# 42
# The Thyroid Gland

## LEARNING OBJECTIVES

*Upon completion of this chapter, the student should be able to answer the following questions:*

1. Describe the anatomy and histology of the thyroid gland, including the structure of the thyroid follicle.
2. Explain how thyroid hormones are synthesized within the thyroid gland, including the processes of iodine uptake, iodination of tyrosine residues in thyroglobulin by thyroid peroxidase/dual oxidase, and coupling to form $T_4$ and $T_3$.
3. Describe the process of endocytosis by which thyroglobulin is retrieved from the follicle lumen and processed to yield $T_3$ and $T_4$, which are secreted into the circulation.
4. Diagram the hypothalamic-pituitary-thyroid axis to show how TSH regulates thyroid function and how thyroid hormones feed back to regulate the axis. List examples of how central input can alter the set point of the axis.
5. Discuss the role of thyroid-binding proteins in the transport and stability of thyroid hormones, the role of thyroid transporters in cellular entry, and the role of peripheral deiodinases in the activation of $T_4$ to $T_3$ or inactivation to reverse $T_3$. Contrast the cellular location and function of the D1 and D2 deiodinases.
6. Describe the mechanisms of thyroid hormone action, including the nature and location of the thyroid hormone receptor and its ability to either repress or activate target gene transcription.
7. Discuss the actions of thyroid hormone during development, especially on the central nervous system (CNS) and skeleton, including the consequences of severe hypothyroidism.
8. Describe the effects of thyroid hormone on basal metabolic rate and thermogenesis, on the cardiovascular system (heart rate, cardiac output, systemic vascular resistance), and on other organ systems (skin, skeletal muscle, digestive tract).

The thyroid gland produces the prohormone tetraiodothyronine ($T_4$, also called *thyroxine*) and the active hormone triiodothyronine ($T_3$). 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 $T_3$. Thyroid hormone acts primarily through a nuclear receptor that regulates gene transcription. $T_3$ is critical for normal brain and bone development and has broad effects on metabolism and cardiovascular function in adults.

## Anatomy and Histology of the Thyroid Gland

The thyroid gland is composed of right and left lobes that sit anterolateral to the trachea (Fig. 42.1). Typically the two lobes are connected by a midventral isthmus. The thyroid gland receives a rich blood supply. It is drained by three sets of veins on each side: the superior, middle, and inferior thyroid veins. The thyroid gland receives sympathetic innervation that is vasomotor but not secretomotor.

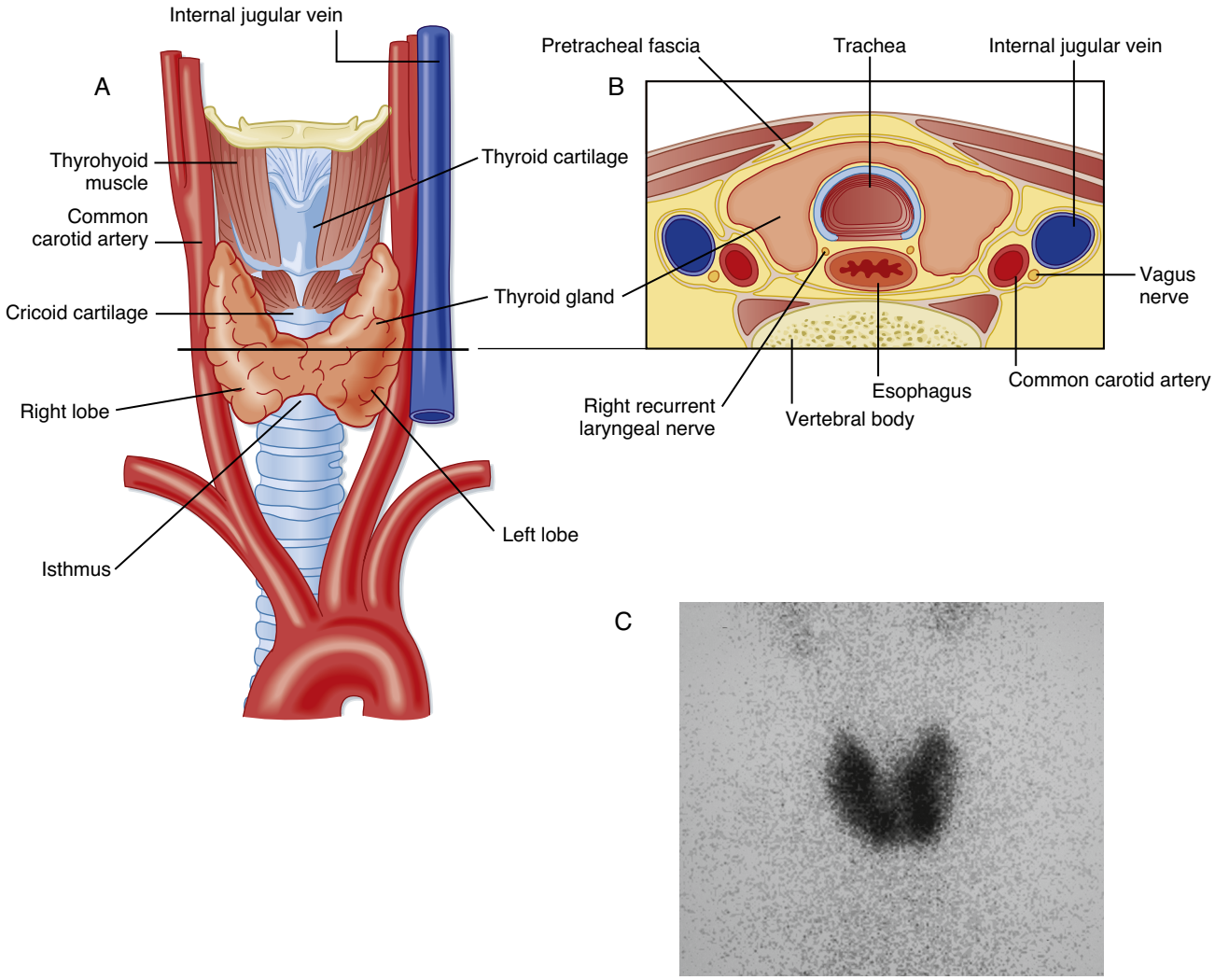
The functional unit of the thyroid gland is the **thyroid follicle,** a spherical structure about 200 to 300 μm in diameter that is surrounded by a single layer of thyroid epithelial cells (Fig. 42.2). The epithelium sits on a basal lamina, the outermost structure of the follicle, and is surrounded by a rich capillary supply. The apical side of the follicular epithelium faces the lumen of the follicle. The follicular lumen itself is filled with **colloid,** which is composed of **thyroglobulin.** This large (660 kDa) protein is secreted into the lumen and iodinated by the thyroid epithelial cells, serving as a scaffold for production of thyroid hormones. The size of the epithelial cells and the amount of colloid are dynamic features that change with 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,** which are the source of the polypeptide hormone **calcitonin** (see Chapter 40).

## Thyroid Hormones

The secretory products of the thyroid gland are **iodothyronines** (Fig. 42.3), a class of hormones formed by the coupling of two iodinated tyrosine molecules. Approximately 90% of the thyroid output is **3,5,3′,5′-tetraiodothyronine** (**thyroxine,** or $\mathbf{T_4}$), which functions as a prohormone. About 10% is **3,5,3′-triiodothyronine ($\mathbf{T_3}$),** the active form of thyroid hormone. Less than 1% of thyroid output is **3,3′,5′-triiodothyronine** (**reverse $\mathbf{T_3}$,** or **r$\mathbf{T_3}$**), which is inactive. Normally these three products are secreted in the same proportions at which they are stored in the gland.

