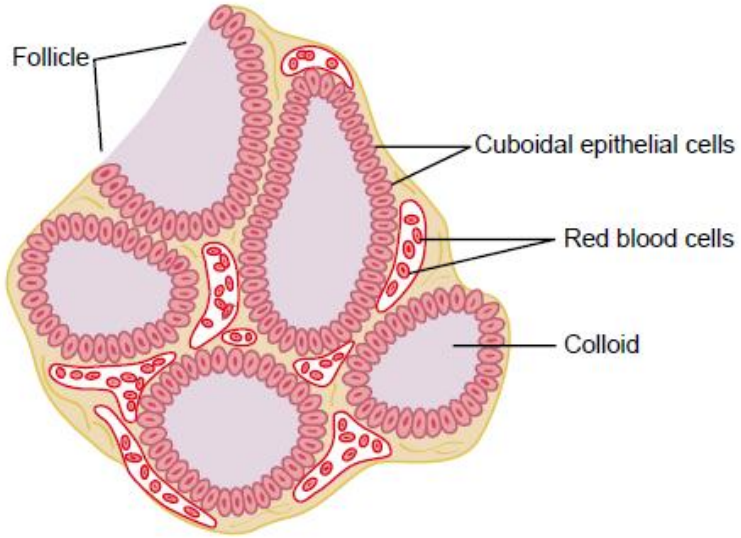
Lecture No . 4



The thyroid gland

The thyroid gland, located immediately below the larynx on each side of and anterior to the trachea, is one of the largest of the endocrine glands, normally weighing 15 to 20 grams in adults. The thyroid secretes two major hormones, *thyroxine* and *triiodothyronine*, commonly called T4 and T3, respectively. Both of these hormones profoundly increase the metabolic rate of the body. Thyroid secretion is controlled primarily by *thyroid-stimulating hormone (TSH)* secreted by the anterior pituitary gland. The thyroid gland also secretes *calcitonin*, an important hormone for calcium metabolism .

Physiologic Anatomy of the Thyroid Gland.

The thyroid gland is composed of large numbers of closed *follicles* (100 to 300 micrometers in diameter) filled with a secretory substance called *colloid* and lined with *cuboidal epithelial cells* that secrete into the interior of the follicles.The major constituent of colloid is the large glycoprotein *thyroglobulin*, which contains the thyroid hormones within its molecule. Once the secretion has entered the follicles, it must be absorbed back through the follicular epithelium into the blood before it can function in the body. The thyroid gland has a blood flow about five times the weight of the gland each minute, which is a blood supply as great as that of any other area of the body, with the possible exception of the adrenal cortex.

Iodine Is Required for Formation of Thyroxine

To form normal quantities of thyroxine, about 50 milligrams of ingested iodine in the form of iodides are required *each year*, or about *1 mg/week*. To prevent iodine deficiency, common table salt is iodized with about 1 part sodium iodide to every 100,000 parts sodium chloride.

Fate of Ingested Iodides

Iodides ingested orally are absorbed from the gastrointestinal tract into the blood in about the same manner as chlorides. Normally most of the iodides are rapidly excreted by the kidneys, but only after about one fifth are selectively removed from the circulating blood by the cells of the thyroid gland and used for synthesis of the thyroid hormones.

Iodide Pump (Iodide Trapping)

The first stage in the formation of thyroid hormones is transport of iodides from the blood into the thyroid glandular cells and follicles. The basal membrane of the thyroid cell has the specific ability to pump the iodide actively to the interior of the cell. This is called *iodide trapping*. In a normal gland, the iodide pump concentrates the iodide to about 30 times its concentration in the blood. When the thyroid gland becomes maximally active, this concentration ratio can rise to as high as 250 times. The rate of iodide trapping by the thyroid is influenced by several factors, the most important being the concentration of TSH; TSH stimulates and hypophysectomy greatly diminishes the activity of the iodide pump in thyroid cells.

