BOOK CHAPTER

The Thyroid Gland

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Endocrine and Reproductive Physiology, 6, 125-141

Objectives

1. Explain the mechanisms of thyroid hormone synthesis.
2. Describe the regulation of thyroid function and the actions of thyroid hormones.
3. Compare and contrast the functions of thyroxine and triiodothyronine.
4. Discuss the peripheral conversion of thyroid hormones by deiodinases.
5. Draw the regulatory feedback loop for the regulation of thyroid function.
6. Understand the etiology, major symptoms, and pathophysiology of the symptoms for Graves disease, Hashimoto thyroiditis, sporadic congenital hypothyroidism, and cretinism.

The thyroid gland produces the prohormone, tetraiodothyronine (T_4), and the active hormone, triiodothyronine (T_3). The synthesis of T_4 and T_3 requires iodine, which can be a limiting factor in some parts of the world. Much of T_3 is also made by peripheral conversion of T_4 to T_3. T_3 acts primarily through a nuclear receptor that regulates gene expression. T_3 is critical for normal brain and skeletal development, and has broad effects on metabolism and cardiovascular function in the adult.

Anatomy and Histology of the Thyroid Gland

The thyroid gland is composed of right and left lobes that sit anterolaterally to the trachea (Fig. 6.1 (f0010)). Normally, the lobes of the thyroid gland are connected by a midventral isthmus. The functional unit of the thyroid gland is the **thyroid follicle** , a spherical structure about 200 to 300 μm in diameter ringed by a single layer of thyroid epithelial cells (Fig. 6.2 (f0015)). The epithelium sits on a basal lamina, surrounded by a rich capillary supply. The apical side of the follicular epithelium faces the lumen of the follicle. The lumen is filled with **colloid** composed of **thyroglobulin** , which is secreted and **iodinated** by the thyroid epithelial cells. The size of the epithelial cells and the amount of colloid are dynamic features that change with the activity of the gland. The thyroid gland contains another type of cell in addition to follicular cells. Scattered within the gland are **parafollicular cells** , or **C cells** . These cells are the source of the polypeptide hormone **calcitonin** , whose function is unclear in humans.

CLINICAL BOX 6.1

Although parafollicular C cells and calcitonin may be of minimal importance in normal humans, C cells can give rise to **medullary thyroid carcinoma** . Medullary cancer is an aggressive form of thyroid cancer, and metastasis to lungs, liver, bone, or other organs drastically reduces survival. Although most medullary cancer is sporadic, about one fifth of cases are familial. The familial forms are due to activating mutations of the ***RET*** **protooncogene** , a tyrosine kinase receptor that interacts with coreceptors and is activated by glial-derived neurotrophic factor and related proteins. Familial medullary thyroid cancer can occur independently of other endocrine glands or as part of a **multiple endocrine neoplasia (MEN)** syndrome, which in this case also involves adrenal medulla chromaffin cells (pheochromocytoma), parathyroid glands, and/or ganglioneuromas. These cancers remain differentiated enough to secrete **calcitonin** , and assay of calcitonin in the blood is useful in assessing treatment and possible recurrence during follow-up. Medullary thyroid cancer is treated by total thyroidectomy and removal of regional lymph nodes. Effective chemotherapy regimens that target the tyrosine kinase receptor, c-ret, have also been developed.

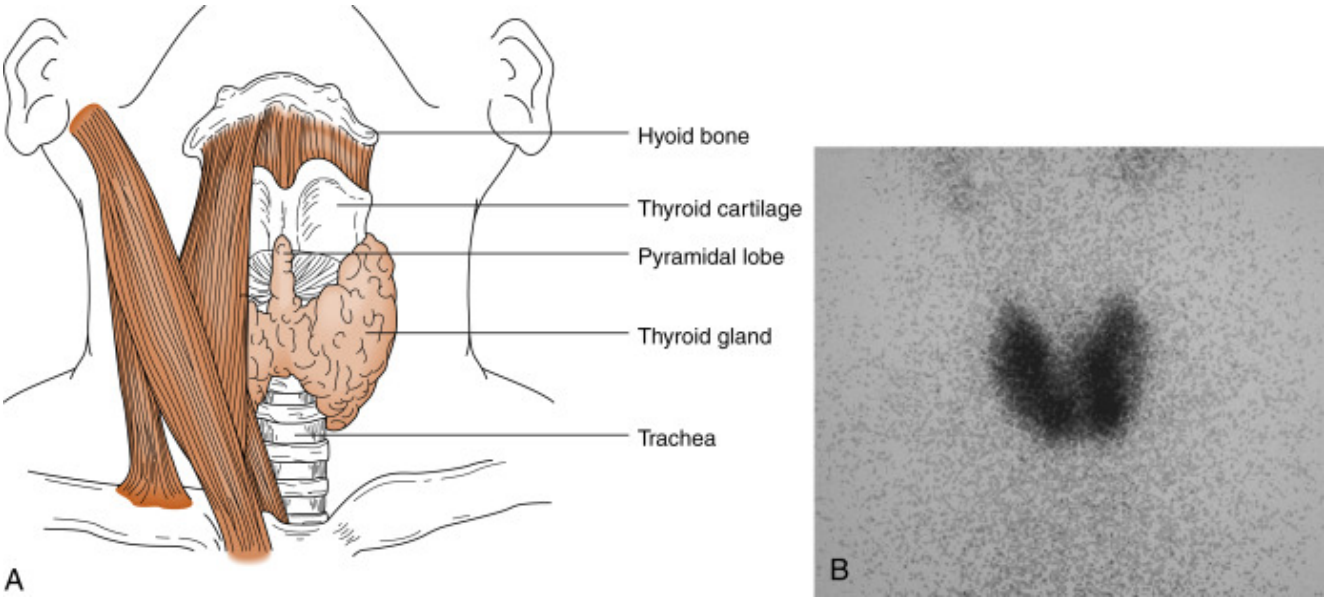

Fig. 6.1

(A) Anatomy of the thyroid gland. (B) Image of pertechnetate uptake by a normal thyroid gland.

Modified from Drake RL, Vogl W, Mitchell AWM: *Gray's Anatomy for Students,* Philadelphia, 2005, Churchill Livingstone.

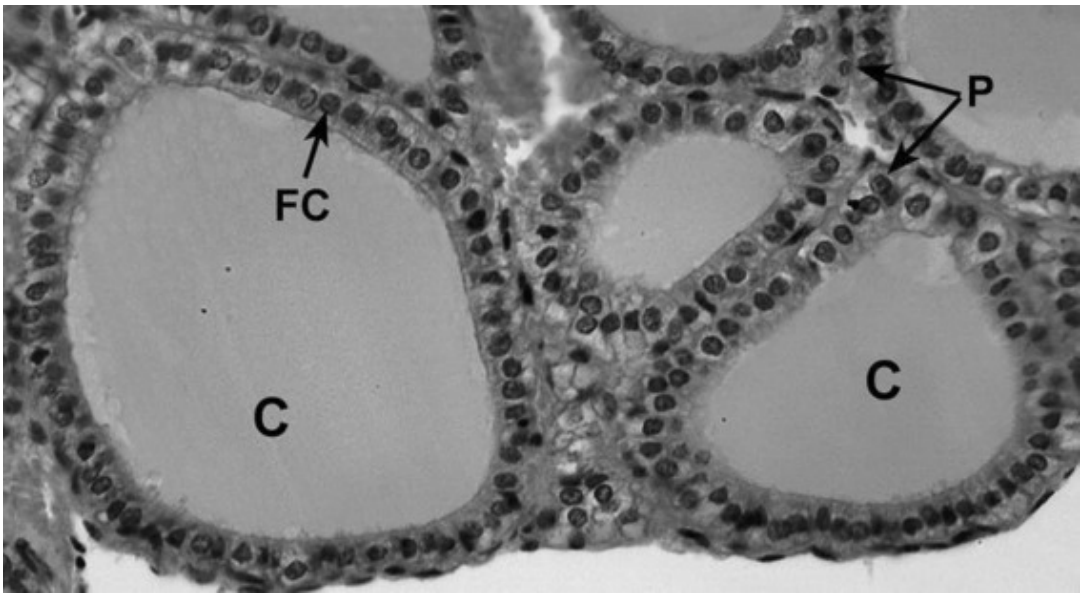

Fig. 6.2

Normal rat thyroid. Single layer of cuboidal epithelial cells (follicular cells; FC) surround colloid *(C)*. Parafollicular cells *(P)* produce calcitonin (see Chapter 4).

Production of Thyroid Hormones

The secretory products of the thyroid gland are **iodothyronines** (Fig. 6.3 (f0020)), a class of hormones resulting from the coupling of two iodinated tyrosine molecules. About 90% of the thyroid output is **3,5,3′,5′-tetraiodothyronine (thyroxine** , or **T $_4$**). T $_4$ is a prohormone. About 10% **is 3,5,3′-triiodothyronine (T $_3$**), which is the active form of thyroid hormone. Less than 1% of thyroid output is **3,3′,5′-triiodothyronine (reverse T $_3$** , or **rT $_3$**), which is inactive. Normally, these three products are secreted in the same proportions at which they are stored in the gland.

