-hormone complex into small **pinocytic vesicles**
3. Then, lysosomes of the cell fuse with these vesicles
4. Digestive enzymes such as proteinases present in lysosomes digest (proteolysis) the thyroglobulin and release the hormones
5. Now, the hormones diffuse through base of the follicular cell and enter the capillaries.

Only T_3 and T_4 are released into the blood. In the peripheral tissues, T_4 is converted into T_3. A small amount of inactive reverse T_3 is also formed. It is the biologically inactive form of T_3 and it is produced when T_4 is converted into T_3.

MIT and DIT are not released into blood. These iodotyrosine residues are deiodinated by an enzyme called iodotyrosine deiodinase, resulting in the release of iodine. The iodine is reutilized by the follicular cells for further synthesis of thyroid hormones. During congenital absence of iodotyrosine deiodinase, MIT and DIT are excreted in urine and the symptoms of iodine deficiency develop.

TRANSPORT OF THYROID HORMONES IN THE BLOOD

Thyroid hormones are transported in the blood by three types of proteins:

1. Thyroxine-binding globulin (TBG)
2. Thyroxine-binding prealbumin (TBPA)
3. Albumin.

1. *Thyroxine-binding Globulin (TBG)*

Thyroxine-binding globulin is a glycoprotein and its concentration in the blood is 1 to 1.5 mg/dL. It has a great affinity for thyroxine and about one third of the hormone combines strongly with this protein.

2. *Thyroxine-binding Prealbumin (TBPA)*

TBPA transports one fourth of the thyroid hormones. It is also called transthyretin (TTR).

3. *Albumin*

Albumin transports about one tenth of the thyroid hormones.

FUNCTIONS OF THYROID HORMONES

Thyroid hormones have two major effects on the body:

I. To increase basal metabolic rate
II. To stimulate growth in children.

The actions of thyroid hormones are:

1. ACTION ON BASAL METABOLIC RATE (BMR)

Thyroxine increases the metabolic activities in most of the body tissues, except brain, retina, spleen, testes and lungs. It increases BMR by increasing the oxygen consumption of the tissues. The action that increases the BMR is called calorigenic action.

In hyperthyroidism, BMR increases by about 60% to 100% above the normal level and in hypothyroidism it falls by 20% to 40% below the normal level.

2. ACTION ON PROTEIN METABOLISM

Thyroid hormone increases the synthesis of proteins in the cells. The protein synthesis is accelerated by the following ways:

i. *By Increasing the Translation of RNA*

Thyroid hormone increases the translation of RNA in the cells. Because of this, the ribosomes are activated and more proteins are synthesized.

ii. *By Increasing the Transcription of DNA to RNA*

Thyroid hormone also stimulates the transcription of DNA to RNA. This in turn accelerates the synthesis of proteins in the cells (see above).

iii. *By Increasing the Activity of Mitochondria*

In addition to acting at nucleus, thyroid hormone acts at mitochondrial level also. It increases the number and the activity of mitochondria in most of the cells of the body. Thyroid hormone accelerates the synthesis of RNA and other substances from mitochondria, by activating series of enzymes. In turn, the mitochondria increase the production of ATP, which is utilized for the energy required for cellular activities.

iv. *By Increasing the Activity of Cellular Enzymes*

Thyroid hormones also increase the activity of at least 100 or more intracellular enzymes such as alpha-glycerophosphate dehydrogenase and oxidative enzymes. These enzymes accelerate the metabolism of proteins and the carbohydrates.

Though thyroxine increases synthesis of protein, it also causes catabolism of proteins.

■ 3. ACTION ON CARBOHYDRATE METABOLISM

Thyroxine stimulates almost all processes involved in the metabolism of carbohydrate.

Thyroxine:

i. Increases the absorption of glucose from GI tract
ii. Enhances the glucose uptake by the cells, by accelerating the transport of glucose through the cell membrane
iii. Increases the breakdown of glycogen into glucose
iv. Accelerates gluconeogenesis.

■ 4. ACTION ON FAT METABOLISM

Thyroxine decreases the fat storage by mobilizing it from adipose tissues and fat depots. The mobilized fat is converted into free fatty acid and transported by blood. Thus, thyroxine increases the free fatty acid level in blood.