### Iodide Balance

Because iodide plays a unique role in thyroid physiology, a description of thyroid hormone synthesis requires some

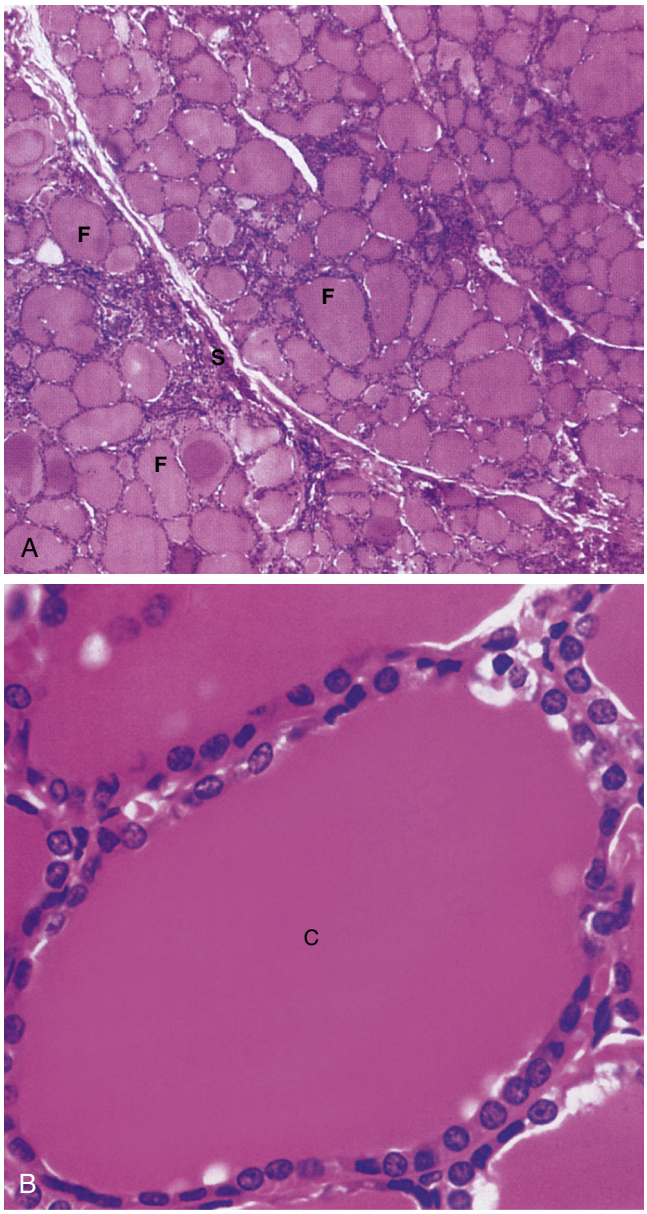



• **Fig. 42.1 A and B,** Anatomy of the thyroid gland. **C,** Image of pertechnetate uptake by a normal thyroid gland. (Modified from Drake RL, et al. *Gray's Anatomy for Students*. Philadelphia: Churchill Livingstone; 2005.)

understanding of iodide turnover (Fig. 42.4). An average of 400 µg of iodide per person is ingested daily in the United States, versus 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, the same amount, 400 µg, is excreted in 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 from a circulating pool that contains approximately 250 to 750 µg of iodide. The total iodide content of the thyroid gland averages 7500 µg, virtually all of which is in the form of stored iodothyronine in colloid thyroglobulin. 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 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 renal excretion of iodide as its concentration in serum falls.

## 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. 42.5). Synthesis of thyroid hormone requires two precursors: iodide and thyroglobulin. Iodide is transported across cells from the basal (vascular) side to the apical (follicular luminal) side of the thyroid epithelium. Thyroglobulin is synthesized and secreted across the apical membrane into the follicular lumen. Thus synthesis involves a basal-to-apical movement of these precursors into the follicular lumen (see Fig. 42.5). Actual synthesis of iodothyronines occurs enzymatically within the follicular lumen close to the apical membrane of the epithelial cells (see later). Secretion of thyroid hormone involves endocytosis of iodinated thyroglobulin




• **Fig. 42.2** Histology of the thyroid gland at low *(upper panel)* and high *(lower panel)* magnification. *C,* Colloid; *F,* thyroid follicles; *S,* connective tissue septa. (From Young B, et al. *Wheater's Functional Histology.* 5th ed. Philadelphia: Churchill Livingstone; 2006.)

and apical-to-basal movement of the endocytotic vesicles, which fuse with lysosomes. Thyroglobulin is enzymatically degraded by lysosomal enzymes, resulting in release of thyroid hormones from the thyroglobulin backbone. Finally, thyroid hormones move across the basolateral membrane, probably through a specific transporter, and ultimately into the blood (Fig. 42.5).

## Synthesis of Iodothyronines on a Thyroglobulin Backbone

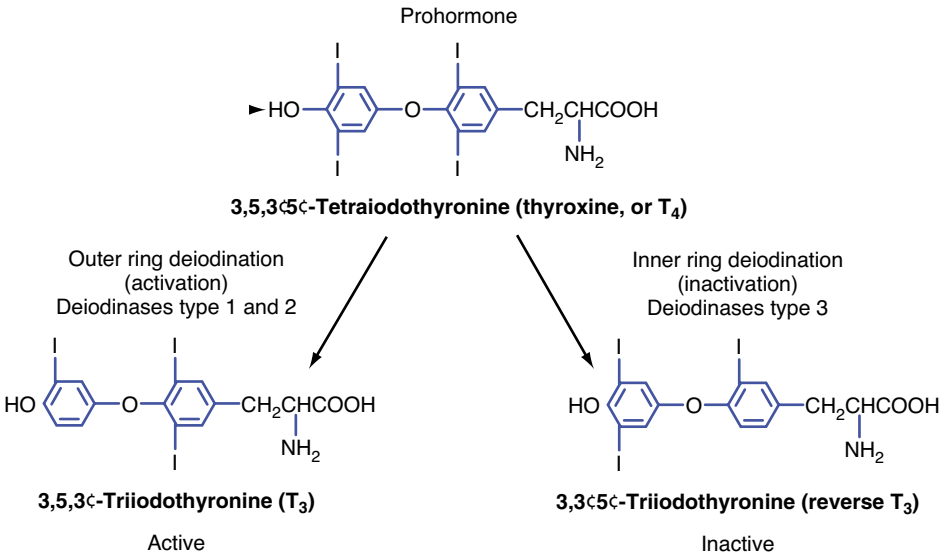
Iodide is actively transported into the gland against chemical and electrical gradients by a **sodium-iodide symporter (NIS)** located in the basolateral membrane of thyroid epithelial cells (see Fig. 42.5). NIS is highly expressed in the thyroid gland, but it is also expressed at lower levels in the placenta, salivary glands, and actively lactating breast. One iodide ion is transported uphill against an iodide gradient while two sodium ions move down their electrochemical gradient from extracellular fluid into the thyroid cell. The driving force for this secondary active transporter is provided by plasma membrane $Na^+,K^+$-ATPase. Expression of the *NIS* gene is inhibited by iodide and stimulated by TSH. 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 percentage of thyroid uptake of iodide can reach 80% to 90%.

The steps in thyroid hormone synthesis are shown in Fig. 42.6. After entering the gland, iodide rapidly moves to the apical plasma membrane of epithelial cells. From there, iodide is transported into the lumen of the follicles by a sodium-independent iodide/chloride transporter called **pendrin.** Iodide is immediately oxidized and incorporated into tyrosine residues within **thyroglobulin** (see Fig. 42.5). A single **iodination** forms a **monoiodotyrosine (MIT);** a second iodination of the same residue produces **diiodotyrosine (DIT)** (see Fig. 42.6). After iodination, two DIT molecules are **coupled** to form $\mathbf{T_4}$**;** one MIT and one DIT are coupled to form $\mathbf{T_3}$**.** 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 ($H_2O_2$). Generation of $H_2O_2$ in the follicular lumen is catalyzed by **dual oxidases (DUOX1, DUOX2)** that are also localized in the apical plasma membrane.