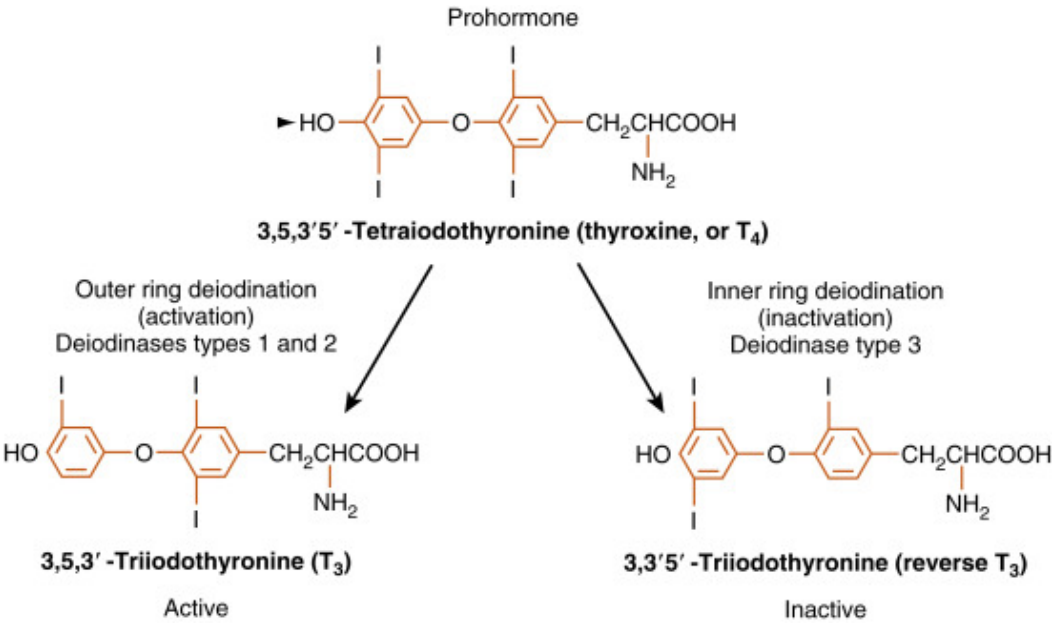

Fig. 6.3

Structure of iodothyronines, T_4, T_3, and reverse T_3.

Because the primary product of the thyroid gland is T_4, yet the active form of thyroid hormone is T_3, the thyroid axis relies heavily on **peripheral conversion** through the action of **thyronine-specific deiodinases** (see Fig. 6.3 (f0020)).

Type 1 deiodinase , which is expressed in the plasma membrane of liver and kidney cells, is a low-affinity enzyme capable of both outer- and inner-ring deiodination of T_4. Current evidence suggests that type 1 deiodinase may function primarily as a scavenger enzyme that removes iodine from sulfated thyroid hormones before they are excreted in bile or urine. However, in hyperthyroidism, type 1 deiodinase is a major contributor to elevated circulating T_3 levels in this disease.

Type 2 deiodinase , on the other hand, is a high-affinity (Km = 1 nM) outer-ring deiodinase that converts T_4 to T_3. It is localized intracellularly in the endoplasmic reticulum and expressed in several cell types, including glial cells of the central nervous system (CNS), the pituitary gland, brown fat, placenta, and skeletal muscle (albeit at low levels). Cell types that express the type 2 deiodinase are able to customize the levels of available T_3 in their local environment. For example, the brain can maintain constant intracellular levels of T_3 by upregulating type 2 deiodinase in hypothyroidism, when free T_4 falls to low levels. Importantly, type 2 deiodinase is also present in the thyrotropes of the pituitary, where it acts as a “thyroid axis sensor” by integrating total circulating free T_3 and T_4. T_3 in the thyrotrope, which either enters the cell as T_3 or is converted from T_4 by the type 2 deiodinase, represents the feedback signal that regulates thyroid-stimulating hormone (TSH) secretion (see later). Brown fat is able to increase heat production in response to adrenergic stimulation of local T_3 production by the type 2 deiodinase (discussed later). In addition to local production of T_3, type 2 deiodinase generates most of the circulating pool of T_3 in humans under **euthyroid** conditions.

Finally, there also exists an “inactivating” deiodinase, called **type 3 deiodinase** . Type 3 deiodinase is a high-affinity, inner-ring deiodinase that converts T_4 to the inactive rT_3. Type 3 deiodinase is increased during hyperthyroidism, which helps to blunt the overproduction of T_4. All forms of iodothyronines are further deiodinated, eventually to noniodinated thyronine (Table 6.1 (t0010)).

TABLE 6.1
Average Thyroid Hormone Turnover

	T_4	T_3	rT_3
Daily production (μg)	90	35	35
From thyroid (%)	100	25	5
From T_4 (%)	—	75	95
Extracellular pool (μg)	850	40	40

	T_4	T_3	rT_3
Plasma concentration			
Total (μg/dL)	8.0	0.12	0.04
Free (ng/dL)	2.0	0.28	0.20
Half-life (days)	7	1	0.8
Metabolic clearance (L/day)	1	26	77
Fractional turnover per day (%)	10	75	90

Iodide Balance

Because of the unique role of **iodide (iodide, or I^-, is the water-soluble ionized form of diatomic iodine, or I_2)** in thyroid physiology, a description of thyroid hormone synthesis requires some understanding of iodide turnover (Fig. 6.4 (f0025)). The average dietary intake of iodide is 400 μg in the United States , compared with a minimum daily requirement of 150 μg for adults, 90 to 120 μg for children, and 200 μg for pregnant women. In the steady state, virtually the same amount, 400 μg, is excreted in the urine. Iodide is actively concentrated in the thyroid gland, salivary glands, gastric glands, lacrimal glands, mammary glands, and choroid plexus. About 70 to 80 μg of iodide is taken up daily by the thyroid gland. The total iodide content of the thyroid gland averages around 7500 μg, virtually all of which is in the form of iodothyronines. In the steady state, 70 to 80 μg of iodide, or about 1% of the total, is released from the gland daily. Of this amount, 75% is secreted as thyroid hormone, and the remainder is secreted as free iodide. The large ratio (100:1) of iodide stored in the form of hormone to the amount turned over daily protects against iodide deficiency for about 2 months. Iodide is also conserved by a marked reduction in the renal excretion of iodide as the concentration in serum falls.

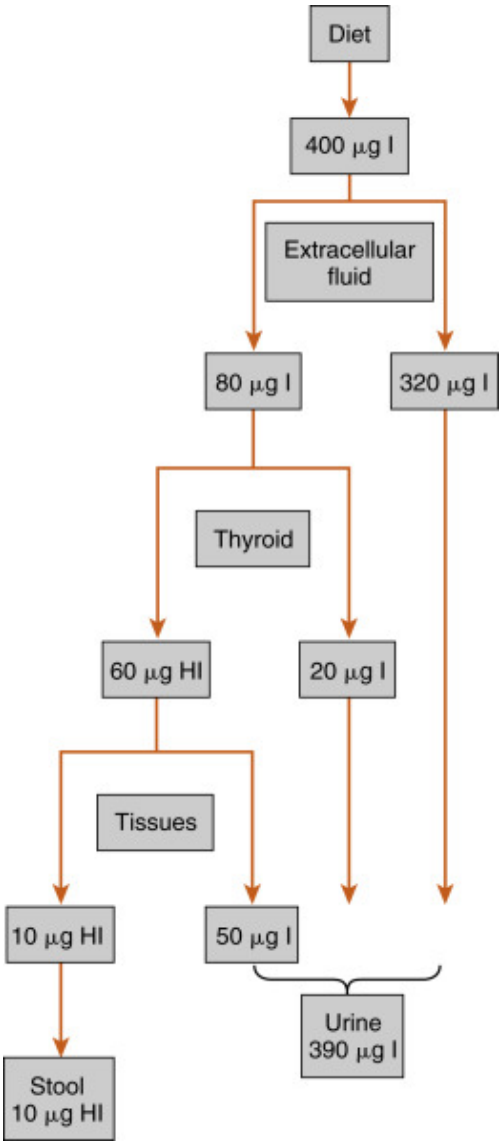

Fig. 6.4

Iodine distribution and turnover in humans.

Overview of Thyroid Hormone Synthesis

To understand thyroid hormone synthesis and secretion, one must appreciate the directionality of each process as it relates to the **polarized thyroid epithelial cell** (Fig. 6.5 (f0030)). Synthesis of thyroid hormone requires two precursors, **thyroglobulin** and **iodide** . Iodide is transported across cells from the basal (vascular) side to the apical (follicular luminal) side of the thyroid epithelium. Amino acids are assembled by translation into thyroglobulin, which is then secreted from the apical membrane into the follicular lumen. Thus synthesis involves a basal-to-apical movement of precursors into the follicular lumen (see Fig. 6.5 (f0030) ; *black arrows*). Actual synthesis of **iodothyronines** occurs enzymatically in the follicular lumen close to the apical membrane of the epithelial cells (see later). Secretion involves fluid phase endocytosis of **iodinated thyroglobulin** and apical-to-basal movement of the endocytic vesicles and their fusion with lysosomes. Thyroglobulin is then enzymatically degraded, which results in the release of **thyroid hormones** from the thyroglobulin peptide backbone. Finally, thyroid hormones move across the basolateral membrane, probably through a specific transporter, and ultimately into the blood. Thus

secretion involves an apical-to-basal movement (see Fig. 6.5 (f0030) ; *orange arrows*). There are also scavenger pathways within the epithelial cell that reuse iodine and amino acids after enzymatic digestion of thyroglobulin (see Fig. 6.5 (f0030) ; *open arrows*).