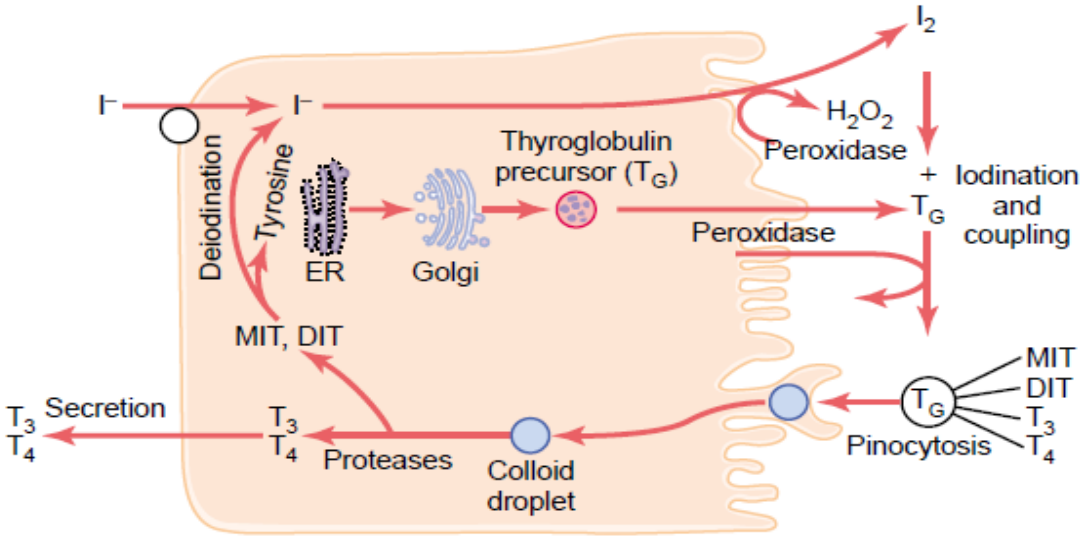


Figure 76–2

Thyroid cellular mechanisms for iodine transport, thyroxine and triiodothyronine formation, and thyroxine and triiodothyronine release into the blood. MIT, monoiodotyrosine; DIT, diiodotyrosine; T_3, triiodothyronine; T_4, thyroxine; T_G, thyroglobulin.

Formation and Secretion of Thyroglobulin by the Thyroid Cells.

The thyroid cells are typical protein-secreting glandular cells. The endoplasmic reticulum and Golgi apparatus synthesize and secrete into the follicles a large glycoprotein molecule called *thyroglobulin*, with a molecular weight of about 335,000. Each molecule of thyroglobulin contains about 70 tyrosine amino acids, and they are the major substrates that combine with iodine to form the thyroid hormones. Thus, the thyroid hormones form *within* the thyroglobulin molecule. That is, the thyroxine and triiodothyronine hormones formed from the tyrosine amino acids remain part of the thyroglobulin molecule during synthesis of the thyroid hormones and even afterward as stored hormones in the follicular colloid.

Oxidation of the Iodide Ion.

The first essential step in the formation of the thyroid hormones is conversion of the iodide ions to an *oxidized form of iodine*, either nascent iodine (I^0) or I_3^- , that is then capable of combining directly with the amino acid tyrosine. This oxidation of iodine is promoted by the enzyme *peroxidase* and its accompanying *hydrogen peroxide*, which provide a potent system capable of oxidizing iodides. The peroxidase is either located in the apical membrane of the cell or attached to it, thus providing the oxidized iodine at exactly the point in the cell where the thyroglobulin molecule issues forth from the Golgi apparatus and through the cell membrane into the stored thyroid gland colloid. When the peroxidase system is blocked or when it is hereditarily absent from the cells, the rate of formation of thyroid hormones falls to zero.

Iodination of Tyrosine and Formation of the Thyroid Hormones—"Organification" of Thyroglobulin.

The binding of iodine with the thyroglobulin molecule is called *organification* of the thyroglobulin. Oxidized iodine even in the molecular form will bind directly but very slowly with the amino acid tyrosine. In the thyroid cells, however, the oxidized iodine is associated with an *iodinase* enzyme that causes the process to occur within seconds or minutes. Therefore, almost as rapidly as the thyroglobulin molecule is released from the Golgi apparatus or as it is secreted through the apical cell membrane into the follicle, iodine binds with about one sixth of the tyrosine amino acids within the thyroglobulin molecule. shows the successive stages of iodination of tyrosine and final formation of the two important thyroid hormones, thyroxine and triiodothyronine. Tyrosine is first iodized to *monoiodotyrosine* and then to *diiodotyrosine*. Then, during the next few minutes, hours, and even days, more and more of the iodotyrosine residues become *coupled* with one another. The major hormonal product of the coupling reaction is the molecule *thyroxine* that remains part of the thyroglobulin molecule. Or one molecule of

monoiodotyrosine couples with one molecule of diiodotyrosine to form *triiodothyronine*, which represents about one fifteenth of the final hormones.