■ 5. ACTION ON PLASMA AND LIVER FATS

Even though there is an increase in the blood level of free fatty acids, thyroxine specifically decreases the cholesterol, phospholipids and triglyceride levels in plasma. So, in hyposecretion of thyroxine, the cholesterol level in plasma increases, resulting in **atherosclerosis.**

Thyroxine also increases deposition of fats in the liver, leading to **fatty liver.** Thyroxine decreases plasma cholesterol level by increasing its excretion from liver cells into bile. Cholesterol enters the intestine through bile and then it is excreted through the feces.

■ 6. ACTION ON VITAMIN METABOLISM

Thyroxine increases the formation of many enzymes. Since vitamins form essential parts of the enzymes, it is believed that the vitamins may be utilized during the formation of the enzymes. Hence, **vitamin deficiency** is possible during hypersecretion of thyroxine.

■ 7. ACTION ON BODY TEMPERATURE

Thyroid hormone increases the heat production in the body, by accelerating various cellular metabolic processes and increasing BMR. It is called **thyroid hormone-induced thermogenesis.** During hypersecretion of thyroxine, the body temperature increases greatly resulting in excess sweating.

■ 8. ACTION ON GROWTH

Thyroid hormones have general and specific effects on growth. Increase in thyroxine secretion accelerates the growth of the body, especially in growing children. Lack of thyroxine arrests the growth. At the same time, thyroxine causes early closure of epiphysis. So, the height of the individual may be slightly less in hypothyroidism.

Thyroxine is more important to promote growth and development of brain during fetal life and first few years of postnatal life. Deficiency of thyroid hormones during this period leads to **mental retardation.**

■ 9. ACTION ON BODY WEIGHT

Thyroxine is essential for maintaining the body weight. Increase in thyroxine secretion decreases the body weight and fat storage. Decrease in thyroxine secretion increases the body weight because of fat deposition.

■ 10. ACTION ON BLOOD

Thyroxine accelerates erythropoietic activity and increases blood volume. It is one of the important general factors necessary for erythropoiesis. Polycythemia is common in hyperthyroidism.

■ 11. ACTION ON CARDIOVASCULAR SYSTEM

Thyroxine increases the overall activity of cardiovascular system.

i. *On Heart Rate*

Thyroxine acts directly on heart and increases the heart rate. It is an important **clinical investigation** for diagnosis of hypothyroidism and hyperthyroidism.

ii. *On the Force of Contraction of the Heart*

Due to its effect on enzymatic activity, thyroxine generally increases the force of contraction of the heart. But in hyperthyroidism or in thyrotoxicosis, the heart may become weak due to excess activity and protein catabolism. So, the patient may die of **cardiac decompensation.**

Cardiac decompensation refers to failure of the heart to maintain adequate circulation associated with **dyspnea, venous engorgement** (veins overfilled with blood) and edema.

iii. *On Blood Vessels*

Thyroxine causes vasodilatation by increasing the metabolic activities. During increased metabolic activities, a large quantity of metabolites is produced. These metabolites cause vasodilatation.

iv. *On Arterial Blood Pressure*

Because of increase in rate and force of contraction of the heart, increase in blood volume and blood flow by the influence of thyroxine, cardiac output increases. This in turn, increases the blood pressure. But, generally, the mean pressure is not altered. Systolic pressure increases and the diastolic pressure decreases. So, only the pulse pressure increases (Chapter 103).

■ 12. ACTION ON RESPIRATION

Thyroxine increases the rate and force of respiration indirectly. The increased metabolic rate (caused by thyroxine) increases the demand for oxygen and formation of excess carbon dioxide. These two factors stimulate the respiratory centers to increase the rate and force of respiration (Chapter 126).

■ 13. ACTION ON GASTROINTESTINAL TRACT

Generally, thyroxine increases the appetite and food intake. It also increases the secretions and movements of GI tract. So, hypersecretion of thyroxine causes diarrhea and the lack of thyroxine causes constipation.

■ 14. ACTION ON CENTRAL NERVOUS SYSTEM

Thyroxine is very essential for the development and maintenance of normal functioning of central nervous system (CNS).

i. *On Development of Central Nervous System*

Thyroxine is very important to promote growth and development of the brain during fetal life and during the first few years of postnatal life. Thyroid deficiency in infants results in abnormal development of synapses, defective myelination and **mental retardation.**

ii. *On the Normal Function of Central Nervous System*

Thyroxine is a stimulating factor for the central nervous system, particularly the brain. So, the normal functioning of the brain needs the presence of thyroxine. Thyroxine also increases the blood flow to brain.