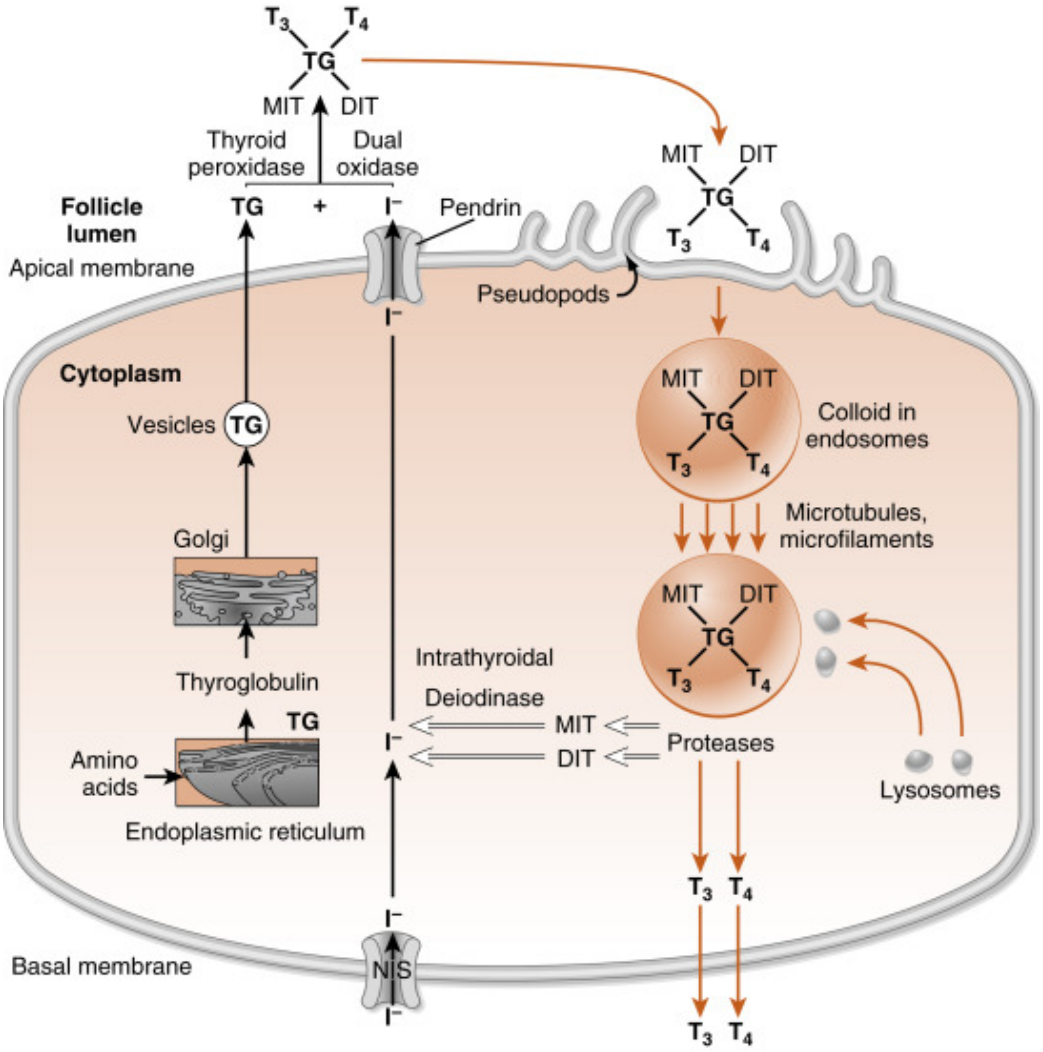

Fig. 6.5

Synthesis *(black arrows)* and secretion *(orange arrows)* of thyroid hormones by the thyroid epithelial cell. *Open arrows* denote pathways involved in the conservation of iodine and amino acids.

Synthesis of Iodothyronines Within a Thyroglobulin Backbone

Iodide is transported into the gland against chemical and electrical gradients by a **Na^+ -I^- symporter (NIS)** located in the basolateral membrane of thyroid epithelial cells. Normally, a thyroid-to-plasma free iodide ratio of 30 is maintained. This so-called **iodide trap** is highly expressed in the thyroid gland, but NIS is also expressed at lower levels in the placenta, salivary glands, and actively lactating breast. One iodide ion is transported uphill against an iodide gradient, whereas two sodium ions move down the electrochemical gradient from the extracellular fluid into the thyroid cell. The energy source for this secondary active transporter is provided by a Na^+, K^+ -ATPase in the plasma membrane. Expression of the *NIS* gene is inhibited by iodide and stimulated by TSH (see later in the text). Numerous inflammatory

cytokines also suppress *NIS* gene expression. A reduction in dietary iodide intake depletes the circulating iodide pool and greatly enhances the activity of the iodide trap. When dietary iodide intake is low, the rates of thyroid uptake of iodide can reach 80% to 90%.

The steps in thyroid hormone synthesis are shown in Fig. 6.6 (f0035) . After entering the gland, iodide rapidly moves to the apical plasma membrane of the epithelial cells. From there, iodide is transported into the lumen of the follicles by a sodium-independent iodide-chloride transporter, named **pendrin** .

CLINICAL BOX 6.2

Pendred syndrome refers to a condition caused by an autosomal recessive mutation in the pendrin gene (referred to as *PDS* or *SLC26A4*). Because iodide is not efficiently transported into the follicular lumen, **hypothyroidism** develops in patients. Some patients exhibit enlarged thyroid glands called **goiters** . This form of hypothyroidism can be treated with replacement thyroxine. Unfortunately, pendrin is also expressed in the inner ear and is required for normal structural development of the inner ear. Thus patients with Pendred syndrome experience hearing loss in infancy or early childhood.

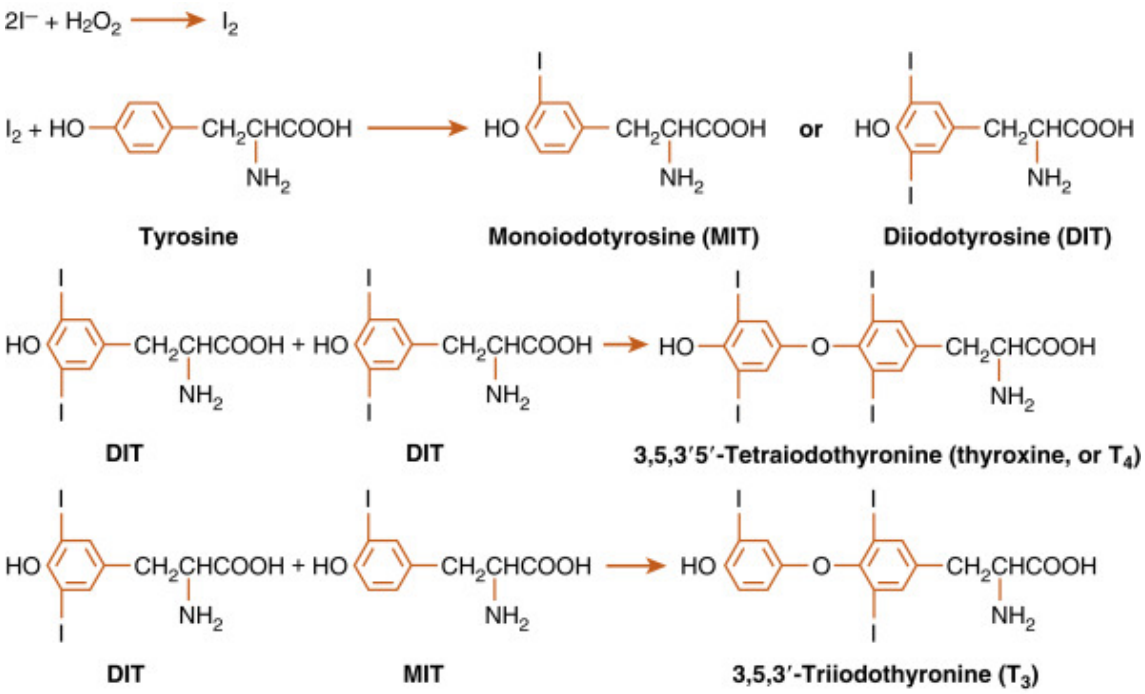

Fig. 6.6

Reactions involved in the generation of iodide, MIT, DIT, T_3 , and T_4 .

Once in the follicular lumen, iodide (I^-) is immediately oxidized and incorporated into tyrosine residues within the primary structure of thyroglobulin. Thyroglobulin is continually synthesized, exocytosed into the follicular lumen and iodinated to form either **monoiodotyrosine (MIT)** or **diiodotyrosine (DIT)** (see Fig. 6.6 (f0035)). After iodination, two DIT molecules are coupled to form T_4 , or one MIT and one DIT molecule are coupled to form T_3 . The coupling occurs between iodinated tyrosines that remain part of the

primary structure of thyroglobulin. This entire sequence of reactions is catalyzed by thyroid peroxidase (TPO), an enzyme complex that spans the apical membrane. The immediate oxidant (electron acceptor) for the reaction is hydrogen peroxide (H_2O_2). H_2O_2 is generated in the thyroid gland by an enzyme called dual oxidase (Duox) that is also localized to the apical membrane.

When iodide availability is restricted, the formation of T_3 is favored. This response provides more active hormone per molecule of organified iodide. The proportion of T_3 is also increased when the gland is hyperstimulated by TSH or other activators.

Secretion of Thyroid Hormones

After thyroglobulin has been iodinated, it is stored in the lumen of the follicle as colloid (see Fig. 6.2 (f0015)). Release of the T_4 and T_3 into the bloodstream requires endocytosis and lysosomal degradation of thyroglobulin (see Fig. 6.5 (f0030); *orange arrows*). Enzymatically released T_4 and T_3 then leave the basal side of the cell and enter the blood.

The MIT and DIT molecules, which also are released during proteolysis of thyroglobulin, are rapidly deiodinated within the follicular cell by an enzyme called **intrathyroidal deiodinase** (see Fig. 6.5 (f0030); *open arrows*). This deiodinase is specific for MIT and DIT and cannot use T_4 and T_3 as substrates. The iodide is then recycled into T_4 and T_3 synthesis. Amino acids from the digestion of thyroglobulin reenter the intrathyroidal amino acid pool and can be reused for protein synthesis. Only minor amounts of intact thyroglobulin leave the follicular cell under normal circumstances.