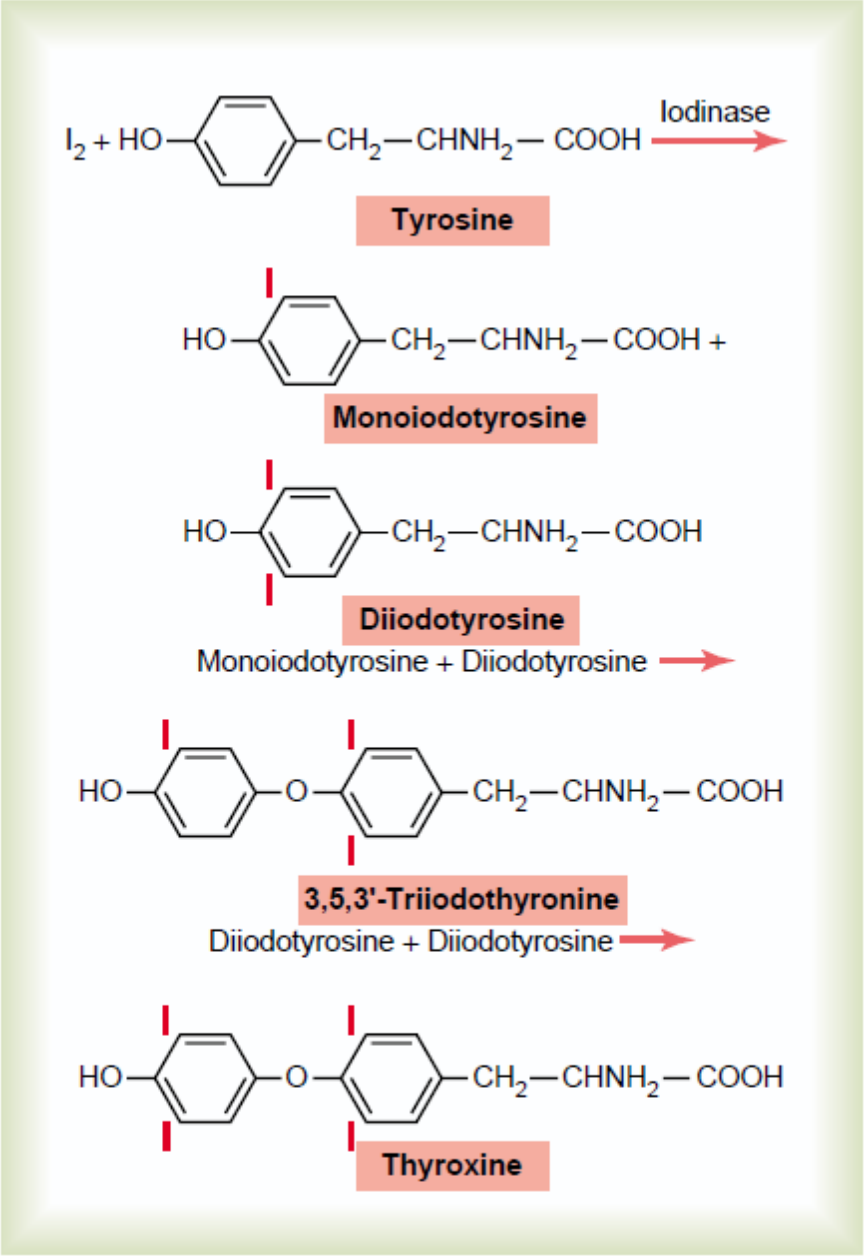


Figure 76–3

Chemistry of thyroxine and triiodothyronine formation.

***Storage of Thyroglobulin*.**

The thyroid gland is unusual among the endocrine glands in its ability to store large amounts of hormone. After synthesis of the thyroid hormones has run its course, each thyroglobulin molecule contains up to 30 thyroxine molecules and a few triiodothyronine molecules. In this form, the thyroid hormones are stored in the follicles in an amount sufficient to

supply the body with its normal requirements of thyroid hormones for 2 to 3 months. Therefore, when synthesis of thyroid hormone ceases, the physiologic effects of deficiency are not observed for several months.