Thus, during the hypersecretion of thyroxine, there is excess stimulation of the CNS. So, the person is likely to have extreme nervousness and may develop psychoneurotic problems such as **anxiety complexes, excess worries** or **paranoid thoughts** (the persons think without justification that other people [illegible] or conspiring against them or harassing them).

Hyposecretion of thyroxine leads to **lethargy** and **somnolence** (excess sleep).

■ 15. ACTION ON SKELETAL MUSCLE

Thyroxine is essential for the normal activity of skeletal muscles. Slight increase in thyroxine level makes the muscles to work with more vigor. But, hypersecretion of thyroxine causes weakness of the muscles due to catabolism of proteins. This condition is called **thyrotoxic myopathy.** The muscles relax very slowly after the contraction. Hyperthyroidism also causes fine muscular **tremor.** Tremor occurs at the frequency of 10 to 15 times per second. It is due to the thyroxine-induced excess neuronal activity, which controls the muscle. The lack of thyroxine makes the muscles more sluggish.

■ 16. ACTION ON SLEEP

Normal thyroxine level is necessary to maintain normal sleep pattern. Hypersecretion of thyroxine causes excessive stimulation of the muscles and central nervous system. So, the person feels tired, exhausted and feels like sleeping. But, the person cannot sleep because of the stimulatory effect of thyroxine on neurons. On the other hand, hyposecretion of thyroxine causes **somnolence.**

■ 17. ACTION ON SEXUAL FUNCTION

Normal thyroxine level is essential for normal sexual function. In men, hypothyroidism leads to complete loss of libido (sexual drive) and hyperthyroidism leads to **impotence.**

In women, hypothyroidism causes menorrhagia and **polymenorrhea** (Chapter 80). In some women, it causes irregular menstruation and occasionally **amenorrhea.** Hyperthyroidism in women leads to **oligomenorrhea** and sometimes **amenorrhea** (Chapter 80).

■ 18. ACTION ON OTHER ENDOCRINE GLANDS

Because of its metabolic effects, thyroxine increases the demand for secretion by other endocrine glands.

■ MODE OF ACTION OF THYROID HORMONES

In the target cells (particularly cells of liver, muscle and kidney), most of the T_4 is deiodinated to form T_3. So, the true intracellular hormone is T_3, rather than T_4. Moreover, T_3 is found freely in the plasma and T_4 is usually bound

with plasma proteins. So, at the site of action, T_3 acts more quickly than T_4. T_3 also has got high binding affinity for thyroid hormone receptor.

Thyroid hormones act by activating the genes and increasing the **genetic transcription** (Chapter 65). In addition, the thyroid hormone also acts at mitochondrial level by stimulating the synthesis of proteins and RNA.

Sequence of Events

1. Thyroid hormones enter the nucleus of cell and bind with thyroid hormone receptors (TR), which are either attached to DNA genetic strands or in close proximity to them.
2. TR is always bound to another receptor called **retinoid X receptor** (RXR). Exact role of RXR is not clear. Thyroid hormones bind with receptors and form the hormone-receptor complex
3. This complex initiates the transcription process by activating the enzymes such as RNA polymerase and phosphoprotein kinases
4. It also stimulates the synthesis of nuclear proteins. Thus, a large number of mRNA is formed, which activate the ribosomes to synthesize the new proteins
5. New proteins are involved in many activities including the enzymatic actions.

■ REGULATION OF SECRETION OF THYROID HORMONES

Secretion of thyroid hormones is controlled by anterior pituitary and hypothalamus through feedback mechanism. Many factors are involved in the regulation of thyroid secretion.

■ ROLE OF PITUITARY GLAND

Thyroid-stimulating Hormone

Thyroid-stimulating hormone (TSH) secreted by anterior pituitary is the major factor regulating the synthesis and release of thyroid hormones. It is also necessary for the growth and the secretory activity of the thyroid gland. Thus, TSH influences every stage of formation and release of thyroid hormones.

Chemistry

Thyroid-stimulating hormone is a peptide hormone with one α-chain and one β-chain.

Half-life and Plasma Level

Half-life of TSH is about 60 minutes. The normal plasma level of TSH is approximately 2 U/mL.