CLINICAL BOX 6.3

Because of its ability to **trap** and incorporate iodine into thyroglobulin (called **organification**), the activity of the thyroid can be assessed by **radioactive iodine uptake (RAIU)**. For this, a tracer dose of ^{123}I is administered, and the RAIU is measured by placing a gamma detector on the neck after 4 to 6 hours and after 24 hours. In the United States, where the diet is relatively rich in iodine, the RAIU is about 15% after 6 hours and 25% after 24 hours (Fig. 6.7 (f0040)). Abnormally high RAIU (> 60%) after 24 hours indicates hyperthyroidism. Abnormally low RAIU (< 5%) after 24 hours indicates hypothyroidism. In individuals with extreme chronic stimulation of the thyroid (Graves disease–associated thyrotoxicosis), iodide is trapped, organified, and released as hormone very rapidly. In these cases of elevated turnover, the 6-hour RAIU will be very high, but the 24-hour RAIU will be lower (Fig. 6.8 (f0045)). A number of anions, such as thiocyanate (SCN^-), perchlorate ($HClO_4^-$), and pertechnetate (TcO_4^-), are inhibitors of iodide transport through the NIS. If iodide cannot be rapidly incorporated into tyrosine (**organification defect**) after its uptake by the cell, administration of one of these anions will, by blocking further iodide uptake, cause a rapid release of the iodide from the gland (see Fig. 6.8 (f0045)). This release occurs as a result of the high thyroid-to-plasma concentration gradient of iodide.

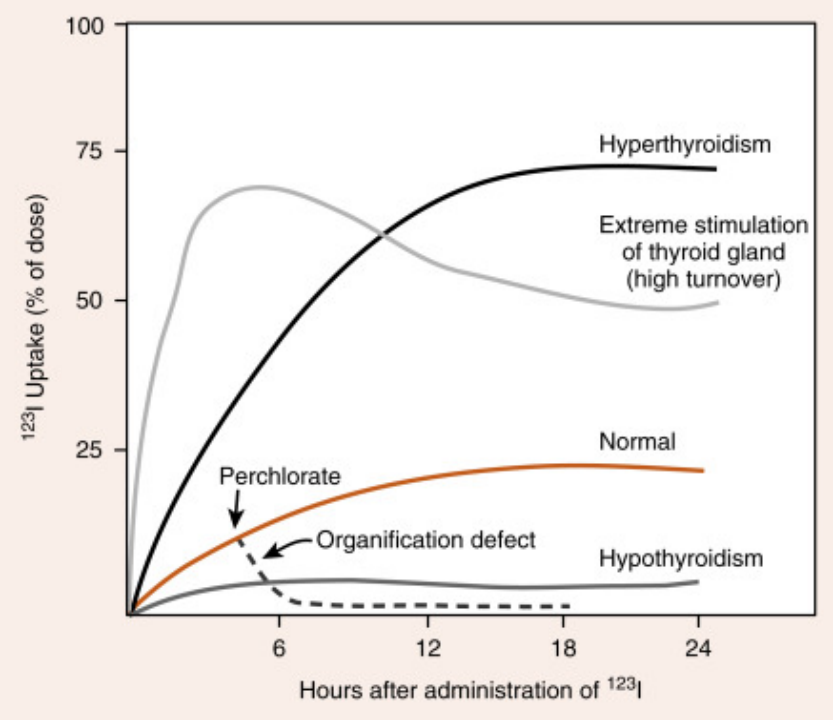

Fig. 6.7

Thyroid gland iodothyronine uptake curves for normal, hypothyroid, hyperthyroid, and organification defective states.

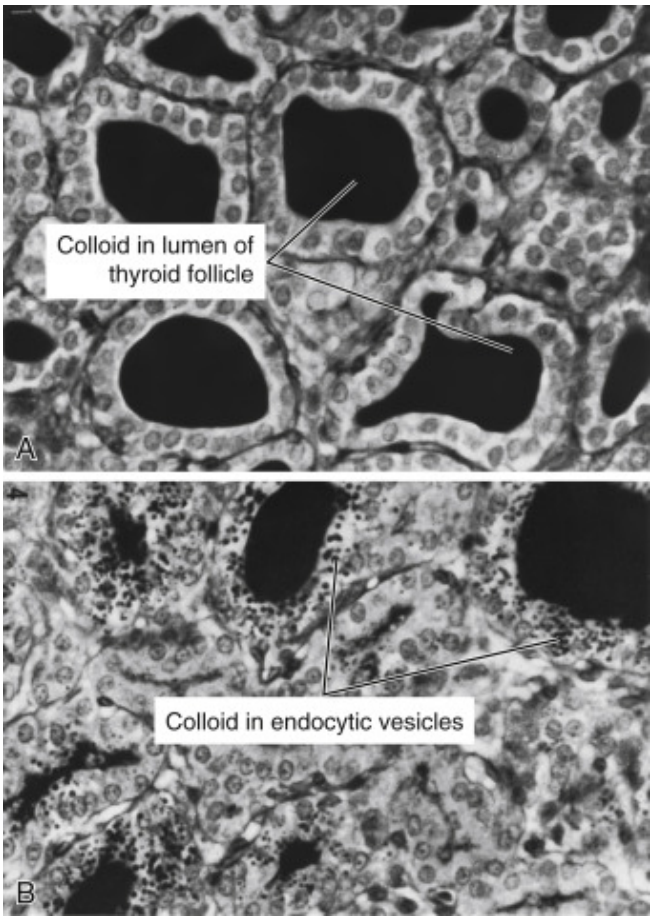

Fig. 6.8

Normal and hyperactive thyroid glands. Note the colloid present in the lumen of thyroid follicles in a normal thyroid gland (*top panel*). In hyperthyroidism, colloid is turning over rapidly, with many follicles depleted of colloid , which can be seen in endocytic vesicles within the follicular cells (*bottom panel*).

The thyroid can be imaged using the iodine isotopes ^{123} I or ^{131} I, or the iodine mimic, pertechnetate (^{99m} Tc), followed by imaging with a rectilinear scanner or gamma camera. Imaging can display the size and shape of the thyroid (see Fig. 6.1B (f0010)), as well as heterogeneities of active versus inactive tissue within the thyroid gland. Such heterogeneities are often due to the development of **thyroid nodules** , which are regions of enlarged follicles with evidence of regressive changes indicating cycles of stimulation and involution. So-called **hot nodules** (i.e., nodules that display a high RAIU on imaging) are usually not cancerous but may lead to thyrotoxicosis (hyperthyroidism; see later in the text.) Cold nodules are 10 times more likely to be cancerous than hot nodules. Such nodules can be sampled to assess for pathology by **fine-needle aspiration biopsy** .

The thyroid can also be imaged by **ultrasonography** , which is superior in resolution to RAIU imaging. Ultrasonography is used to guide the physician during fine-needle aspiration biopsy of a nodule. Highest resolution of the thyroid gland is achieved with **magnetic resonance imaging** .

Transport and Metabolism of Thyroid Hormones

Secreted T_4 and T_3 circulate in the bloodstream almost entirely bound to proteins. Normally, only about 0.04% of total plasma T_4 and 0.4% of total plasma T_3 exist in the free state (see Table 6.1 (t0010)). Free T_3 is biologically active and mediates thyroid hormone effects on peripheral tissues as well as in negative feedback on the pituitary and hypothalamic (see later). The major binding protein is **thyroxine-binding globulin (TBG)** . TBG is synthesized in the liver and binds one molecule of T_4 or T_3 .

About 70% of circulating T_4 and T_3 is bound to TBG; 10% to 15% is bound to another specific thyroid-binding protein, called **transthyretin (TTR)** . **Albumin** binds 15% to 20%, and 3% is bound to lipoproteins. Ordinarily, only alterations in TBG concentration significantly affect total plasma T_4 and T_3 levels. Two important biologic functions have been ascribed to TBG. First, it maintains a large circulating **reservoir** of T_4 that buffers any acute changes in thyroid gland function. Second, the binding of plasma T_4 and T_3 to proteins prevents the loss of these relatively small hormone molecules in the urine and thereby helps conserve iodide. TTR, in particular, provides thyroid hormones to the CNS.

CLINICAL BOX 6.4

There are several transporters that mediate thyroid hormone transport across cell membranes **Thyroid hormone transporters** include sodium taurocholate cotransporting polypeptide (NCTP), organic anion transporting polypeptide (OATP), L-type amino acid transporter (LAT), and the monocarboxylate transporters (MCT). These transporters show specificity with respect to T_4 versus T

$_3$ binding and cell-specific expression. MCT8 is required for neuronal uptake of thyroid hormones. Mutations in MCT8 are linked to severe psychomotor deficits (Allan-Herndon-Dudley syndrome) that cannot be treated with exogenous T_3 or T_4.

Regulation of Thyroid Function

The most important regulator of thyroid gland function and growth is the **hypothalamic-pituitary-thyroid axis** (see Chapter 5). TSH stimulates every aspect of thyroid function. TSH has early, intermediate, and long-term actions on the thyroid epithelium. Immediate actions of TSH involve induction of pseudopod extension, endocytosis of colloid, and formation of colloid droplets in the cytoplasm, which represent thyroglobulin within endocytic vesicles. Shortly thereafter, iodide uptake and TPO activity increase. Concurrently, TSH stimulates glucose entry into the hexose monophosphate shunt pathway, which generates the NADPH that is needed for the peroxidase reaction. TSH also stimulates the proteolysis of thyroglobulin and the release of T_4 and T_3 from the gland. Intermediate effects of TSH on the thyroid gland occur after a delay of hours to days and involve protein synthesis and the expression of numerous genes, including those encoding NIS, thyroglobulin, and TPO. Sustained TSH stimulation leads to the long-term effects of hypertrophy and hyperplasia of the follicular cells. Capillaries proliferate, and thyroid blood flow increases. These actions, which underlie the growth-promoting effects of TSH on the gland, are supported by the local production of growth factors. A noticeably enlarged thyroid gland is called a **goiter** .