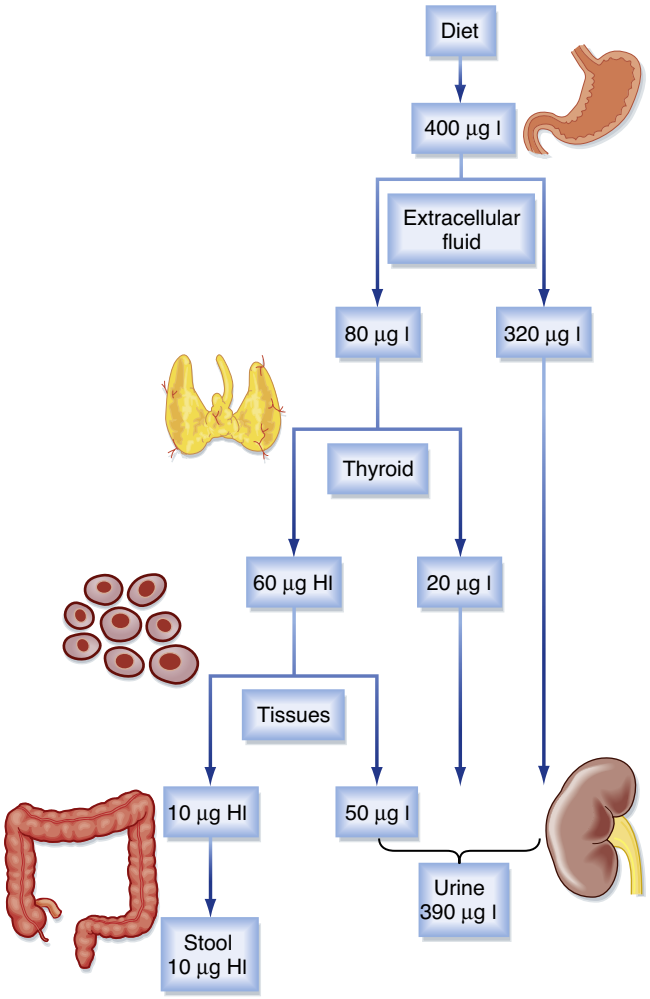
When iodide availability is restricted, formation of $T_3$ is favored because this provides more active hormone per molecule of organified iodide. The proportion of $T_3$ also increases when the thyroid gland is hyperstimulated by TSH or other activators.

## Secretion of Thyroid Hormones

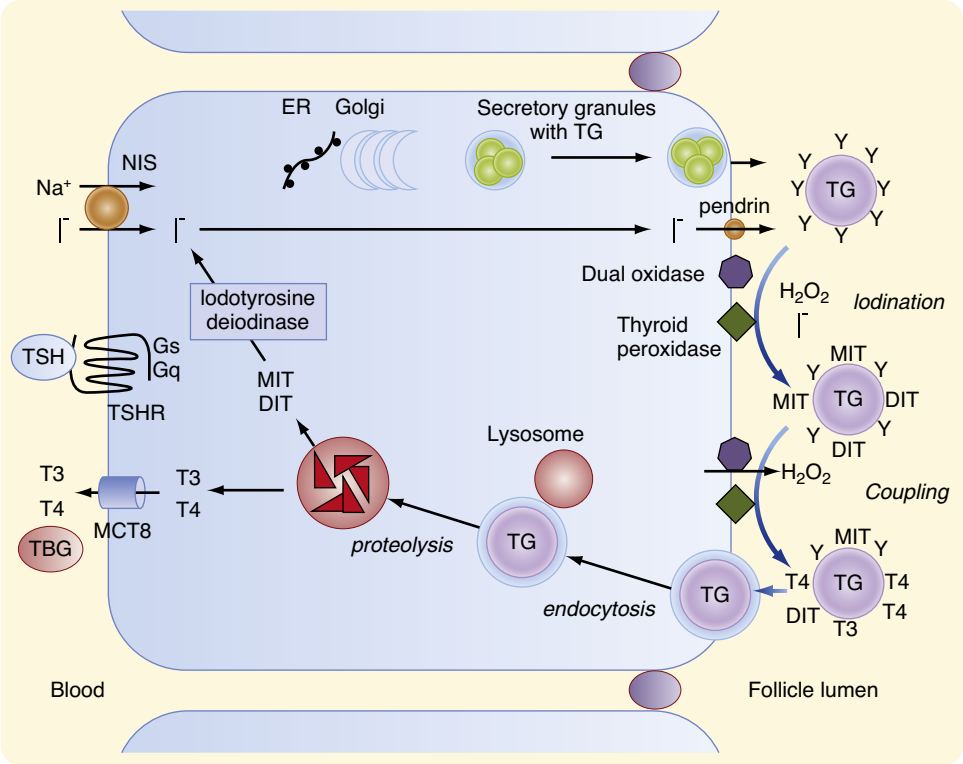
Once thyroglobulin has been iodinated, it is stored in the lumen of the follicle as colloid (see Fig. 42.2). Release of $T_4$ and $T_3$ into the bloodstream is initiated by endocytosis of colloid from the follicular lumen by the processes of macro- and micropinocytosis. Endocytotic vesicles then fuse with lysosomes and thyroglobulin is degraded (Fig. 42.7; also see Fig. 42.5). MIT and DIT molecules, which also are released during proteolysis of thyroglobulin, are rapidly deiodinated within the follicular cell by the enzyme **iodotyrosine deiodinase** (see Fig. 42.5). This deiodinase is specific for MIT and DIT and cannot use $T_4$ and $T_3$ as substrates. The iodide is then recycled into synthesis of $T_4$ and $T_3$. 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. Enzymatically



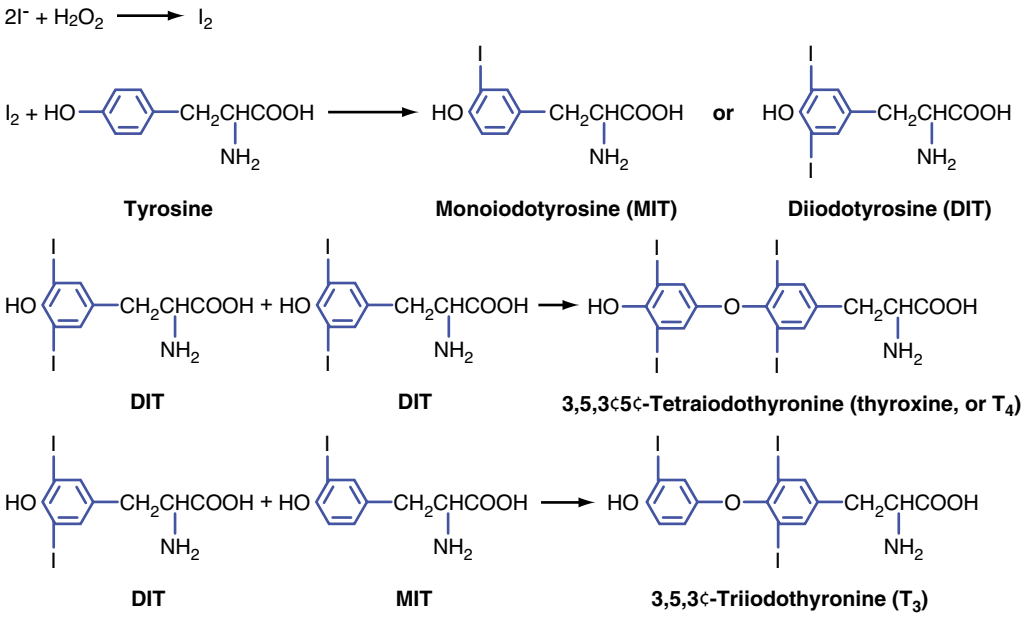

• **Fig. 42.3** Structure of the iodothyronines $T_4$, $T_3$, and reverse $T_3$.




• **Fig. 42.4** Iodine distribution and turnover in humans. *HI,* Hormone-associated iodine.




• **Fig. 42.5** Synthesis and secretion of thyroid hormones by the thyroid epithelial cell. *MIT,* Monoiodotyrosine; *NIS,* sodium-iodide symporter; *TBG,* thyroxine-binding globulin; *TG*, thyroglobulin; *TSH,* thyroid-stimulating hormone; *TSHR*, TSH receptor.