Actions of Thyroid-stimulating Hormone

Thyroid-stimulating hormone increases:

1. The number of follicular cells of thyroid
2. The conversion of cuboidal cells in thyroid gland into columnar cells and thereby it causes the development of thyroid follicles
3. Size and secretory activity of follicular cells
4. Iodide pump and iodide trapping in follicular cells
5. Thyroglobulin secretion into follicles
6. Iodination of tyrosine and coupling to form the hormones
7. Proteolysis of the thyroglobulin, by which release of hormone is enhanced and colloidal substance is decreased.

Immediate effect of TSH is proteolysis of the thyroglobulin, by which thyroxine is released within 30 minutes. Effect of TSH on other stages in thyroxine synthesis takes place after some hours, days or weeks.

Mode of Action of TSH

TSH acts through cyclic AMP mechanism.

■ ROLE OF HYPOTHALAMUS

Hypothalamus regulates thyroid secretion by controlling TSH secretion through thyrotropic-releasing hormone (TRH). From hypothalamus, TRH is transported through the hypothalamo-hypophyseal portal vessels to the anterior pituitary. After reaching the pituitary gland, the TRH causes the release of TSH.

■ FEEDBACK CONTROL

Thyroid hormones regulate their own secretion through negative feedback control, by inhibiting the release of TRH from hypothalamus and TSH from anterior pituitary (Fig. 67.4).

■ ROLE OF IODIDE

Iodide is an important factor regulating the synthesis of thyroid hormones. When the dietary level of iodine is moderate, the blood level of thyroid hormones is normal. However, when iodine intake is high, the enzymes necessary for synthesis of thyroid hormones are inhibited by iodide itself, resulting in suppression of hormone synthesis. This effect of iodide is called **Wolff-Chaikoff effect.**

■ ROLE OF OTHER FACTORS

Many other factors are involved in the regulation of thyroid secretion in accordance to the needs of the body.

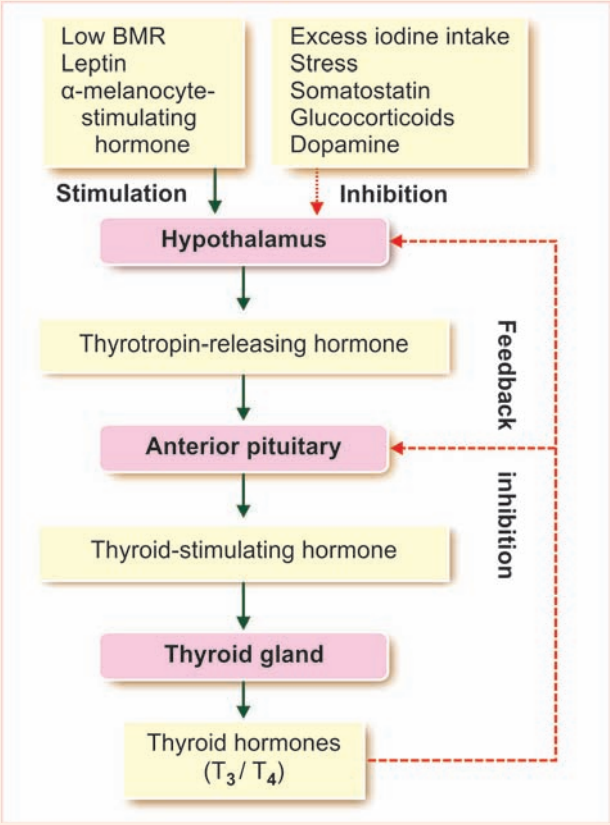

FIGURE 67.4: Regulation of secretion of thyroid hormones

Factors increasing the secretion of thyroid hormones:

1. Low basal metabolic rate
2. Leptin
3. α-melanocyte-stimulating hormone

Leptin (from adipose tissue) and **α-melanocyte-stimulating hormone** (from pituitary) increase the release of TRH and synthesis of T_4. The low body temperature also stimulates the synthesis of thyroid hormones. However, this occurs only in infants.

Factors decreasing the secretion of thyroid hormones:

1. Excess iodide intake
2. Stress
3. Somatostatin
4. Glucocorticoids
5. Dopamine.

These factors decrease the secretion of thyroid hormones, by inhibiting the release of TRH.

■ APPLIED PHYSIOLOGY – DISORDERS OF THYROID GLAND

■ HYPERTHYROIDISM

Increased secretion of thyroid hormones is called hyperthyroidism.