CLINICAL BOX 6.5

Goiter can develop in response to multiple imbalances and disease within the hypothalamus-pituitary-thyroid axis, occurring in the context of a hypothyroid, euthyroid (normal), or hyperthyroid status. These imbalances include the following elements:

Primary Hypothyroidism

- Lack of adequate iodine in the diet (nontoxic goiter, endemic goiter)
- Benign nodules or mutation of growth-related gene (nontoxic goiter)
- Sporadic hypothyroidism of unknown etiology (nontoxic goiter)
- Chronic thyroiditis (Hashimoto disease; autoimmune-induced deficiency in thyroid function)

Hyperthyroidism

- Excessive stimulation of the TSH receptor by an autoantibody (Graves disease)
- Excessive secretion of TSH from a TSH-producing tumor (i.e., secondary hyperthyroidism)
- Thyroid hormone–producing (toxic) adenoma (nodular) or toxic multinodular goiter
- An inactivating mutation in thyroid receptor β-2 (TRβ2; see later)

The regulation of thyroid hormone secretion by TSH is under exquisite negative feedback control. Circulating thyroid hormones act on the pituitary gland to decrease TSH secretion, primarily by repressing TSHβ subunit gene expression. The pituitary gland expresses the high-affinity type 2 deiodinase. Thus small changes in free T_4 in the blood result in significant changes in intracellular T_3 in the pituitary thyrotrope. Because the diurnal variation of TSH secretion is small, thyroid hormone secretion and plasma concentrations are relatively constant. Only small nocturnal increases in secretion of TSH and release of T_4 occur. Thyroid hormones also feed back on the hypothalamic TRH-secreting neurons. In these neurons, T_3 inhibits the expression of the prepro- *TRH* gene.

Another important regulator of thyroid gland function is iodide itself, which has a biphasic action. At relatively low levels of iodide intake, the rate of thyroid hormone synthesis is directly related to iodide availability. However, if the intake of iodide exceeds 2 mg/day, the intraglandular concentration of iodide reaches a level that suppresses Duox activity and the *NIS* and *TPO* genes, and thereby the mechanism of hormone biosynthesis. This autoregulatory phenomenon is known as the **Wolff-Chaikoff effect** . As the intrathyroidal iodide level subsequently falls, *NIS* and *TPO* genes are de-repressed, and the production of thyroid hormone returns to normal. In unusual instances, the inhibition of hormone synthesis by iodide can be great enough to induce thyroid hormone deficiency. The temporary reduction in hormone synthesis by excess iodide can also be used therapeutically in hyperthyroidism, especially before thyroid surgery to prevent **thyroid storm** (thyrotoxicosis) during the procedure.

Thyroid hormones increase oxygen use, energy expenditure, and heat production. Therefore it is logical to expect that the availability of active thyroid hormone correlates with changes in the body's caloric and thermal status. In fact, ingestion of excess calories, particularly in the form of carbohydrate, increases the production and plasma concentration of T_3 as well as the individual's metabolic rate. On the other hand, serious illness, injury or starvation leads to inactivation of thyroid hormone by type 3 deiodinase, outer-ring deiodinase activity declines. Moreover, central input depresses the function of the thyroid hormone axis, causing TSH levels to drop below those expected given the reduced level circulating thyroid hormones. This has been termed *nonthyroidal illness syndrome* or *sick euthyroid syndrome* , because this does not reflect thyroid pathology, but represents an adaptation to illness or injury allowing energy to be conserved for fighting infection, to support reparative processes, or to prolong the availability of nutrients.

CLINICAL BOX 6.6

Graves disease represents the most common form of hyperthyroidism; it occurs most frequently between the ages of 20 and 50 years and is 10 times more common in women than in men. Graves disease is an autoimmune disorder in which autoantibodies are produced against the TSH receptor. The nature of specific autoantibodies depends on the epitope that they are directed against. The most critical type is called the **thyroid-stimulating immunoglobulin (TSI)** . The hyperthyroidism is often accompanied by a diffuse goiter due to hyperplasia and hypertrophy of the gland. The follicular epithelial cells become tall columnar cells, and the colloid shows a scalloped periphery indicative of rapid turnover.

The primary clinical state found in Graves disease is **thyrotoxicosis** —the state of excessive thyroid hormone in the blood and tissues. The patient with thyrotoxicosis presents one of the most striking pictures in clinical medicine. The large increase in metabolic rate is accompanied by the highly characteristic symptom of weight loss despite an increased intake of food. The increased heat production causes discomfort in warm environments, excessive sweating, and a greater intake of water. The increase in adrenergic activity is manifested by a rapid heart rate, palpitations, hyperkinesis, tremor, anxiety, and irritability. Weakness is caused by a loss of muscle mass as well as by an impairment of muscle function. Other symptoms include a labile emotional state, breathlessness during exercise, and difficulty in swallowing or breathing due to compression of the esophagus or trachea by the enlarged thyroid gland (goiter). The most common cardiovascular sign is sinus tachycardia. There is an increased cardiac output associated with widened pulse pressure due to a positive inotropic effect coupled with a decrease in vascular resistance. Major clinical signs in Graves disease are **exophthalmos** (abnormal protrusion of the eyeball; Fig. 6.9 (f0050)) and **periorbital edema** due to recognition by the anti-TSH receptor antibodies of a similar epitope within the orbital fibroblasts.

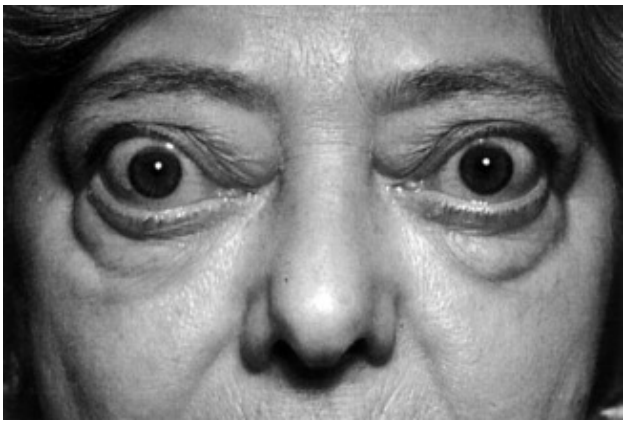

Fig. 6.9
Severe exophthalmos of Graves disease. Note lid retraction, periorbital edema, and proptosis.
From Hall R, Evered DC: *Color Atlas of Endocrinology,* 2nd ed., London, 1990, Mosby-Wolfe.

Graves disease is diagnosed by an elevated serum free and total T_4 or T_3 level (i.e., thyrotoxicosis) and the clinical signs of diffuse goiter and ophthalmopathy. In most cases, the thyroid uptake of iodine or pertechnetate is excessive and diffuse. Serum TSH levels are low, because the hypothalamus and the pituitary gland are inhibited by the high levels of T_4 and T_3. Assaying TSH levels, and for the presence of circulating TSI, will distinguish Graves disease (a primary endocrine disorder) from a rare adenoma of the pituitary thyrotrophs (a secondary endocrine disease). The latter etiology generates elevated TSH levels unaccompanied by TSI.

Treatment of Graves disease is usually removal of the thyroid tissue, followed by lifelong replacement therapy with T_4. Thyroid tissue can be ablated by either the radiation effects of ^{131}I or by surgery. Surgical removal of the gland rarely but potentially precipitates a massive release of hormone, causing

a thyroid storm, which causes potentially life-threatening tachycardia, arrhythmia, and heart failure. An alternative to removal of thyroid tissue is administration of **antithyroid drugs** that inhibit TPO activity.

Mechanism of Thyroid Hormone Action

Free T_4 and T_3 enter cells by a carrier-mediated, energy-dependent process. The transport of T_4 is rate limiting for the intracellular production of T_3. Within the cell, most, if not all, of the T_4 is converted to T_3 (or rT_3). Many of the T_3 actions are mediated through its binding one of members of the **thyroid hormone receptor (TR) family**. The TR family belongs to the nuclear hormone receptor superfamily of transcription factors. TRs bind to a specific DNA sequence, termed a thyroid-response element (TRE), usually as a heterodimer with retinoid X receptor (RXR). As discussed in Chapter 1, gene activation by T_3 involves (1) the unliganded TR/RXR bound to a TRE and recruiting corepressor proteins that deacetylate DNA in the vicinity of the regulated gene; (2) binding of T_3 and the dissociation of corepressor proteins; and (3) recruitment of coactivator proteins that, in part, acetylate DNA and activate the gene in question (see Fig. 1.24 in Chapter 1). However, T_3 also represses gene expression, indicating that other mechanisms exist, probably in a cell type–specific and gene-specific manner.

In humans, there are two TR genes, *THRA* and *THRB* **,** located on chromosomes 17 and 3, respectively, that encode the classic nuclear thyroid hormone receptors. THRA encodes **TRα,** which is alternatively spliced to form two main isoforms. **TRα1** is a bona fide TR, whereas the other isoform does not bind T_3. THRB encodes **TRβ1** and **TRβ2,** both of which are high-affinity receptors for T_3. The tissue distribution of TRα1 and TRβ1 is widespread. TRα1 is especially expressed in cardiac and skeletal muscle, and TRα1 is the dominant TR that transduces thyroid hormone actions on the heart. By contrast, TRβ1 is expressed more in the brain, liver, and kidneys. TRβ2 expression is restricted to the pituitary and critical areas of the hypothalamus, as well as the cochlea and retina. T_3-bound TRβ2 is responsible for inhibiting the expression of the prepro- *TRH* gene in the paraventricular neurons of the hypothalamus and of the β-subunit *TSH* gene in pituitary thyrotropes. Thus negative feedback effects of thyroid hormone on both TRH and TSH secretion are largely mediated by TRβ2. T_3 also downregulates *TRβ2* gene expression in the pituitary gland.