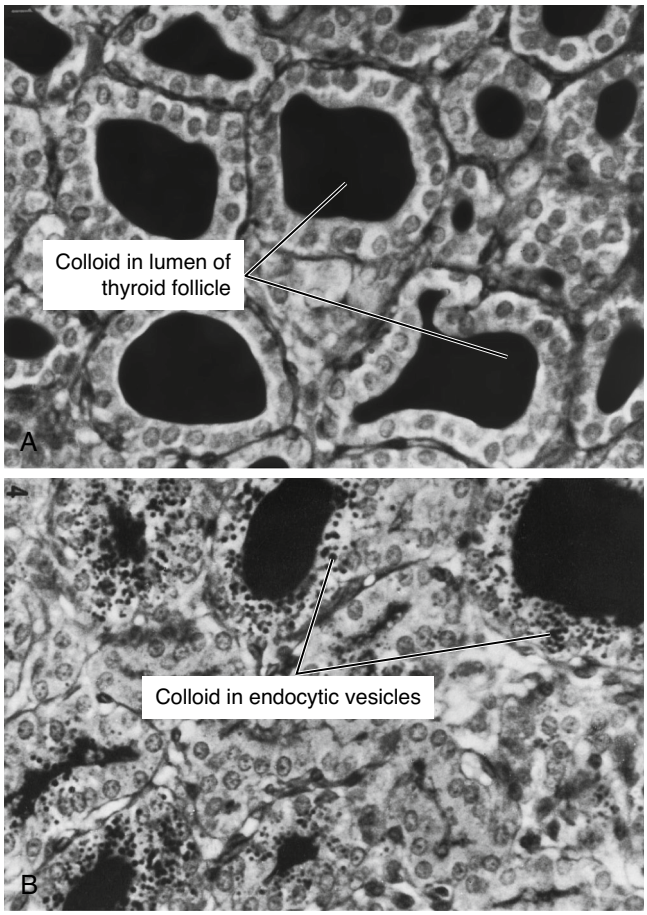



• **Fig. 42.6** Reactions involved in the generation of iodide, MIT, DIT, $T_3$, and $T_4$.

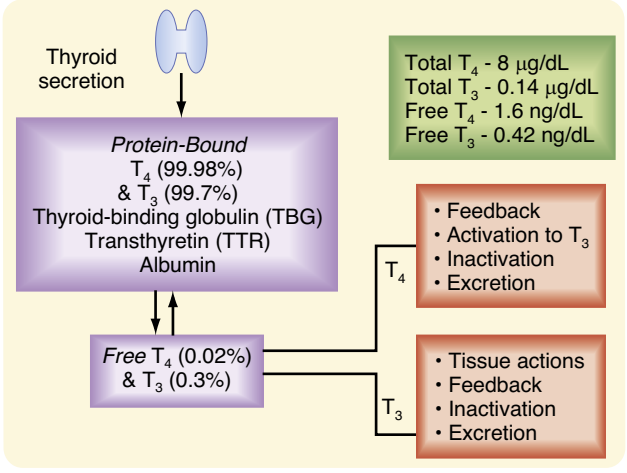
released $T_4$ and $T_3$ are transported across the basal side of the cell and enter the blood.

## Transport of Thyroid Hormones

Secreted $T_4$ and $T_3$ circulate in the bloodstream almost entirely bound to proteins. Normally only about 0.03% of total plasma $T_4$ and 0.3% of total plasma $T_3$ exist in the free state (Fig. 42.8). Free $T_3$ is biologically active and mediates the effects of thyroid hormone on peripheral tissues in addition to exerting negative feedback on the pituitary and hypothalamus. The major binding protein is **thyroxine-binding globulin (TBG),** which 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




• **Fig. 42.7** Before **(A)** and minutes after **(B)** rapid induction of thyroglobulin endocytosis by TSH. (From Wollman SH, et al. *J Cell Biol.* 1964;21:191.)




• **Fig. 42.8** Transport of $T_4$ and $T_3$ in serum by transport proteins and percentages of bound and free hormone.

**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 biological 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, binding of plasma $T_4$ and $T_3$ to proteins prevents loss of these relatively small hormone molecules in urine and thereby helps conserve iodide. TTR transports $T_4$ in cerebrospinal fluid and provides thyroid hormones to the CNS.

## IN THE CLINIC

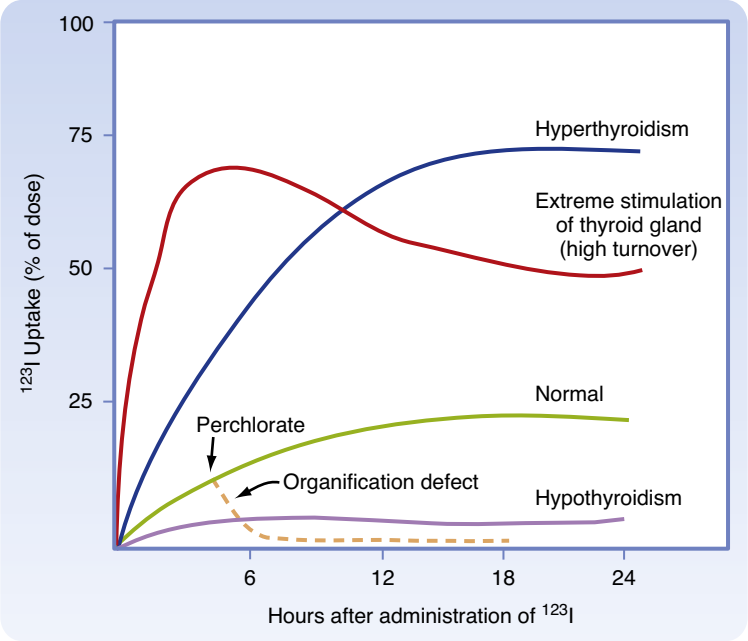
Because of its ability to trap and incorporate iodine into thyroglobulin (called **organification**), the activity of the thyroid can be assessed by **radioactive iodine uptake (RAIU).** In this test a tracer dose of $^{123}I$ is administered and RAIU is measured by placing a gamma detector on the neck at 4 to 6 hours and at 24 hours. In the United States, where the diet is relatively rich in iodine, RAIU is typically around 15% after 6 hours and 25% after 24 hours (Fig. 42.9). 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 (e.g., Graves' disease–associated thyrotoxicosis), iodide is trapped, organified, and released as hormone very rapidly. In these cases of elevated turnover, 6-hour RAIU will be very high but 24-hour RAIU will be lower (see Fig. 42.8). A number of anions, such as thiocyanate ($CNS^-$), perchlorate ($HClO_4^-$), and pertechnetate ($TcO_4^-$), are competitive or noncompetitive inhibitors of iodide transport via 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 rapid release of iodide from the gland (see Fig. 42.9). This release occurs as a result of the high thyroid-plasma concentration gradient.

The thyroid can be imaged with a rectilinear scanner or gamma camera after administration of a tracer, $^{123}I$, $^{131}I$, or the iodine-mimic pertechnetate ($^{99m}Tc$). Imaging can display the size and shape of the thyroid (see Fig. 42.1C) 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 due to cycles of stimulation and involution. **"Hot" nodules** (i.e., nodules that display high RAIU on imaging) are not usually cancerous but may lead to thyrotoxicosis (hyperthyroidism). **"Cold" nodules** are 10 times more likely to be cancerous. Such nodules can be sampled for pathological analysis 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. The highest resolution of the thyroid is achieved with **magnetic resonance imaging (MRI).**

## Cellular Entry and Peripheral Conversion of Thyroid Hormones

For many years it was thought that the lipophilic nature of thyroid hormones allowed them to cross the plasma membrane by passive diffusion. However, it is now known that thyroid hormones require transporters to facilitate cellular entry. This is accomplished by a variety of transport proteins (20 or more) belonging to multiple gene families. These include the monocarboxylate transporters MCT8 and MCT10, which are




• **Fig. 42.9** Thyroid gland iodothyronine uptake curves for normal, hypothyroid, hyperthyroid, and defective organification states.

capable of transporting both $T_4$ and $T_3$ across the plasma membrane (Fig. 42.13; also see Fig. 42.5). Recently, mutations in MCT8 have been shown to cause an X-linked developmental syndrome in humans characterized by elevated $T_3$ levels, muscle hypoplasia, and severe neurological and intellectual impairment. Another transporter, OATP1C1, plays a role in transport of $T_4$ across the blood-brain barrier. The relative importance and tissue distribution of other thyroid hormone transporters remains to be elucidated, adding another layer of complexity to our understanding of thyroid hormone function.

