Chapter 20: The Thyroid Gland

OBJECTIVES

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After studying this chapter, you should be able to:

- Describe the development, anatomy, and histology of the thyroid gland, and how these relate to its function, as well as the changes in histology that accompany the activation of secretion with reabsorption of thyroglobulin from the colloid.
- Define the chemical nature of the thyroid hormones and how they are synthesized. Understand the critical role of iodine in the thyroid gland and how its transport is controlled, as well as how it is incorporated into the tyrosine residues of thyroglobulin at the interface between thyrocytes and colloid via the process of organification.
- Describe the relative roles of binding to albumin, transthyretin, and thyroxine-binding globulin in the transport of thyroid hormones, the availability of free hormones, and peripheral metabolism.
- Identify the role of the hypothalamus and pituitary in regulating thyroid function and the feedback loops that establish the level of secretion of thyroid hormones.
- Define the effects of the thyroid hormones in homeostasis, metabolism, and growth.
- Understand the basis of conditions where thyroid function is abnormal and how they can be treated.

INTRODUCTION

The thyroid gland is one of the larger endocrine glands of the body. The gland has two primary functions. The first is to secrete the thyroid hormones, which maintain the level of metabolism in the tissues that is optimal for their normal function. Thyroid hormones stimulate O_2 consumption by most of the cells in the body, help regulate lipid and carbohydrate metabolism, and thereby influence body mass and mentation. Consequences of thyroid gland dysfunction depend on the life stage at which they occur. The thyroid is not essential for life, but its absence or hypofunction during fetal and neonatal life results in severe mental retardation and dwarfism. In adults, hypothyroidism is accompanied by mental and physical slowing and poor resistance to cold. Conversely, excess thyroid secretion leads to body wasting, nervousness, tachycardia, tremor, and excess heat production. Thyroid function is controlled by the thyroid-stimulating hormone (TSH, thyrotropin) that is secreted by the anterior lobe of the pituitary. The secretion of this hormone is in turn increased by thyrotropin-releasing hormone (TRH) from the hypothalamus and is also subject to negative feedback control by high circulating levels of thyroid hormones acting on the anterior pituitary and the hypothalamus.

The second function of the thyroid gland is to secrete calcitonin, a hormone that regulates circulating levels of calcium. This function of the thyroid gland is discussed in Chapter 21 in the broader context of whole body calcium homeostasis.

DEVELOPMENT, STRUCTURE, AND CELL TYPES OF THE THYROID GLAND

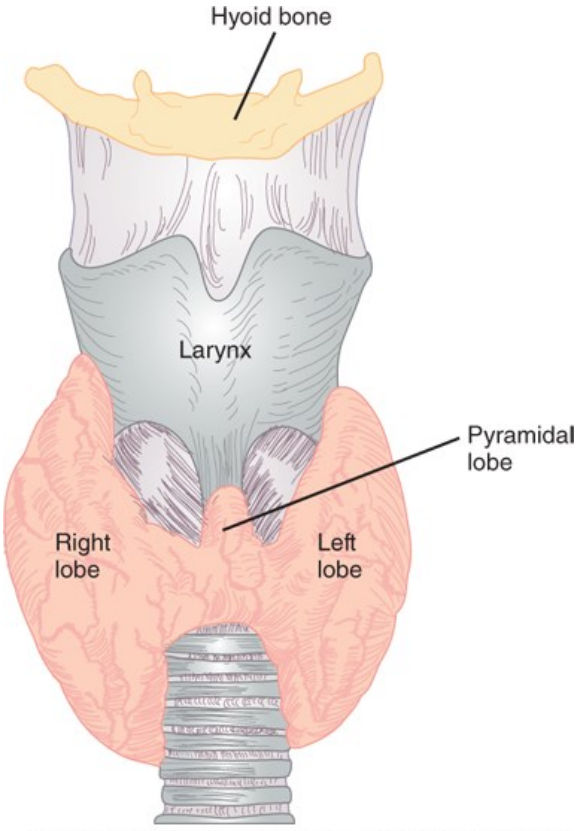
GROSS ANATOMY

The thyroid is a butterfly-shaped gland that straddles the trachea in the front of the neck. It develops from an evagination of the floor of the pharynx,

and a **thyroglossal duct** marking the path of the thyroid from the tongue to the neck sometimes persists in the adult. The two lobes of the human thyroid are connected by a bridge of tissue, the **thyroid isthmus,** and there is sometimes a **pyramidal lobe** arising from the isthmus in front of the larynx (**Figure 20–1**). The gland is well vascularized, and the thyroid has one of the highest rates of blood flow per gram of tissue of any organ in the body.

FIGURE 20–1

The human thyroid.