CLINICAL BOX 6.7

An understanding of TR subtypes and tissue expression is of more than academic interest because inactivating mutant genes have been found increasingly to be causes of clinical syndromes manifested by **resistance to thyroid hormone (RTH) syndrome**. The most common mutations occur in the pituitary-hypothalamus-specific TRβ2 subtype. In these patients, there is incomplete negative thyroid hormone feedback at the hypothalamic-pituitary level. Thus T_4 levels are elevated, but TSH is not suppressed. When the resistance is purely at the hypothalamic-pituitary level, the patient may exhibit

signs of hyperthyroidism due to excess effects of high thyroid hormone levels on peripheral tissue, particularly on the heart through TRα1. These individuals have clinical signs such as goiter, short stature, decreased weight, tachycardia, hearing loss, monochromatic vision, and decreased IQ.

As an additional example, the beneficial effect of thyroid hormones on the serum lipoprotein profile have been attributed to TRβ2 actions in the liver. There has therefore been ongoing interest in TRβ2 as a potential therapeutic target for development of TRβ2-specific ligands as a means to prevent atherosclerosis and cardiovascular disease.

Physiologic Effects of Thyroid Hormone

Thyroid hormone acts on essentially all cells and tissues, and imbalances in thyroid function represent one of the most common endocrine diseases. Thyroid hormone has many direct actions, but it also acts in subtle ways to optimize the actions of several other hormones and neurotransmitters. One way to categorize the most prevalent actions of thyroid hormone is to recall the 4 Bs: brain, bone, BMR and β-adrenergic—referring to CNS development, skeletal development, basal metabolic rate, and sympathomimetic actions on the cardiovascular system.

Cardiovascular Effects

Perhaps the most clinically important actions of thyroid hormone are those on cardiovascular physiology. T_3 increases cardiac output, ensuring sufficient oxygen delivery to the tissues (Fig. 6.10 (f0055)). The resting heart rate and the stroke volume are increased. The speed and force of myocardial contractions are enhanced (positive chronotropic and inotropic effects, respectively), and the diastolic relaxation time is shortened (positive lusitropic effect). Systolic blood pressure is modestly augmented, and diastolic blood pressure is decreased. The resultant widened pulse pressure reflects the combined effects of the increased stroke volume and the reduction in total peripheral vascular resistance that result from blood vessel dilation in skin, muscle, and heart. These effects in turn are partly secondary to the increase in tissue production of heat and metabolites that thyroid hormone induces (see later). In addition, however, thyroid hormone decreases systemic vascular resistance by dilating resistance arterioles in the peripheral circulation. Total blood volume is increased by activating the renin-angiotensin-aldosterone axis and thereby increasing renal tubular sodium reabsorption (see Chapter 7).

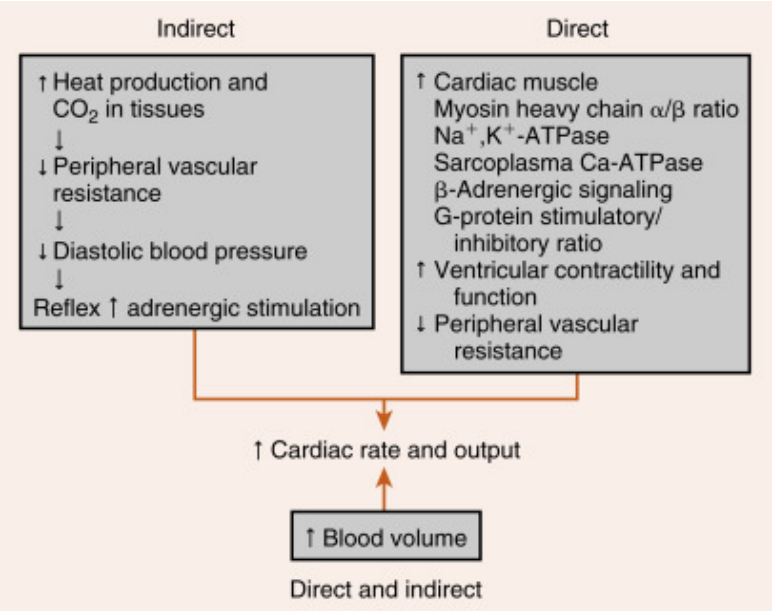

Fig. 6.10

Mechanisms by which thyroid hormone increases cardiac output. The indirect mechanisms are probably quantitatively more important.

The cardiac inotropic effects of T_3 are both direct (Fig. 6.11 (f0060)) and indirect, through enhanced responsiveness to catecholamines (see Chapter 7). Myocardial calcium uptake is increased, which enhances contractile force. Thyroid hormone inhibits expression of the **Na-Ca antiporter,** thereby increasing intramyocellular Ca^{2+} concentrations. T_3 increases the velocity and strength of myocardial contraction. T_3 promotes the expression of the faster and stronger α-isoform and represses the slower, weaker β-isoform of cardiac myosin heavy chain. T_3 also increases the **ryanodine Ca^{2+} channels** in the sarcoplasmic reticulum, promoting Ca^{2+} release from the sarcoplasmic reticulum during systole. The **calcium adenosine triphosphatase (ATPase) of the sarcoplasmic reticulum (SERCA)** is increased by T_3, which facilitates sequestration of calcium during diastole and shortens the relaxation time.

CLINICAL BOX 6.8

Thyroid hormone levels in the normal range are necessary for optimal cardiac performance. **Hypothyroidism** in humans reduces stroke volume, left ventricular ejection fraction, cardiac output, and the efficiency of cardiac function. The latter defect is shown by the fact that the stroke work index [(stroke volume/left ventricular mass) × peak systolic blood pressure] is decreased even more than is myocardial oxidative metabolism. The rise in systemic vascular resistance may contribute to this cardiac debility. On the other hand, **hyperthyroidism** increases cardiac output and reduces peripheral resistance, generating a widened pulse pressure. T_3 increases UCP2 and UCP3 in cardiac muscle, which uncouples ATP production from oxygen use during the β-oxidation of free fatty acids. This can cause high-output cardiac failure. When hyperthyroidism develops in aging individuals, the cardiac effects of thyroid hormone may include rapid atrial arrhythmias, flutter, and fibrillation.

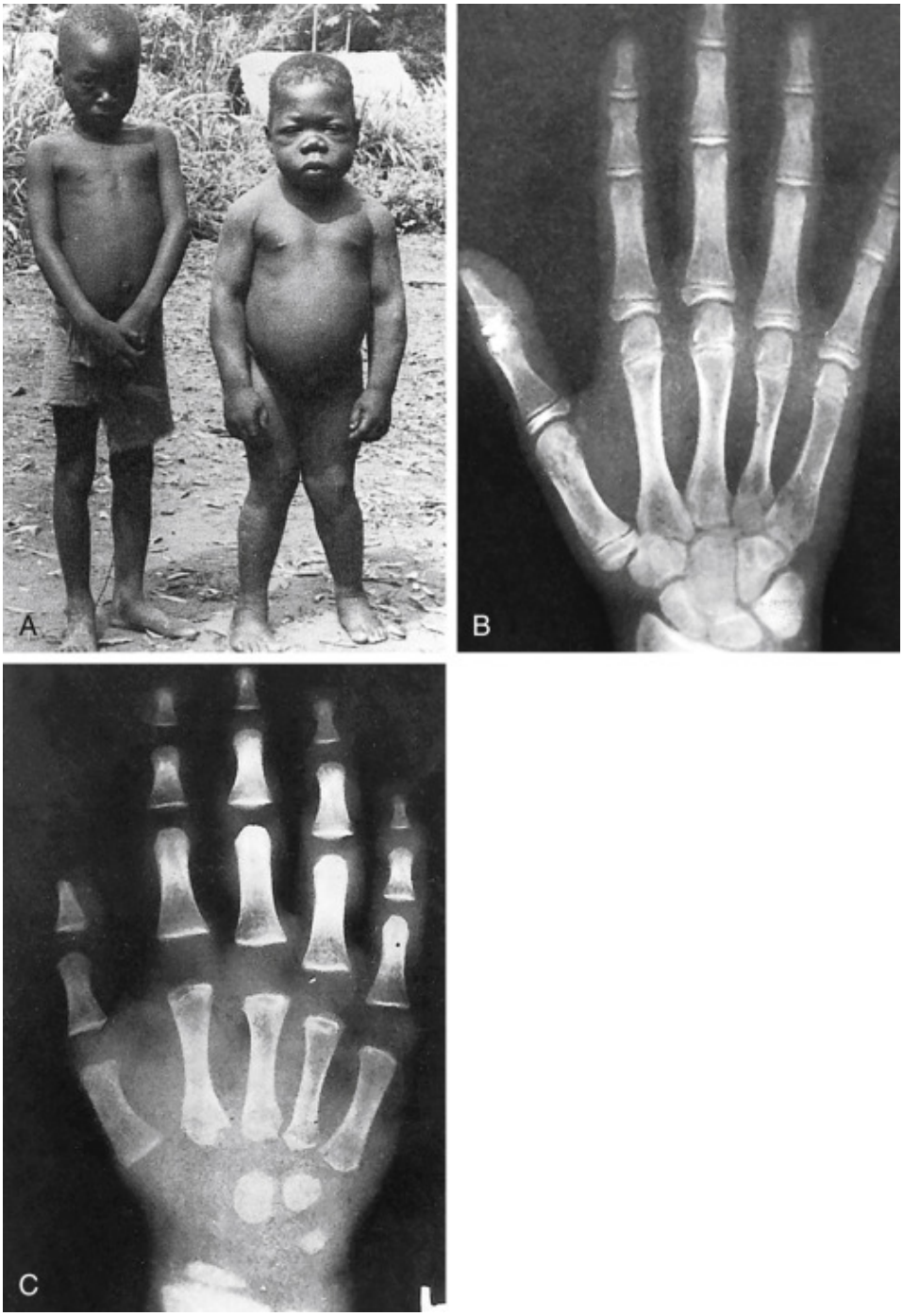

Fig. 6.11

(A) A normal 6-year-old child *(left)* and a congenitally hypothyroid 17-year-old child *(right)* from the same village in an area of endemic hypothyroidism. Note especially the short stature, obesity, malformed legs, and dull expression of the hypothyroid child. Other features are a prominent abdomen, a flat and broad nose, a hypoplastic mandible, dry and scaly skin, delayed puberty, muscle weakness and cognitive disability. Hand radiographs of a 13-year-old normal child (B) and a 13-year-old hypothyroid child (C). Note that the hypothyroid child has a marked delay in development of the small bones of the hands, in ossification centers at either end of the fingers, and in the ossification center of the distal end of the radius. A **,** From Delange FM: Endemic cretinism. In Braverman LE, Utiger RD, editors: *Werner and Ingbar's the Thyroid,* 7th ed., Philadelphia, 1996, Lippincott-Raven. B **,** From Tanner JM, Whitehouse RH, Marshall WA, et al: *Assessment of Skeletal Maturity and Prediction of Adult Height (TW2 method),* New York, 1975, Academic Press. C **,** From Andersen HJ:

Nongoitrous hypothyroidism. In Gardner LI, editor: *Endocrine and Genetic Diseases of Childhood and Adolescence,* Philadelphia, 1975, Saunders.