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. 42.3). These enzymes vary in terms of their specificity, substrate affinity, tissue distribution, and subcellular localization. **Type 1 (D1)** and **Type 2 (D2)** deiodinases can both convert $T_4$ to $T_3$. Although D1 exhibits relatively low (micromolar) affinity for $T_4$, it is expressed at the plasma membrane in liver and kidneys, large organs characterized by high blood flow that allows rapid release of hormone into the blood. D1 thereby contributes to the available circulating pool of $T_3$ for uptake by tissues in which local generation of $T_3$ is low or absent. Somewhat paradoxically, expression of D1 is increased in hyperthyroidism and contributes to the elevated circulating $T_3$ levels in hyperthyroid disorders.

D2 is a high-affinity (nanomolar) outer ring deiodinase that is localized to the endoplasmic reticulum, where it converts $T_4$ to $T_3$. Tissues that express D2, including the central nervous system, anterior pituitary, and brown fat, can therefore customize intracellular $T_3$ levels irrespective of circulating $T_3$ levels. Despite its intracellular location, D2 provides most of the circulating $T_3$. The brain maintains constant levels of $T_3$, even when circulating $T_4$ falls to low levels, due to the presence of D2 in glial cells. Accordingly, expression of D2 is increased during hypothyroidism. D2 plays a key role in feedback control of the thyroid axis by regulating **thyroid-stimulating hormone (TSH)** secretion from pituitary thyrotropes. These cells express D2, which promotes intracellular conversion of $T_4$ to $T_3$, which then mediates the negative feedback. This mechanism permits an integrated feedback response to the total circulating pool of $T_3$ and $T_4$. Finally, there is an "inactivating" deiodinase called **type 3 deiodinase (D3).** This high-affinity inner ring deiodinase converts $T_4$ to inactive $rT_3$. D3 is increased during hyperthyroidism, which helps blunt overproduction of $T_4$. In addition, D3 expression is increased during illness or starvation (see "In the Clinic" on Non-Thyroidal Illness Syndrome).

Paradoxically, a small percentage of athyroid patients report experiencing symptoms of hypothyroidism despite thyroxine replacement therapy that normalizes TSH levels. Whether this might be attributable to deiodinase polymorphisms in these patients is an area of active research.

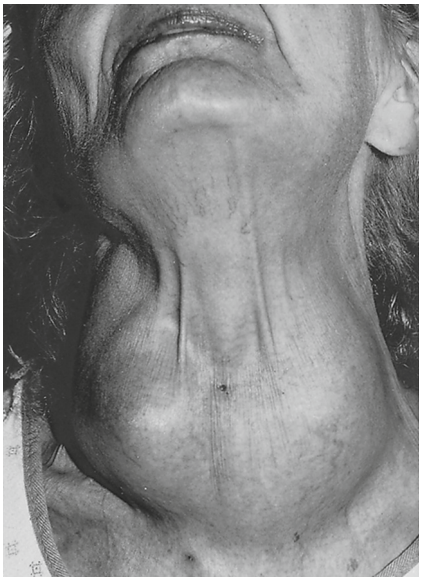
## AT THE CELLULAR LEVEL

Regulation of thyroid hormone secretion by TSH is under exquisite negative-feedback control (see Chapter 41). Circulating thyroid hormones feed back on the pituitary gland to decrease TSH secretion, primarily by repressing TSHβ subunit gene expression. As mentioned earlier, feedback control in thyrotropes represents an integrated response to circulating levels of free $T_4$ and $T_3$. Because the diurnal variation in 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 hypothalamic thyroid-releasing hormone (TRH)–secreting neurons. In these neurons, $T_3$ inhibits expression of the prepro-TRH gene.

Autoregulation of thyroid gland function is caused by iodide itself, which has a biphasic action. At relatively low levels of iodide intake, the rate of thyroid hormone synthesis is directly related to the availability of iodide. However, if the intake of iodide exceeds 2 mg/day, the intraglandular concentration of iodide reaches a level that paradoxically suppresses TPO activity, blocking hormone biosynthesis. This phenomenon is known as the **Wolff-Chaikoff effect.** Adaptation to high iodide intake normally occurs by reducing expression of NIS, which causes the intrathyroidal iodide level to fall. TPO activity then returns to normal, and thyroid hormone synthesis resumes within days to weeks. In unusual instances, failure of NIS to downregulate leads to prolonged inhibition of hormone synthesis by iodide and resultant hypothyroidism. The temporary reduction in hormone synthesis by excess iodide has also been used therapeutically in hyperthyroidism.

## Regulation of Thyroid Function

The most important regulator of thyroid gland function and growth is TSH, which in turn is regulated by the release of hypothalamic **thyroid-releasing hormone (TRH)** into the portal circulation (see Chapter 41). TSH stimulates every aspect of thyroid function, including immediate, intermediate, and long-term actions on the thyroid epithelium. Rapid actions of TSH include pinocytosis of colloid droplets that contain iodinated thyroglobulin into the cytoplasm as endosomes (see Fig. 42.7). The endosomes then fuse with lysosomes, resulting in proteolysis of iodinated thyroglobulin and release of $T_4$ and $T_3$ from the gland. TSH stimulates iodide uptake and TPO activity. It also stimulates entry of glucose into the hexose monophosphate shunt pathway, which generates the reduced nicotinamide adenine dinucleotide phosphate (NADPH) needed for the peroxidase reaction. Intermediate effects of TSH on the thyroid gland occur after hours to days and involve protein synthesis and 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 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 local production of growth factors. A noticeably enlarged thyroid gland is called a *goiter* (Fig. 42.10). Endemic goiter is due to lack of adequate iodine in the diet, which results in low thyroid hormone and elevated TSH levels.



• **Fig. 42.10** The thyroid gland is located in the anterior aspect of the neck, where it is easily visualized when enlarged (goiter).

### IN THE CLINIC

**Graves' disease** is the most common form of **hyperthyroidism.** It occurs most frequently between the ages of 20 and 50 and is 5–10 times more common in women than in men. Graves' disease is an autoimmune disorder in which activating autoantibodies are produced against the TSH receptor. Hyperthyroidism driven by the antibody is often accompanied by a diffuse goiter as a result of 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 blood and tissues. A patient with thyrotoxicosis presents one of the most striking pictures in clinical medicine. The large increase in metabolic rate is manifested as weight loss despite increased food intake. Excess heat production causes discomfort in warm environments, sweating, and greater intake of water. Enhanced sympathetic activity produces a rapid heart rate, hyperkinesis, tremor, nervousness, and a wide-eyed stare. Weakness is caused by a loss of muscle mass as well as impaired muscle function. Other symptoms include a labile emotional state, breathlessness during exercise, and difficulty swallowing or breathing because of compression of the esophagus or trachea by the enlarged thyroid gland. The most common cardiovascular sign is sinus tachycardia. There is increased cardiac output associated with a widened pulse pressure secondary to a positive inotropic effect coupled with decreased systemic vascular resistance. A common clinical sign in Graves' disease is **exophthalmos** (abnormal protrusion of the eyeball) and **periorbital edema.** This is caused by autoantibody binding to the TSH receptor expressed on orbital fibroblasts, leading to increased production of mucopolysaccharides, expansion of orbital fat and edema of extraocular muscles.

Graves' disease is usually diagnosed by elevated serum free and total $T_4$ and $T_3$ and the clinical signs of diffuse goiter and ophthalmopathy. Serum TSH levels are low because the hypothalamus and pituitary are inhibited by the high levels of $T_4$ and $T_3$. In most cases, radioiodine uptake by the thyroid is excessive and diffuse. Assay of TSH levels and the presence of circulating thyroid-stimulating immunoglobulin will distinguish Graves' disease (a primary disorder) from a rare adenoma of pituitary thyrotropes (a secondary disorder) that produces high levels of TSH.