Release of Thyroxine and Triiodothyronine from the Thyroid Gland

Thyroglobulin itself is not released into the circulating blood in measurable amounts; instead, thyroxine and triiodothyronine must first be cleaved from the thyroglobulin molecule, and then these free hormones are released. This process occurs as follows: The apical surface of the thyroid cells sends out pseudopod extensions that close around small portions of the colloid to form *pinocytic vesicles* that enter the apex of the thyroid cell. Then *lysosomes* in the cell cytoplasm immediately fuse with these vesicles to form digestive vesicles containing digestive enzymes from the lysosomes mixed with the colloid. Multiple *proteases* among the enzymes digest the thyroglobulin molecules and release thyroxine and triiodothyronine in free form. These then diffuse through the base of the thyroid cell into the surrounding capillaries. Thus, the thyroid hormones are released into the blood. About three quarters of the iodinated tyrosine in the thyroglobulin never becomes thyroid hormones but remains monoiodotyrosine and diiodotyrosine. During the digestion of the thyroglobulin molecule to cause release of thyroxine and triiodothyronine, these iodinated tyrosines also are freed from the thyroglobulin molecules. However, they are not secreted into the blood. Instead, their iodine is cleaved from them by a *deiodinase enzyme* that makes virtually all this iodine available again for recycling within the gland for forming additional thyroid hormones. In the congenital absence of this deiodinase enzyme, many persons become iodine-deficient because of failure of this recycling process.

Transport of Thyroxine and Triiodothyronine to Tissues:

Thyroxine and Triiodothyronine Are Bound to Plasma Proteins.

On entering the blood, over 99 per cent of the thyroxine and triiodothyronine combines immediately with several of the plasma proteins, all of which are synthesized by the liver. They combine mainly with *thyroxine-binding globulin* and much less so with *thyroxine-binding prealbumin* and *albumin*.

Thyroxine and Triiodothyronine Are Released Slowly to Tissue Cells.

Because of high affinity of the plasma-binding proteins for the thyroid hormones, these substances— in particular, thyroxine—are released to the tissue cells slowly. Half the thyroxine in the blood is released to the tissue cells about every 6 days, whereas half the triiodothyronine—

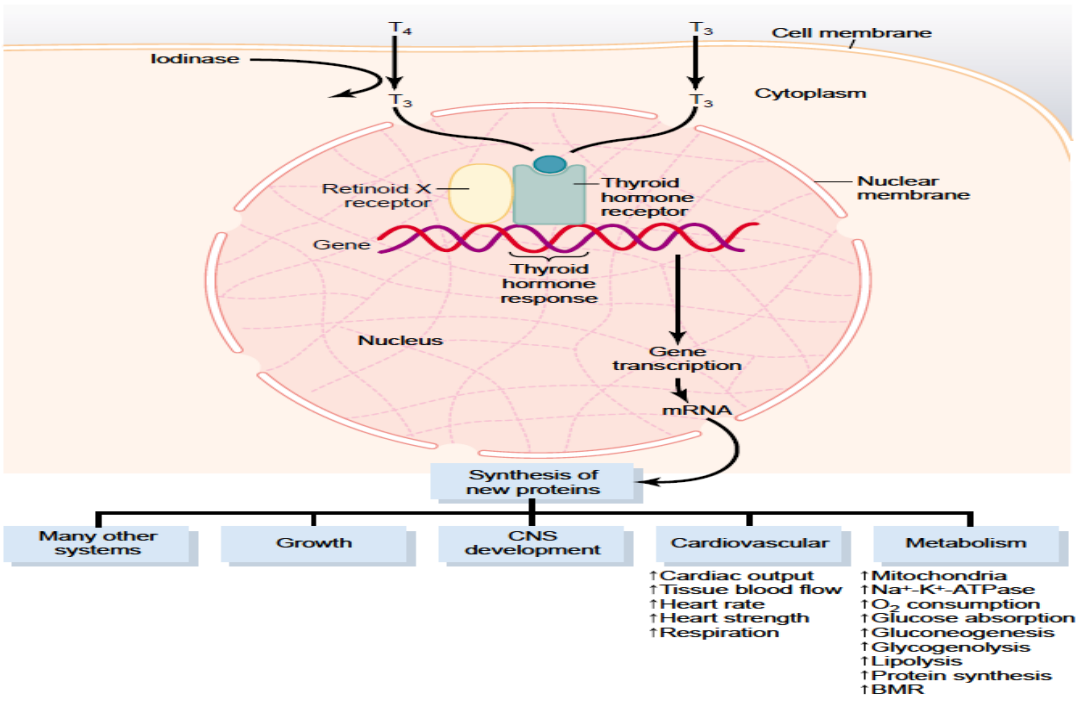
because of its lower affinity—is released to the cells in about 1 day. On entering the tissue cells, both thyroxine and triiodothyronine again bind with intracellular proteins, the thyroxine binding more strongly than the triiodothyronine. Therefore, they are again stored, but this time in the target cells themselves, and they are used slowly over a period of days or weeks.