Effects on Basal Metabolic Rate

Thyroid hormones increase the basal metabolic rate (BMR), defined as the basal rate of oxygen consumption and heat production. A deficiency in thyroid hormone availability causes cold intolerance, whereas hyperthyroidism is associated with heat intolerance associated with compensatory increases in heat loss through thyroid hormone–mediated increases in **blood flow** , **sweating** , and **ventilation** . Thyroid hormone–regulated thermogenesis occurs primarily in skeletal muscle, which represents 30% to 40% of body mass, and in brown fat. The best understood mechanism occurs in brown fat, where expression of the type 2 deiodinase is upregulated by adrenergic stimulation, leading to increased generation of T_3 . Thyroid hormone, in turn, stimulates expression of uncoupling protein-1 (UCP1), which uncouples the mitochondrial proton gradient from ATP production, with the energy stored in the gradient dissipated as heat. Recent studies have demonstrated that adult humans have more brown fat than previously recognized, but the relative contribution of brown fat to thermogenesis in adult humans remains unclear. In skeletal muscle, multiple mechanisms of thyroid hormone–induced thermogenesis have been proposed, including maintenance of the sodium gradient by the Na/K ATPase, increased calcium pumping by SERCA, and uncoupling of ATP production in mitochondria. Thyroid hormone increases expression of SERCA in skeletal muscle and increases expression of the UCP1 homologue UCP3 in skeletal muscle. However, the precise role of UCP3 in skeletal muscle thermogenesis remains to be determined.

Increased oxygen use ultimately depends on an increased supply of substrates for oxidation. T_3 augments glucose absorption from the gastrointestinal tract and increases glucose turnover (glucose uptake, oxidation, and synthesis). In adipose tissue, thyroid hormone enhances lipolysis by increasing the number of β-adrenergic receptors (see later in the text). Thyroid hormone also enhances clearance of chylomicrons. Thus lipid turnover (free fatty acid release from adipose tissue and oxidation) is augmented in hyperthyroidism.

Protein turnover (release of muscle amino acids, protein degradation, and to a lesser extent, protein synthesis and urea formation) is also increased by thyroid hormones. T_3 potentiates the respective stimulatory effects of epinephrine, norepinephrine, glucagon, cortisol, and growth hormone on gluconeogenesis, lipolysis, ketogenesis, and proteolysis of the labile protein pool. The overall metabolic effect of thyroid hormone has been aptly described as accelerating the response to starvation.

T_3 regulates lipoprotein metabolism and cholesterol synthesis and clearance. Hypothyroidism is associated with an increase in TG-rich lipoproteins and low-density lipoprotein and a decrease in high-density lipoproteins.

The metabolic clearance of adrenal and gonadal steroid hormones, some B vitamins, and some administered drugs is also increased by thyroid hormone.

Respiratory Effects

T_3 stimulates oxygen use and also enhances oxygen supply. Appropriately, T_3 increases the **resting respiratory rate, minute ventilation** , and the **ventilatory responses** to hypercapnia and hypoxia. These actions maintain a normal arterial P_{O_2} when O_2 use is increased, and a normal P_{CO_2} when CO_2 production is increased. T_3 promotes erythropoietin production, hemoglobin synthesis, and absorption of folate and vitamin B_{12} from the gastrointestinal tract. Hypothyroidism in women is also associated with loss of iron due to excessive uterine bleeding (menorrhagia; see later). Thus hypothyroidism may be accompanied by various types of **anemia** .

Skeletal Muscle Function

Normal function of skeletal muscles also requires optimal amounts of thyroid hormone. This requirement may also be related to the regulation of energy production and storage. In hyperthyroidism, glycolysis and glycogenolysis are increased, and glycogen and creatine phosphate are reduced. The inability of muscle to take up and phosphorylate creatine leads to increased urinary excretion of creatine. Muscle pain and weakness can occur in both hypothyroidism and hyperthyroidism.

Effects on the Autonomic Nervous System and Catecholamine Action

There is synergism between catecholamines and thyroid hormones. Thyroid hormones are synergistic with catecholamines in increasing metabolic rate, heat production, heart rate, motor activity, and CNS excitation. T_3 enhances sympathetic nervous system activity by increasing the number of β-adrenergic receptors in heart muscle and by increasing the generation of intracellular second messengers, such as cyclic adenosine monophosphate (cAMP).

Effects on Growth and Maturation

Another major effect of thyroid hormone is to promote growth and maturation. A small but crucial amount of thyroid hormone crosses the placenta, and the fetal thyroid axis becomes functional at midgestation. Thyroid hormone is extremely important for normal neurologic development and for proper bone formation in the fetus. Insufficient fetal thyroid hormone causes **congenital hypothyroidism** (formerly known as *cretinism*) in the infant, characterized by irreversible mental retardation and short stature.

Effects on Bone, Hard Tissues, and Dermis

Thyroid hormone stimulates endochondral ossification, linear growth of bone, and maturation of the epiphyseal bone centers. T_3 enhances the maturation and activity of chondrocytes in the cartilage growth plate, in part by increasing local growth factor production and action. Although thyroid hormone is not required for linear growth until after birth, it is essential for normal maturation of growth centers in the bones of the developing fetus. T_3 also stimulates adult bone remodeling.

The progression of tooth development and eruption depends on thyroid hormone, as does the normal cycle of growth and maturation of the epidermis, its hair follicles, and nails. The normal degradative processes in these structural and integumentary tissues are also stimulated by thyroid hormone. Thus either too much or too little thyroid hormone can lead to hair loss and abnormal nail formation.

Thyroid hormone alters the structure of subcutaneous tissue by inhibiting the synthesis, and increasing the degradation, of mucopolysaccharides (glycosaminoglycans) and fibronectin in the extracellular connective tissue. In hypothyroidism, the skin is thickened, cool, and dry, and the face becomes puffy because of the accumulation of subcutaneous glycosaminoglycans and other matrix molecules (**myxedema**).

Effects on the Nervous System

Thyroid hormone regulates the timing and pace of CNS development. Thyroid hormone deficiency in utero and in early infancy decreases growth of the cerebral and cerebellar cortex, proliferation of axons, branching of dendrites, synaptogenesis, myelinization, and cell migration. Irreversible brain damage results when thyroid hormone deficiency is not recognized and treated promptly after birth. The structural defects described earlier are paralleled by biochemical abnormalities. Decreased thyroid hormone levels reduce: cell size; RNA and protein content; tubulin- and microtubule-associated protein; protein and lipid content of myelin; local production of critical growth factors; and the rates of protein synthesis.

Thyroid hormone also enhances wakefulness, alertness, responsiveness to various stimuli, auditory sense, awareness of hunger, memory, and learning capacity. Normal emotional tone also depends on proper thyroid hormone availability. Furthermore, the speed and amplitude of peripheral nerve reflexes are increased by thyroid hormone, as is the motility of the gastrointestinal tract.

CLINICAL BOX 6.9

Hypothyroidism in the fetus or early childhood leads to congenital hypothyroidism. Affected individuals present with severe intellectual disability, short stature with incomplete skeletal development (see Fig. 6.11 (f0060)), coarse facial features, and a protruding tongue. The most common cause of hypothyroidism in children is iodide deficiency. Iodide is not plentiful in the environment, and deficiency of iodide is a major cause of hypothyroidism in certain mountainous regions of South America, Africa, and Asia as well as in some developed countries. This tragic form of **hypothyroidism** can be easily prevented by public health programs that add iodide to table salt or that provide yearly injections of a slowly absorbed iodide preparation. **Congenital defects** are a less common cause of neonatal and childhood hypothyroidism. In most cases, the thyroid gland simply does not develop (**thyroid gland dysgenesis**). Less frequent causes of childhood hypothyroidism are mutations in genes involved in thyroid hormone production (e.g., genes for NIS, TPO, thyroglobulin, and pendrin) and blocking antibodies to the TSH receptor (see later). The severity of neurologic and skeletal defects is closely linked to the time of diagnosis and replacement treatment with thyroid hormone (T_4), with early treatment resulting in normal cognitive ability and subtle neurologic deficits. Hypothyroid babies usually appear normal at birth because of maternal thyroid hormones. However, in geographic areas of endemic iodide deficiency, the mother may be hypothyroid and unable to make up for the fetal defects. **Neonatal screening** (T_4 or TSH levels) has played a major role in the detection and prevention of severe congenital hypothyroidism. If hypothyroidism at birth remains untreated for only 2 to 4 weeks, the central nervous system will not develop normally in the first year of life. Developmental milestones, such as sitting, standing, and walking, will be late, and severe irreversible cognitive disabilities can result.