Causes of Hyperthyroidism

Hyperthyroidism is caused by:

1. Graves' disease
2. Thyroid adenoma.

1. *Graves' disease*

Graves' disease is an autoimmune disease and it is the most common cause of hyperthyroidism. Normally, TSH combines with surface receptors of thyroid cells and causes the synthesis and secretion of thyroid hormones. In Graves' disease, the B lymphocytes (plasma cells) produce autoimmune antibodies called **thyroid-stimulating autoantibodies** (TSAbs). These antibodies act like TSH by binding with membrane receptors of TSH and activating cAMP system of the thyroid follicular cells. This results in hypersecretion of thyroid hormones.

Antibodies act for a long time even up to 12 hours in contrast to that of TSH, which lasts only for an hour or so. The high concentration of thyroid hormones caused by the antibodies suppresses the TSH production also. So, the concentration of TSH is low or almost zero in plasma of most of the hyperthyroid patients.

2. *Thyroid adenoma*

Sometimes, a localized tumor develops in the thyroid tissue. It is known as thyroid adenoma and it secretes large quantities of thyroid hormones. It is not associated with autoimmunity. As far as this adenoma remains active, the other parts of thyroid gland cannot secrete the hormone. This is because, the hormone secreted from adenoma depresses the production of TSH.

Signs and Symptoms of Hyperthyroidism

1. Intolerance to heat as the body produces lot of heat due to increased basal metabolic rate caused by excess of thyroxine
2. Increased sweating due to vasodilatation
3. Decreased body weight due to fat mobilization
4. Diarrhea due to increased motility of GI tract
5. Muscular weakness because of excess protein catabolism
6. Nervousness, extreme fatigue, inability to sleep, mild tremor in the hands and psychoneurotic symptoms such as hyperexcitability, extreme anxiety or worry. All these symptoms are due to the excess stimulation of neurons in the central nervous system
7. Toxic goiter (see below)
8. Oligomenorrhea or amenorrhea (Chapter 80)
9. Exophthalmos (see below)
10. Polycythemia
11. Tachycardia and atrial fibrillation

12. Systolic hypertension
13. Cardiac failure.

Exophthalmos

Protrusion of eye balls is called exophthalmos. Most, but not all hyperthyroid patients develop some degree of protrusion of eyeballs.

Causes for exophthalmos

Exophthalmos in hyperthyroidism is due to the edematous swelling of retro-orbital tissues and degenerative changes in the extraocular muscles.

Effect of exophthalmos on vision

Severe exophthalmic condition leads to blindness because of two reasons:

1. Protrusion of the eyeball, which stretches and damages the optic nerve, resulting in **blindness** or
2. Due to the protrusion of eyeballs, the eyelids cannot be closed completely while blinking or during sleep. So, the constant exposure of eyeball to atmosphere causes dryness of the cornea, leading to irritation and infection. It finally results in ulceration of the cornea leading to blindness.

■ HYPOTHYROIDISM

Decreased secretion of thyroid hormones is called hypothyroidism. Hypothyroidism leads to myxedema in adults and cretinism in children.

Myxedema

Myxedema is the hypothyroidism in adults, characterized by generalized edematous appearance.

Causes for myxedema

Myxedema occurs due to diseases of thyroid gland, genetic disorder or iodine deficiency. In addition, it is also caused by deficiency of thyroid-stimulating hormone or thyrotropin-releasing hormone.

Common cause of myxedema is the autoimmune disease called **Hashimoto's thyroiditis,** which is common in late middle-aged women (Chapter 17). In most of the patients, it starts with glandular inflammation called **thyroiditis** caused by autoimmune antibodies. Later it leads to destruction of the glands.

Signs and symptoms of myxedema

Typical feature of this disorder is an edematous appearance throughout the body. It is associated with the following symptoms:

1. Swelling of the face
2. Bagginess under the eyes
3. Non-pitting type of edema, i.e. when pressed, it does not make pits and the edema is hard. It is because of accumulation of proteins with **hyaluronic acid** and **chondroitin sulfate,** which form a hard tissue with increased accumulation of fluid
4. Atherosclerosis: It is the hardening of the walls of arteries because of accumulation of fat deposits and other substances. In myxedema, it occurs because of increased plasma level of cholesterol which leads to deposition of cholesterol on the walls of the arteries.

Atherosclerosis produces **arteriosclerosis,** which refers to thickening and stiffening of arterial wall. Arteriosclerosis causes hypertension.