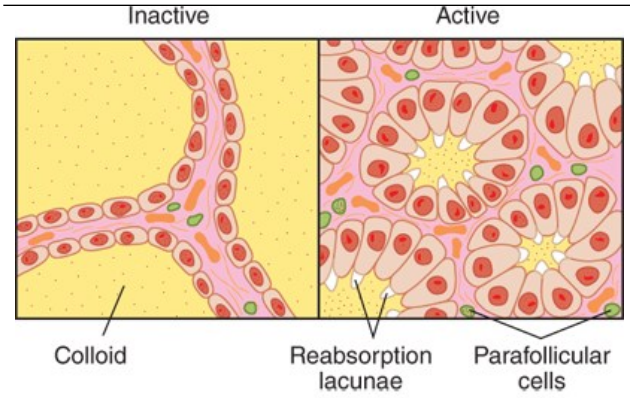


HISTOLOGY

The portion of the thyroid concerned with the production of thyroid hormone consists of multiple **follicles.** Each spherical follicle is surrounded by a single layer of polarized epithelial cells and filled with proteinaceous material called **colloid.** Colloid consists predominantly of the glycoprotein, thyroglobulin. When the gland is inactive, the colloid is abundant, the follicles are large, and the cells lining them are flat. When the gland is active, the follicles are small, the cells are cuboid or columnar, and areas where the colloid is being actively reabsorbed into the thyrocytes are visible on histology as “reabsorption lacunae” (**Figure 20–2**).

FIGURE 20–2

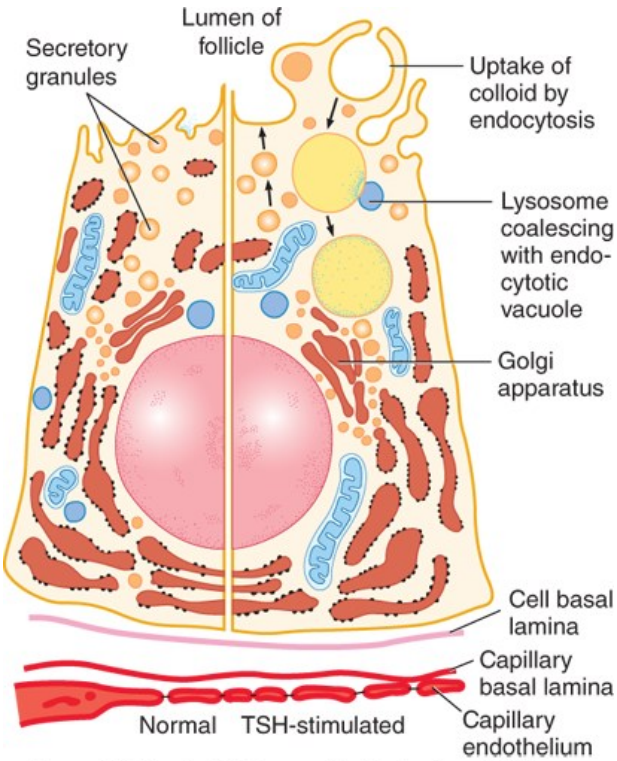
Thyroid histology. The appearance of the gland when it is inactive (left) and actively secreting (right) is shown. Note the small, punched-out “reabsorption lacunae” in the colloid next to the cells in the active gland.



Microvilli project into the colloid from the apexes of the thyrocytes and canaliculi extend into them. The endoplasmic reticulum is prominent, a feature common to most glandular cells, and secretory granules containing thyroglobulin are seen (**Figure 20–3**). The individual thyroid cells rest on a basal lamina that separates them from the adjacent capillaries. The capillaries are fenestrated, like those of other endocrine glands (see Chapter 31).

FIGURE 20–3

Thyrocyte. Left: Normal pattern. **Right:** After TSH stimulation. The arrows on the right show the secretion of thyroglobulin into the colloid. On the right, endocytosis of the colloid and merging of a colloid-containing vacuole with a lysosome are also shown. The cell rests on a capillary with gaps (fenestrations) in the endothelial wall.



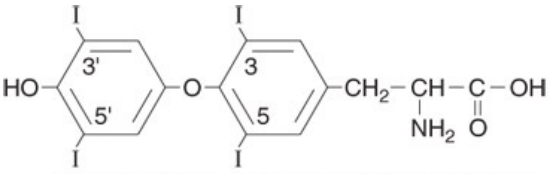
FORMATION & SECRETION OF THYROID HORMONES

CHEMISTRY

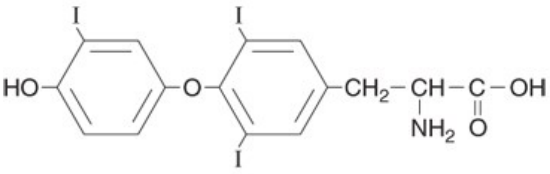
The primary hormone secreted by the thyroid is **thyroxine (T_4),** along with much lesser amounts of **triiodothyronine (T_3).** T_3 has much greater biologic activity than T_4 and is also specifically generated at its site of action in peripheral tissues by deiodination of T_4 (see below). Both hormones are iodine-containing amino acids **(Figure 20–4)**. Small amounts of reverse triiodothyronine (3,3′,5′-triiodothyronine, RT_3) and other compounds are also found in thyroid venous blood. Whether RT_3 is biologically active remains unclear.