Treatment of Graves' disease usually involves removal of the thyroid gland, followed by lifelong replacement therapy with thyroxine. Thyroid tissue can be removed either by radioablation with $^{131}I$ or by surgery. With surgical removal of the gland, precautions must be taken to avoid a massive, potentially life-threatening release of thyroid hormones known as **thyroid storm.** An alternative to removal of thyroid tissue is administration of **antithyroid drugs** that inhibit TPO activity.

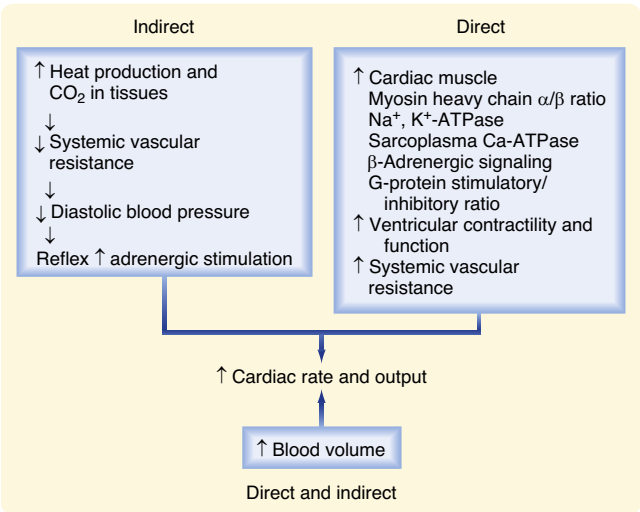
## Physiological Effects of Thyroid Hormone

Thyroid hormone acts on essentially all cells and tissues, and imbalances in thyroid function constitute some of the most common endocrine diseases. Thyroid hormone has many direct actions, but it also acts in a permissive manner to optimize the actions of several other hormones and neurotransmitters.

### Cardiovascular Effects

Perhaps the most clinically important actions of thyroid hormone are those on cardiovascular physiology. $T_3$ increases cardiac output, thereby ensuring sufficient $O_2$ delivery to tissues (Fig. 42.11). The resting heart rate and 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 systemic vascular resistance secondary to blood vessel dilation in skin, muscle, and heart. These effects in turn are partly due to the increase in tissue production of heat and $CO_2$ that thyroid hormone induces (see Effects on Basal Metabolic Rate and Thermogenesis). In addition, however, thyroid hormone decreases systemic resistance by dilating arterioles in the peripheral circulation. Total blood volume is increased by activation of the renin-angiotensin-aldosterone axis, thereby increasing renal tubular sodium reabsorption (see Chapter 34).

The cardiac inotropic effects of $T_3$ are both direct and indirect. The latter are due primarily to enhanced responsiveness to catecholamines (see Chapter 43). Direct inotropic effects (see Fig. 42.11) involve regulation of multiple proteins that enhance contractility, including increased **α-myosin heavy chain** expression and inhibition of the plasma membrane **$Na^+/Ca^{++}$ exchanger. Sarcoplasmic reticulum $Ca^{++}$-ATPase (SERCA)** is increased by $T_3$, whereas phospholamban is decreased. As a result, sequestration of calcium during diastole is enhanced and the relaxation time is shortened. Increased **ryanodine $Ca^{++}$ channels** in the sarcoplasmic reticulum promote release of $Ca^{++}$ from the sarcoplasmic reticulum during systole.




• **Fig. 42.11** Mechanisms by which thyroid hormone increases cardiac output. The indirect mechanisms are probably quantitatively more important.

### IN THE CLINIC

Thyroid hormone levels in the normal range are necessary for optimum cardiac performance. A deficiency of thyroid hormone 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 to a greater extent than myocardial oxidative metabolism. The rise in systemic vascular resistance may contribute to this cardiac debility. In contrast, excess thyroid hormone enhances cardiac output by increasing both heart rate and stroke volume. Pulse pressure is widened by increased systolic pressure and decreased diastolic pressure due to decreased systemic vascular resistance. Thyrotoxicosis is associated with palpitations, atrial fibrillation, and mitral valve prolapse (see Chapter 15).

### Effects on Basal Metabolic Rate and Thermogenesis

Increased $O_2$ 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 induces enzymes for the synthesis of fatty acids, including acetyl-CoA carboxylase and fatty acid synthase, and enhances lipolysis by increasing the number of β-adrenergic receptors (see Effects on the Autonomic Nervous System and Catecholamine Action). Thyroid hormone also enhances the clearance of chylomicrons. Thus lipid turnover (free fatty acid release from adipose tissue and oxidation) is augmented.

**Protein turnover** (release of muscle amino acids, protein degradation, and to a lesser extent protein synthesis and urea formation) is also increased. $T_3$ 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 physiological response to starvation. In addition, thyroid hormone stimulates synthesis of bile acids from cholesterol and promotes biliary secretion. The net effect is a decrease in the body pool and plasma levels of total and low-density lipoprotein cholesterol. Metabolic clearance of adrenal and gonadal steroid hormones, some B vitamins, and certain administered drugs is also increased by thyroid hormone.

Thyroid hormones stimulate **thermogenesis** by affecting both adenosine triphosphate (ATP) utilization and the efficiency of ATP synthesis. ATP utilization is enhanced by upregulation of several energy-dependent processes, including $Na^+$,$K^+$-ATPase and SERCA, particularly in skeletal muscle, where calcium cycling between the cytoplasm and sarcoplasmic reticulum uses ATP and generates heat. Recently, it has been demonstrated that brown fat in humans, once thought to be important only in neonates, appears to play a role in facultative thermogenesis in adults. Imaging studies have demonstrated the presence of brown fat in the mediastinum, particularly in lean individuals, and metabolic activity in brown fat is enhanced by exposure to cold. Brown fat expresses **uncoupling protein-1 (UCP1**), also called *thermogenin,* which causes the proton gradient across the inner mitochondrial membrane to be dissipated as heat, which is then disseminated to the rest of the body by the circulation. UCP1 is regulated by thyroid hormone, and brown fat expresses D2, providing intracellular conversion of $T_4$ to $T_3$. Brown fat thermogenesis involves a synergistic interaction between thyroid hormones and the sympathetic nervous system. Catecholamines promote lipolysis and upregulate expression of D2. $T_3$ in turn upregulates adrenergic receptors and enhances catecholamine responsiveness. Hyperthyroidism is accompanied by heat intolerance, whereas hypothyroidism is accompanied by cold intolerance.

## Respiratory Effects

Thyroid hormone stimulates $O_2$ utilization and enhances $O_2$ delivery. Appropriately, $T_3$ increases the **resting respiratory rate, minute ventilation,** and the **ventilatory response** to hypercapnia and hypoxia. These actions maintain a normal arterial $P_{O_2}$ when $O_2$ utilization is increased and a normal $P_{CO_2}$ when $CO_2$ production is increased. Additionally, the hematocrit increases slightly to enhance $O_2$-carrying capacity. This increase results from stimulation of **erythropoietin** production by the kidney.

## Skeletal Muscle Effects

Normal function of skeletal muscles also requires optimal amounts of thyroid hormone. This requirement may be related to regulation of energy production and storage. Glycolysis and glycogenolysis are increased, whereas glycogen and creatine phosphate are reduced by thyroid hormone excess. The inability of muscle to take up and phosphorylate creatine leads to its increased urinary excretion.

## Effects on the Autonomic Nervous System and Catecholamine Action

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

## Effects on Growth and Maturation

A 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 neurological development and proper bone formation in the fetus. In infants, insufficient fetal thyroid hormone causes congenital hypothyroidism, characterized by irreversible intellectual disability and short stature (see In the Clinic box).