Thyroid Hormones Increase Cellular Metabolic Activity

The thyroid hormones increase the metabolic activities of almost all the tissues of the body. The basal metabolic rate can increase to 60 to 100 per cent above normal when large quantities of the hormones are secreted. The rate of utilization of foods for energy is greatly accelerated. Although the rate of protein synthesis is increased, at the same time the rate of protein catabolism is also increased.The growth rate of young people is greatly accelerated. The mental processes are excited, and the activities of most of the other endocrine glands are increased.

Thyroid Hormones Increase the Number and Activity of Mitochondria.

When thyroxine or triiodothyronine is given to an animal, the mitochondria in most cells of the animal's body increase in size as well as number. Furthermore, the total membrane surface area of the mitochondria increases almost directly in proportion to the increased metabolic rate of the whole animal. Therefore, one of the principal functions of thyroxine might be simply to increase the number and activity of mitochondria, which in turn increases the rate of formation of adenosine triphosphate (ATP) to energize cellular function. However, the increase in the number and activity of mitochondria could be the *result* of increased activity of the cells as well as the cause of the increase.



Effect of Thyroid Hormone on Growth

An important effect of thyroid hormone is to promote growth and development of the brain during fetal life and for the first few years of postnatal life. If the fetus does not secrete sufficient quantities of thyroid hormone, growth and maturation of the brain both before birth and afterward are greatly retarded, and the brain remains smaller than normal. the effect of thyroid hormone on growth is manifest mainly in growing children. In those who are hypothyroid, the rate of growth is greatly retarded. In those who are hyperthyroid, excessive skeletal growth often occurs, causing the child to become considerably taller at an earlier age. However, the bones also mature more rapidly and the epiphyses close at an early age, so that the duration of growth and the eventual height of the adult may actually be shortened.

Effects of Thyroid Hormone on Specific Bodily Mechanisms

1-Stimulation of Carbohydrate Metabolism.
2-Stimulation of Fat Metabolism
3-Effect on Plasma and Liver Fats.
4-Increased Requirement for Vitamins.
5-Increased Basal Metabolic Rate.
6-Effect on Body Weight
7-Effect of Thyroid Hormones on the Cardiovascular System
8-Increased Respiration
9-Excitatory Effects on the Central Nervous System
10-Effect on the Function of the Muscles
11-Effect on Other Endocrine Glands
12-Effect of Thyroid Hormone on Sexual Function

Anterior Pituitary Secretion of TSH Is Regulated by Thyrotropin-Releasing Hormone from the Hypothalamus

Anterior pituitary secretion of TSH is controlled by a hypothalamic hormone, *thyrotropin-releasing hormone (TRH)*, which is secreted by nerve endings in the median eminence of the hypothalamus. From the median eminence, the TRH is then transported to the anterior pituitary by way of the hypothalamichypophysial portal blood. TRH has been obtained in pure form. It is a simple substance, a tripeptide amide—*pyroglutamyl-histidylproline- amide*. TRH directly affects the anterior pituitary gland cells to increase their output of TSH. When the blood portal system from the hypothalamus to the anterior pituitary gland becomes blocked, the rate of secretion of TSH by the anterior pituitary decreases greatly but is not reduced to zero. The molecular mechanism by which TRH causes the TSH-secreting cells of the anterior pituitary to produce TSH is first to bind with TRH receptors in the pituitary cell membrane. This in turn *activates the phospholipase second messenger*

system inside the pituitary cells to produce large amounts of phospholipase C, followed by a cascade of other second messengers, including calcium ions and diacyl glycerol, which eventually leads to TSH release.