Other general features of hypothyroidism in adults are:

1. Anemia
2. Fatigue and muscular sluggishness
3. Extreme somnolence with sleeping up to 14 to 16 hours per day
4. Menorrhagia and polymenorrhea
5. Decreased cardiovascular functions such as reduction in rate and force of contraction of the heart, cardiac output and blood volume
6. Increase in body weight
7. Constipation
8. Mental sluggishness
9. Depressed hair growth
10. Scaliness of the skin
11. Frog-like husky voice
12. Cold intolerance.

Cretinism

Cretinism is the hypothyroidism in children, characterized by stunted growth.

Causes for cretinism

Cretinism occurs due to congenital absence of thyroid gland, genetic disorder or lack of iodine in the diet.

Features of cretinism

1. A newborn baby with thyroid deficiency may appear normal at the time of birth because thyroxine might have been supplied from mother. But a few weeks after birth, the baby starts developing the signs like sluggish movements and **croaking sound** while crying. Unless treated immediately, the baby will be mentally retarded permanently.
2. Skeletal growth is more affected than the soft tissues. So, there is stunted growth with bloated

body. The tongue becomes so big that it hangs down with dripping of saliva. The big tongue obstructs swallowing and breathing. The tongue produces characteristic guttural breathing that may sometimes **choke** the baby.

Cretin Vs dwarf

A cretin is different from pituitary dwarf. In cretinism, there is mental retardation and the different parts of the body are disproportionate. Whereas, in dwarfism, the development of nervous system is normal and the parts of the body are proportionate (Fig. 67.5). The reproductive function is affected in cretinism but it may be normal in dwarfism.

■ GOITER

Goiter means enlargement of the thyroid gland. It occurs both in hypothyroidism and hyperthyroidism.

Goiter in Hyperthyroidism – Toxic Goiter

Toxic goiter is the enlargement of thyroid gland with increased secretion of thyroid hormones, caused by thyroid tumor.

Goiter in Hypothyroidism – Non-toxic Goiter

Non-toxic goiter is the enlargement of thyroid gland without increase in hormone secretion. It is also called **hypothyroid goiter** (Fig. 67.6).

Based on the cause, the non-toxic hypothyroid goiter is classified into two types.

1. Endemic colloid goiter
2. Idiopathic non-toxic goiter.

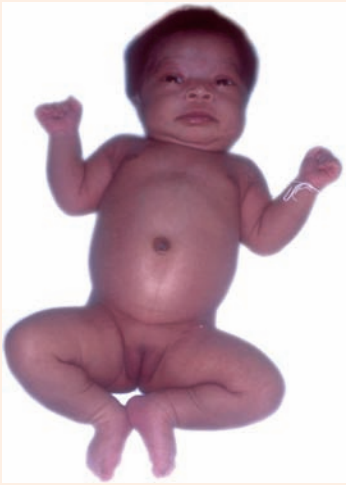

FIGURE 67.5: Cretinism (3-month-old baby)
(*Courtesy:* Prof Mafauzy Mohamad)

1. *Endemic colloid goiter*

Endemic colloid goiter is the non-toxic goiter caused by iodine deficiency. It is also called **iodine deficiency goiter.** Iodine deficiency occurs when intake is less than 50 µg/day. Because of lack of iodine, there is no formation of hormones. By feedback mechanism, hypothalamus and anterior pituitary are stimulated. It increases the secretion of TRH and TSH. The TSH then causes the thyroid cells to secrete tremendous amounts of thyroglobulin into the follicle. As there are no hormones to be cleaved, the thyroglobulin remains as it is and gets accumulated in the follicles of the gland. This increases the size of gland.

In certain areas of the world, especially in the Swiss Alps, Andes, Great Lakes region of United States and in India, particularly in Kashmir Valley, the soil does not contain enough iodine. Therefore, the foodstuffs also do not contain iodine. The endemic colloid goiter was very common in these parts of the world before the introduction of iodized salts.

2. *Idiopathic non-toxic goiter*

Idiopathic non-toxic goiter is the goiter due to unknown cause. Enlargement of thyroid gland occurs even without iodine deficiency. The exact cause is not known. It is suggested that it may be due to thyroiditis and deficiency of enzymes such as **peroxidase, iodinase** and **deiodinase,** which are required for thyroid hormone synthesis.

Some foodstuffs contain **goiterogenic substances** (goitrogens) such as **goitrin.** These substances contain antithyroid substances like propylthiouracil. **Goitrogens** suppress the synthesis of thyroid hormones. Therefore, TSH secretion increases, resulting in enlargement of the gland. Such goitrogens are found in vegetables like turnips and cabbages. Soybean also contains some amount of goitrogens.