## Effects on Bone, Hard Tissue, and Dermis

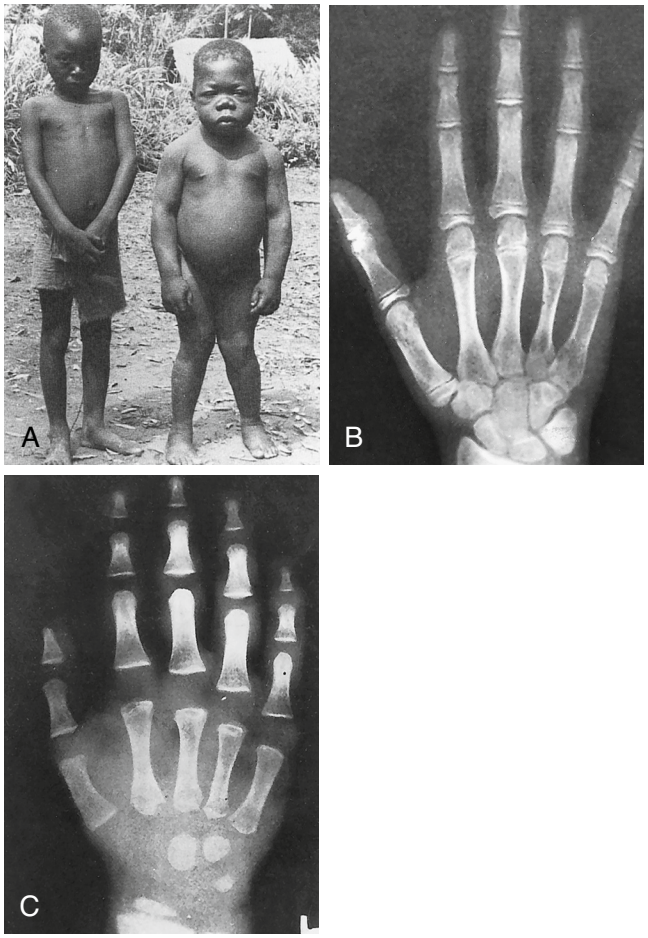
Thyroid hormone promotes endochondral ossification, linear bone growth, and maturation of the epiphyseal bone centers. $T_3$ enhances maturation and activity of chondrocytes in the cartilage growth plate, in part by increasing local growth factor production and action. During linear postnatal growth, $T_3$ supports the actions of growth hormone, insulin-like growth factor-I, and other growth factors. $T_3$ also supports normal 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 stimulated by thyroid hormone. Thus, either too much or too little thyroid hormone can lead to hair loss and abnormal nail formation. Thyroid hormone regulates the structure of subcutaneous tissue by inhibiting synthesis and increasing degradation of mucopolysaccharides (glycosaminoglycans) and fibronectin in the extracellular connective tissue (see later description of myxedema).

## Effects on the Nervous System

Thyroid hormone regulates the timing and pace of development of the CNS. Thyroid hormone deficiency in utero and in early infancy inhibits growth of the cerebral and cerebellar cortex, proliferation of axons and branching of dendrites, synaptogenesis, myelination, and cell migration. Irreversible CNS impairment results when neonatal thyroid hormone deficiency is not recognized and treated promptly. These morphological defects 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 rates of protein synthesis.

Thyroid hormone also enhances wakefulness, alertness, responsiveness to various stimuli, auditory sense, awareness of hunger, memory, and learning capacity. In addition, normal emotional tone depends on proper thyroid hormone availability. Furthermore, the speed and amplitude of




• **Fig. 42.12 A,** Normal 6-year-old child *(left)* and a congenitally hypothyroid 17-year-old *(right)* from the same village in an area of endemic hypothyroidism. Radiographs of the hand comparing a normal 13-year-old **(B)** to that of a 13-year-old suffering from hypothyroidism **(C)**. Note that the patient with hypothyroidism has a marked delay in development of the small bones of the hands, in growth plates at either end of the fingers, and in the growth plate of the distal radius. (**A,** From Delange FM. In: Braverman LE, Utiger RD, eds. *Werner and Ingbar's The Thyroid.* 7th ed. Philadelphia: Lippincott-Raven; 1996. **B,** From Tanner JM, et al. *Assessment of Skeletal Maturity and Prediction of Adult Height (TW2 Method).* New York: Academic Press; 1975. **C,** From Andersen HJ. In: Gardner LI, ed. *Endocrine and Genetic Diseases of Childhood and Adolescence.* Philadelphia: Saunders; 1975.)

peripheral nerve reflexes are increased by thyroid hormone, as is motility of the gastrointestinal tract.

## Effects on Reproductive Organs and Endocrine Glands

In both women and men, thyroid hormone plays an important permissive role in regulation of reproductive function. The normal ovarian cycle of follicular development, maturation, and ovulation, the homologous testicular process of spermatogenesis, and maintenance of the healthy pregnant state are all disrupted by significant deviations in 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.

## IN THE CLINIC

**Hypothyroidism** refers to insufficient production of thyroid hormones and can occur as primary, secondary, or tertiary endocrine disease (see Chapter 41). In primary hypothyroidism, $T_4$ and $T_3$ levels are abnormally low and TSH is high. In secondary and tertiary hypothyroidism, both thyroid hormones and TSH are low. The response of TSH levels to synthetic TRH can be used to distinguish between pituitary and hypothalamic disease.

Hypothyroidism in the fetus or early childhood leads to **congenital hypothyroidism** (formerly called *cretinism* [Fig. 42.12]). Affected individuals have severe intellectual disability, short stature with incomplete skeletal development, coarse facial features, and a protruding tongue. The most common cause of hypothyroidism in children worldwide is iodide deficiency. Historically, iodide deficiency was viewed as a major cause of hypothyroidism in certain mountainous regions of South America, Africa, and Asia, but recent evidence suggests that the problem is even more widespread. This tragic form of **endemic hypothyroidism** can be prevented by public health programs that add iodide to table salt or provide yearly injections of a slowly absorbed iodide preparation. **Congenital defects** are a less common cause of neonatal/child 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., NIS, TPO, thyroglobulin, pendrin) or blocking antibodies to the TSH receptor. The severity of the neurological and skeletal defects is closely linked to the timing of diagnosis and thyroid hormone ($T_4$) replacement, with early treatment resulting in a normal cognitive ability and subtle neurological deficits. On the other hand, if hypothyroidism at birth remains untreated for only 2 to 4 weeks, the CNS will not mature normally in the first year of life. Developmental milestones such as sitting, standing, and walking will be late, and severe irreversible cognitive deficits can result. Hypothyroid babies usually appear normal at birth because of protection by maternal thyroid hormones. **Neonatal screening** ($T_4$ and TSH levels) has therefore played a critical role in diagnosis and prevention of congenital hypothyroidism.

Hypothyroidism in adults who are not iodide deficient most often results from another autoimmune disorder known as **Hashimoto's disease** (formerly called *lymphocytic thyroiditis*). In contrast to the stimulatory effect of autoantibodies seen in Graves' disease, thyroid autoantibodies in Hashimoto's disease (against TPO, thyroglobulin, or TSH receptor) cause apoptosis of thyroid cells and destruction of thyroid follicles. These antibodies fix complement and promote lysis of thyroid cells, causing release of thyroglobulin into the circulation. The thyroid gland becomes infiltrated by both B and T lymphocytes, which may cause enlargement of the gland.