Feedback Effect of Thyroid Hormone to Decrease Anterior Pituitary Secretion of TSH

Increased thyroid hormone in the body fluids decreases secretion of TSH by the anterior pituitary. When the rate of thyroid hormone secretion rises to about 1.75 times normal, the rate of TSH secretion falls essentially to zero. Almost all this feedback depressant effect occurs even when the anterior pituitary has been separated from the hypothalamus. Therefore it is probable that increased thyroid hormone inhibits anterior pituitary secretion of TSH mainly by a direct effect on the anterior pituitary gland itself. Regardless of the mechanism of the feedback, its effect is to maintain an almost constant concentration of free thyroid hormones in the circulating body fluids.

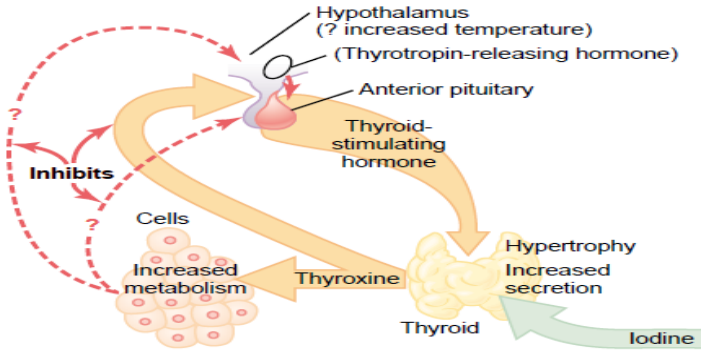


Figure 76–7

Regulation of thyroid secretion.

Diseases of the Thyroid

A-Hyperthyroidism

Most effects of hyperthyroidism are obvious from the preceding discussion of the various physiologic effects of thyroid hormone. However, some specific effects should be mentioned in connection especially with the development, diagnosis, and treatment of hyperthyroidism.

Causes of Hyperthyroidism

1-Toxic Goiter, Thyrotoxicosis, Graves' Disease

In most patients with hyperthyroidism, the thyroid gland is increased to two to three times normal size, with tremendous hyperplasia and infolding of the follicular cell lining into the follicles, so that the number of cells is increased greatly. Also, each cell increases its rate of secretion several fold; radioactive iodine uptake studies indicate that some of these hyperplastic glands secrete thyroid hormone at rates 5 to 15times normal.

***2-Thyroid Adenoma*.** Hyperthyroidism occasionally results from a localized adenoma (a tumor) that develops in the thyroid tissue and secretes large quantities of thyroid hormone. This is different from the more usual type of hyperthyroidism, in that it usually is not associated with evidence of any autoimmune disease. An interesting effect of the adenoma is that as long as it continues to secrete large quantities of thyroid hormone, secretory function in the remainder of the thyroid gland is almost totally inhibited because the thyroid hormone from the adenoma depresses the production of TSH by the pituitary gland.

Symptoms of Hyperthyroidism

(1) a high state of excitability.
(2) intolerance to heat.
(3) increased sweating.
(4) mild to extreme weight loss (sometimes as much as 100 pounds).
(5)varying degrees of diarrhea.
(6) muscle weakness.
(7) nervousness or other psychic disorders.
(8) extreme fatigue but inability to sleep.
(9) tremor of the hands.

B-Hypothyroidism

The effects of hypothyroidism, in general, are opposite to those of hyperthyroidism, but there are a few physiologic mechanisms peculiar to hypothyroidism. hypothyroidism, like hyperthyroidism, probably is initiated by autoimmunity against the thyroid gland, but immunity that destroys the gland rather than stimulates it.The thyroid glands of most of these patients first have autoimmune "thyroiditis," which means thyroid inflammation. This causes progressive deterioration and finally fibrosis of the gland, with resultant diminished or absent secretion of thyroid hormone. Several other types of hypothyroidism also occur, often associated with development of enlarged thyroid glands, called *thyroid goiter*, as follows.

Symptoms of Hypothyroidism

include fatigue and extreme somnolence with sleeping up to 12 to 14 hours a day, extreme muscular sluggishness, slowed heart rate, decreased cardiac output, decreased blood volume, sometimes increased body weight, constipation, mental sluggishness, failure of many trophic functions in the body evidenced by depressed growth of hair and scaliness of the skin, development of a froglike husky voice, and, in severe cases, development of an edematous appearance throughout the body called myxedema.