Effects on Reproductive Organs and Endocrine Glands

In both women and men, thyroid hormone plays an important, permissive role in the regulation of reproductive function. The normal ovarian cycle of follicular development, maturation, and ovulation; the homologous testicular process of spermatogenesis; and the maintenance of the healthy pregnant state are all disrupted by significant deviations of thyroid hormone levels from the normal range. In part, these deleterious effects may be caused by alterations in the metabolism or availability of steroid hormones. For example, thyroid hormone stimulates hepatic synthesis and release of sex steroid–binding globulin.

Thyroid hormone also has significant effects on other parts of the endocrine system. Pituitary production of growth hormone is increased by thyroid hormone, whereas that of prolactin is decreased. Adrenocortical secretion of cortisol (see Chapter 7), as well as the metabolic clearance of this hormone, is stimulated, but plasma free cortisol levels remain normal. The ratio of estrogens to androgens (see Chapter 9) is increased in men (in whom breast enlargement may occur with hyperthyroidism). Decreases in both parathyroid hormone and in 1,25-dihydroxyvitamin D production are compensatory consequences of the effects of thyroid hormone on bone resorption (see Chapter 4).

Kidney size, renal plasma flow, glomerular filtration rate, and transport rates for a number of substances are also increased by thyroid hormone.

CLINICAL BOX 6.10

Hypothyroidism in adults who do not have iodide deficiency most often results from idiopathic atrophy of the gland, which is thought to be preceded by a chronic autoimmune inflammatory reaction. In this form of **lymphocytic (Hashimoto) thyroiditis** , the antibodies that are produced may block hormone synthesis or thyroid gland growth, or they may have cytotoxic effects. Other causes of hypothyroidism include iatrogenic causes (e.g., radiochemical damage or surgical removal for treatment of hyperthyroidism), nodular goiters, and pituitary or hypothalamic disease.

The clinical picture of hypothyroidism in adults is in many respects the exact opposite of that seen in hyperthyroidism. The lower-than-normal metabolic rate leads to weight gain without an appreciable increase in caloric intake. The decreased thermogenesis lowers body temperature and causes intolerance to cold, decreased sweating, and dry skin. Adrenergic activity is decreased, and therefore bradycardia may occur. Movement, speech, and thought are all slowed, and lethargy, sleepiness, and a lowering of the upper eyelids (ptosis) occur. An accumulation of mucopolysaccharides—extracellular matrix—in the tissues also causes an accumulation of fluid. This nonpitting **myxedema** produces puffy features (Fig. 6.12 (f0065)): an enlarged tongue; hoarseness; joint stiffness; effusions in the pleural, pericardial, and peritoneal spaces; and pressure on peripheral and cranial nerves, entrapped by excess ground substance. Constipation, loss of hair, menstrual dysfunction, and anemia are other symptoms. In adults lacking thyroid hormone, positron emission tomography demonstrates a generalized reduction in cerebral blood flow and glucose metabolism. This abnormality may explain the psychomotor impairment and depressed affect exhibited by hypothyroid individuals.

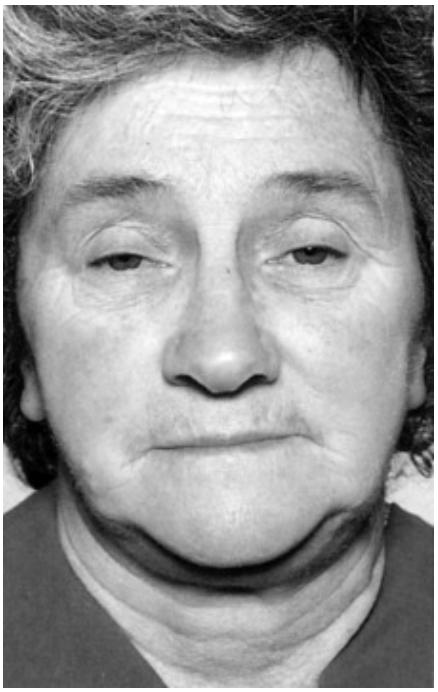

Fig. 6.12
Adult hypothyroidism. Note puffy face, puffy eyes, frowzy hair, and dull, apathetic appearance.
From Hall R, Evered DC: *Color Atlas of Endocrinology,* 2nd ed., London, 1990, Mosby-Wolfe.

Replacement therapy with T_4 is the standard of care in adults who require thyroid replacement therapy. Generally, T_3 is not needed because it will be generated by deiodinases from the administered T_4. Furthermore, due to the short half-life of T_3, more frequent dosing is required, making it is challenging to maintain constant physiologic levels of active hormone. Nevertheless, studies are ongoing to determine whether there may be a subset of patients who would benefit from replacement with a combination of T_3 and T_4.

Summary

1. The thyroid gland is situated in the ventral neck, composed of right and left lobes anterolateral to the trachea and connected by an isthmus.

2. The thyroid gland is the source of tetraiodothyronine (thyroxine, T_4) and triiodothyronine (T_3).

3. The basic endocrine unit in the gland is a follicle that consists of a single spherical layer of epithelial cells surrounding a central lumen that contains colloid or stored hormone.

4. Iodide is taken up into thyroid cells by a sodium iodide symporter in the basolateral plasma membrane.

5. T_4 and T_3 are synthesized from tyrosine and iodide by the enzyme complex, thyroid peroxidase. Tyrosine is incorporated in peptide linkages within the protein thyroglobulin. After iodination, two iodotyrosine molecules are coupled to yield the iodothyronines.

6. Secretion of stored T_4 and T_3 requires retrieval of thyroglobulin from the follicle lumen by endocytosis. To support hormone synthesis, iodide is conserved by recycling the iodotyrosine molecules that escape coupling within thyroglobulin.

7. More than 99.5% of the T_4 and T_3 circulates bound to the following proteins: thyroid-binding globulin (TBG), transthyretin, and albumin. Only the free fractions of T_4 and T_3 are biologically active.

8. T_4 functions as a prohormone whose disposition is regulated by three types of deiodinases. Monodeiodination of the outer ring yields 75% of the daily production of T_3, which is the principal active hormone. Alternatively, monodeiodination of the inner ring yields reverse T_3, which is biologically inactive. Proportioning of T_4 between T_3 and reverse T_3 regulates the availability of active thyroid hormone.

9. Thyroid-stimulating hormone (TSH; thyrotropin) acts on the thyroid gland through its plasma membrane receptor and cAMP to stimulate all steps in the production of T_4 and T_3. These steps include iodide uptake, iodination and coupling, and retrieval from thyroglobulin. TSH also stimulates glucose oxidation, protein synthesis, and growth of thyroid epithelial cells.

10. TSH is increased by hypothalamic TRH. T_3 negatively feeds back on TSH and, to a lesser extent, TRH.

11. T_3 binds to thyroid hormone receptor (TR) subtypes that exist linked to thyroid regulatory elements (TREs) in target DNA molecules. As a result, induction or repression of gene expression increases or decreases a large number of enzymes, as well as structural and functional proteins.

12. Thyroid hormone increases and is a major regulator of the basal metabolic rate. Additional important actions of thyroid hormone are to increase heart rate, cardiac output, and ventilation, and to decrease peripheral resistance. The corresponding increase in heat production leads to increased sweating. Substrate mobilization and disposal of metabolic products are enhanced. As part of normal cardiopulmonary function, T_3 is required for erythrocyte production and function.

13. T_3 is absolutely required for normal development and function of the CNS. In the absence of the hormone, as in congenital hypothyroidism, brain development and cognitive ability may be severely impaired. In the adult, T_3 optimizes normal brain function. Hypothyroidism and hyperthyroidism can cause erratic behavior and depression.

14. T_3 also regulates skeletal development and is crucial to normal growth. In hypothyroidism, growth is retarded and the bones fail to mature. In adults, T_3 increases the rates of bone resorption and

degradation of skin and hair. T_3 is required for normal muscle function and normal integrity of the skin, nails, and hair.

15. T_3 regulates several organs within the endocrine system. T_3 is required for normal reproductive function, including fertility, normal menstrual cycling and blood loss, ovulation, spermatogenesis, and erectile function.

Self-Study Problems

1. Explain how the thyroid status of a patient presenting with a goiter can be hyperthyroid, hypothyroid, or euthyroid.

2. Explain how a thyroid hormone receptor mutation can result in a deficiency in cardiac function without any change in TSH.

3. Draw predicted radioactive iodine uptake (RAIU) curves that would be associated with inactivating mutations of the following genes compared with normal:

a. TSH-R

b. Thyroid peroxidase

c. NIS

4. Why do serum T_4 levels approximately double in pregnancy? Are pregnant women hyperthyroid?

5. Describe the peripheral transport and metabolism of T_4 and its importance in maintaining a euthyroid state.

6. Explain how a patient's thyroid status may be altered when battling a severe illness.

7. How does T_3 affect cardiac function?

8. Why is it critically important to screen thyroid function in newborn infants?

Keywords and Concepts

Basal metabolic rate (BMR)

Colloid

Congenital hypothyroidism

Diiodotyrosine (DIT)

Euthyroid

Exophthalmos

Extrathyroidal pools

Follicular cells

Glycosaminoglycan (GAG)

Goiter

Graves disease

Hashimoto thyroiditis

Hyperthyroid

Hypothyroid

Iodide

Iodide trap

Iodothyronine

Iodotyrosine

Monoiodotyrosine (MIT)

Myxedema

Organification

Radioactive iodide uptake (RAIU)

Reverse T_3 (rT_3)

Subacute thyroiditis

Thyroglobulin (TG)

Thyroid peroxidase (TPO)

Thyroid-responsive element

Thyrotropin, thyroid-stimulating hormone (TSH)

Thyrotropin-releasing hormone (TRH)

Thyroxine (T_4)

Thyroxine-binding globulin (TBG)

Transthyretin (TTR)

Triiodothyronine (T_3)

Wolff-Chaikoff effect