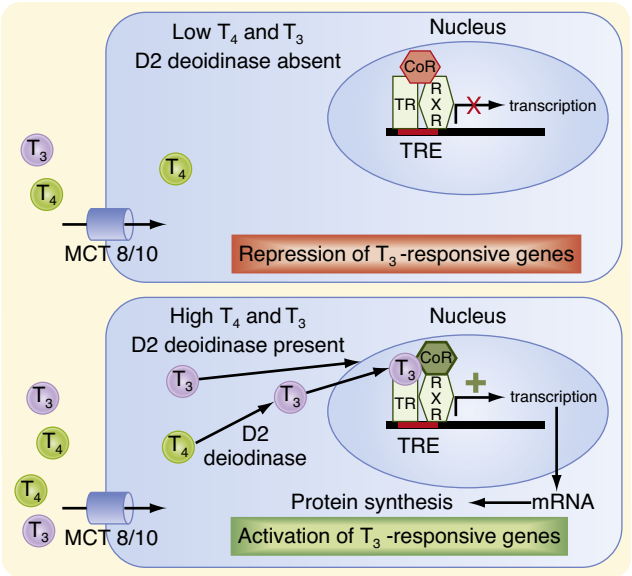
Other causes of hypothyroidism include iatrogenic causes (e.g., radiochemical damage or surgical removal for treatment of hyperthyroidism), nodular goiters, and pituitary or hypothalamic disease. Treatment of patients with the antiarrhythmic drug amiodarone, which contains a large amount of iodine, may cause either hypo- or hyperthyroidism. Thyroid function must be carefully monitored in patients taking this medication.

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 lowering of the upper eyelids (ptosis) occur. Accumulation of negatively charged mucopolysaccharides in connective tissues attracts sodium and fluid. The resulting nonpitting **myxedema** produces puffy features, 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 signs. 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 emotional state of hypothyroid individuals.

Replacement therapy with a daily dose of $T_4$ that normalizes TSH levels is usually curative in hypothyroid adults. In most patients, $T_3$ is not needed because it is generated as needed by peripheral D1 and D2. Furthermore, administration of $T_3$ is complicated by its high potency and short half-life, requiring frequent dosing and causing difficulty in maintaining consistent physiological levels of $T_3$.

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 43) as well as metabolic clearance of this hormone are stimulated, but plasma-free cortisol levels remain normal. The ratio of estrogens to androgens (see Chapter 44) is increased in men (in whom breast enlargement may occur with hyperthyroidism). Decreases in both parathyroid hormone and 1,25-dihydroxyvitamin D production are compensatory consequences of the effects of thyroid hormone on bone resorption (see Chapter 40). Kidney size, renal plasma flow, glomerular filtration rate, and transport rates for a number of substances are also increased by thyroid hormone.




• **Fig. 42.13** Mechanisms of thyroid hormone action, including the role of MCT transporters, D2 deiodinase, and TR-RXR heterodimers. *CoA,* Coactivator; *CoR,* co-repressor; *MCT*, monocarboxylate transporter; *RXR*, retinoid X receptor; *TR*, thyroid hormone receptor; *TRE*, thyroid hormone response element.

## IN THE CLINIC

**Nonthyroidal illness syndrome (NTIS),** also known as *euthyroid sick syndrome,* occurs in severely ill patients who require hospitalization. NTIS is characterized by decreased levels of both circulating thyroid hormone and TSH caused by centrally mediated suppression of the hypothalamic-pituitary-thyroid axis. TRH production by the hypothalamus is reduced, so TSH levels may be low or inappropriately normal in the face of reduced $T_4$ and $T_3$. In addition, peripheral metabolism of $T_4$ to inactive $rT_3$ is increased by upregulation of D3. A similar response is seen upon prolonged fasting. Although it remains incompletely understood, NTIS has been proposed to represent a physiological energy-sparing adaptation to chronic illness or starvation. For this reason, thyroid status should not be assessed in critically ill patients.

## AT THE CELLULAR LEVEL

### Mechanism of Thyroid Hormone Action

Many but not all $T_3$ actions are mediated through its binding to one of the members of the **thyroid hormone receptor (TR) family.** The TR family belongs to the nuclear hormone receptor superfamily of transcription factors (see also Chapter 3). In humans there are two TR genes, ***THRA*** and ***THRB*,** located on chromosomes 17 and 3, respectively, that encode the nuclear TRs. *THRA* encodes **$TR_\alpha$,** which is alternatively spliced to form two main isoforms. $TR_{\alpha1}$ is a bonafide TR, whereas the other isoform does not bind $T_3$. THRB encodes **$TR_{\beta1}$** and **$TR_{\beta2}$,** which are high-affinity receptors for $T_3$. The tissue distribution of $TR_{\alpha1}$ and $TR_{\beta1}$ is widespread. $TR_{\alpha1}$ is strongly expressed in cardiac and skeletal muscle. $TR_{\alpha1}$ is the primary mediator of thyroid hormone action on the heart. In contrast, $TR_{\beta1}$ is expressed mainly in brain, liver, and kidney. $TR_{\beta2}$ expression is restricted to the pituitary and critical areas of the hypothalamus, as well as the cochlea and retina. $T_3$ acting via $TR_{\beta2}$ is responsible for inhibiting expression of the prepro-TRH gene in the paraventricular neurons of the hypothalamus and the β subunit TSH gene in pituitary thyrotropes. Thus the negative-feedback effects of thyroid hormone on both TRH and TSH secretion are largely mediated by $TR_{\beta2}$.

TR forms heterodimers with RXR (see Fig. 42.13). Unliganded TR-RXR binds to thyroid response elements in target genes and recruits co-repressors that inhibit basal gene transcription. Upon $T_3$ binding, the co-repressors are released, and coactivators are recruited to the hormone-receptor complex, inducing gene transcription.

An understanding of TR subtypes is important because inactivating TR mutations have been found to cause **thyroid hormone resistance** syndromes. The most common mutations occur in the $TR_{\beta2}$ subtype, resulting in incomplete negative feedback at the hypothalamic-pituitary level. Thus $T_4$ levels are elevated, but TSH is not suppressed. When resistance is predominantly at the hypothalamic-pituitary level, the patient may exhibit signs of hyperthyroidism due to effects of elevated thyroid hormone levels on peripheral tissues, particularly on the heart, mediated by $TR_{\alpha1}$. TR isoforms may also offer potential therapeutic targets. For example, research is underway to develop $TR_\beta$-specific agonists that have beneficial effects on lipid and cholesterol metabolism without the risk of adverse cardiovascular side effects.

There is emerging evidence for nongenomic actions of $T_3$ and $T_4$ that are mediated by receptors acting in the plasma membrane, mitochondria, or cytoplasm. In some cases, these are modified versions of the nuclear thyroid receptors. For example, truncated isoforms of $TR_{\alpha 1}$ have been reported that bind $T_3$ in the plasma membrane to mediate nongenomic effects in bone or that bind $T_4$ in the cytoplasm to regulate microfilament organization. It has also been reported that an integrin, $\alpha_v\beta_3$, can act as a $T_4$ receptor at the cell surface to regulate cellular proliferation and angiogenesis by a nongenomic mechanism. The interplay between the classical genomic and nongenomic actions of thyroid hormones is likely to be another active area of future research.

## Key Concepts

1. The thyroid gland is situated in the ventral aspect of the neck and is 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 of dual oxidase and thyroid peroxidase. Tyrosine residues in thyroglobulin undergo iodination, after which 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. Thyroglobulin is then degraded in endolysosomes to liberate $T_4$ and $T_3$. Iodide is conserved by recycling any iodotyrosine molecules that did not undergo coupling within thyroglobulin.
7. TSH acts on the thyroid gland via its plasma membrane receptor 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 epithelial cells.
8. More than 99.5% of $T_4$ and $T_3$ circulates bound to the following proteins: thyroid-binding globulin, transthyretin, and albumin. Only the free fractions of $T_4$ and $T_3$ are biologically active.
9. $T_4$ functions largely 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.
10. Thyroid hormone is a major positive regulator of the basal metabolic rate and thermogenesis. Other important actions of thyroid hormone are increased heart rate, cardiac output, and ventilation and decreased systemic vascular resistance. Substrate mobilization and disposal of metabolic products are enhanced.
11. Thyroid hormone actions on the CNS and skeleton are crucial for normal growth and development. Absence of the hormone causes congenital hypothyroidism, characterized by poor brain development, short stature, and immature skeletal development. In adults, thyroid hormone supports bone remodeling and degradation of skin and hair.
12. $T_3$ binds to thyroid hormone receptor subtypes responsible for the various actions of thyroid hormone. The thyroid hormone receptor heterodimerizes with RXR to regulate thyroid response elements on target genes, resulting in induction or repression in the presence or absence of $T_3$, respectively.