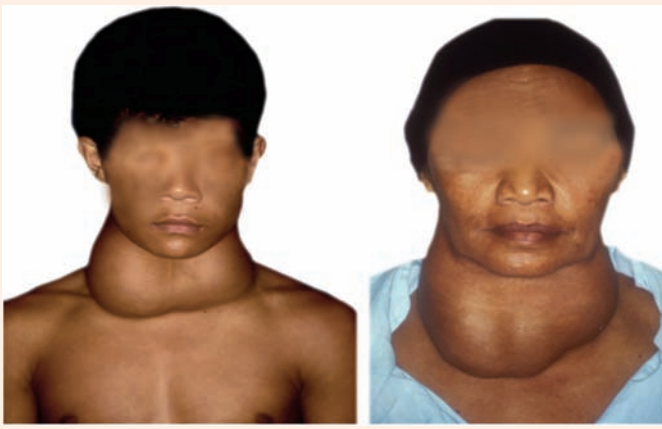

FIGURE 67.6: Non-toxic goiter
(*Courtesy:* Prof Mafauzy Mohamad)

The goitrogens become active only during low iodine intake.

TREATMENT FOR THYROID DISORDERS

TREATMENT FOR HYPERTHYROIDISM

1. *By using Antithyroid Substances*

Antithyroid substances are the drugs which suppress the secretion of thyroid hormones. Hyperthyroidism in early stage can be treated by antithyroid substances.

Three well-known antithyroid substances are:

i. Thiocyanate
ii. Thiourylenes
iii. High concentration of inorganic iodides.

i. *Thiocyanate*

Thiocyanate prevents synthesis of thyroxine by inhibiting iodide trapping. The active pump which transports iodide into the thyroid cells, can transport thiocyanate ions also. So, administration of thiocyanate in high concentrations causes competitive inhibition of iodide transport into the cell. So, iodide trapping is inhibited, leading to the inhibition of synthesis of thyroxine.

ii. *Thiourylenes*

Thiourylenes are the thiourea-related substances such as propylthiouracil and methimazole, which prevent the formation of thyroid hormone from iodides and tyrosine. It is achieved partly by blocking peroxidase enzyme activity and partly by blocking coupling of iodinated tyrosine to form either T_3 or T_4.

During the use of these two antithyroid substances, even though the synthesis of thyroid hormone is inhibited, the formation of thyroglobulin is not stopped. The deficiency of the hormone increases the TSH secretion, which increases the size of thyroid gland with more secretion of thyroglobulin. Thyroglobulin accumulates in the gland and causes enlargement of the gland, resulting in non-toxic goiter.

iii. *High concentration of inorganic iodides*

Iodides in high concentration decrease all phases of thyroid activity, including the release of hormones. So, the size of the gland is also reduced with decreased blood supply. Because of this, iodides are frequently administered to hyperthyroid patients for 2 or 3 weeks prior to surgical removal of the thyroid gland.

2. *By Surgical Removal*

In advanced cases of hyperthyroidism, treatment by using antithyroid substances is not possible. So, thyroid gland of these patients must be removed. Surgical removal of thyroid gland is called **thyroidectomy.** Before surgery, the patient is prepared by reducing the basal metabolic rate. It is done by injecting propylthiouracil for several weeks, until basal metabolic rate reaches almost the basal level. The high concentration of iodides is administered for 2 weeks. It decreases the size of the gland and blood supply to a very great extent. Because of these precautions, the mortality after the operation decreases very much.

TREATMENT FOR HYPOTHYROIDISM

The only treatment for hypothyroidism is the administration of thyroid extract or ingestion of pure thyroxine in the form of tablets, orally.

THYROID FUNCTION TESTS

Functional status of thyroid gland is assessed by the following tests:

1. Measurement of plasma level of T_3 and T_4: For hyperthyroidism or hypothyroidism, the most accurate diagnostic test is the direct measurement of concentration of "free" thyroid hormones in the plasma, i.e. T_3 and T_4.
2. Measurement of TRH and TSH: There is almost total absence of these two hormones in hyperthyroidism. It is because of negative feedback mechanism, by the increased level of thyroid hormones.
3. Measurement of basal metabolic rate: In hyperthyroidism, basal metabolic rate is increased by about 30% to 60%. Basal metabolic rate is decreased in hypothyroidism by 20% to 40%.