FIGURE 20–4

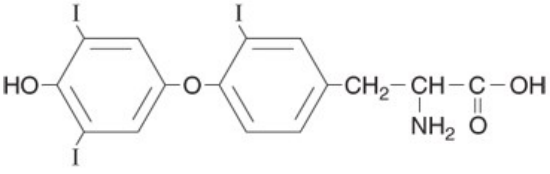
Thyroid hormones. The numbers in the rings in the T_4 formula indicate the numbers of positions in the molecule. RT_3, reverse triiodothyronine.



3,5,3',5'-Tetraiodothyronine (thyroxine, T_4)



3,5,3'-Triiodothyronine (T_3)



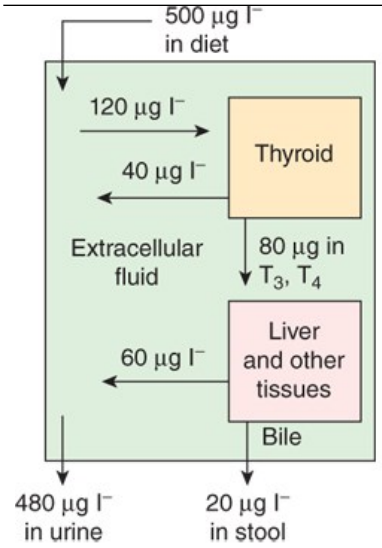
3,3',5'-Triiodothyronine (RT_3)

IODINE HOMEOSTASIS

Iodine is an essential raw material for thyroid hormone synthesis. Dietary iodide is absorbed by the intestine and enters the circulation; its subsequent fate is summarized in **Figure 20–5**. The minimum daily iodine intake that will maintain normal thyroid function is 150 µg in adults. In most developed countries, supplementation of table salt means that the average dietary intake is approximately 500 µg/day. The principal organs that take up circulating I^- are the thyroid, which uses it to make thyroid hormones, and the kidneys, which excrete it in the urine. About 120 µg/day enter the thyroid at normal rates of thyroid hormone synthesis and secretion. The thyroid secretes 80 µg/day in the form of T_3 and T_4, while 40 µg/day diffuses back into the extracellular fluid (ECF). Circulating T_3 and T_4 are metabolized in the liver and other tissues, with the release of a further 60 µg of I^- per day into the ECF. Some thyroid hormone derivatives are excreted in the bile, and some of the iodine in them is reabsorbed (enterohepatic circulation), but there is a net loss of I^- in the stool of approximately 20 µg/day. The total amount of I^- entering the ECF is thus 500 + 40 + 60, or 600 µg/day; 20% of this I^- enters the thyroid, whereas 80% is excreted in the urine.

FIGURE 20–5

Iodide metabolism. The figure shows the movement of iodide among various body compartments on a daily basis.

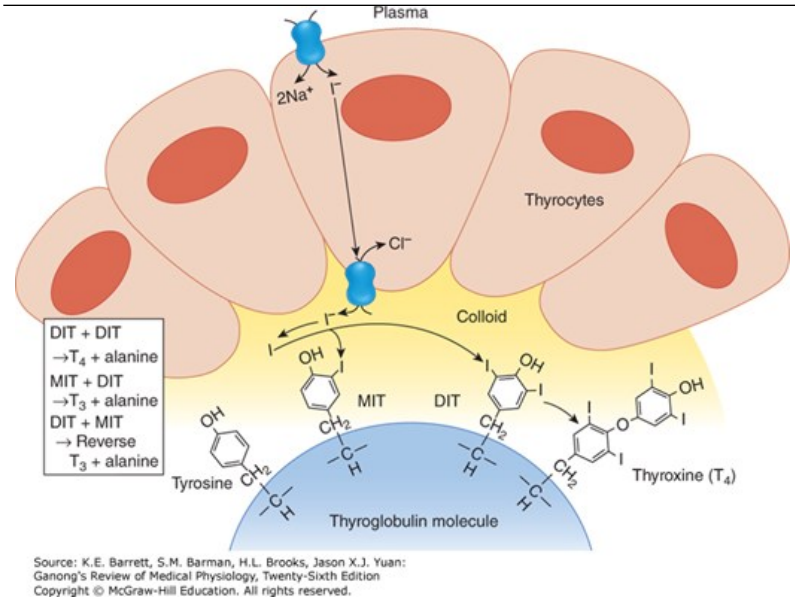


IODIDE TRANSPORT ACROSS THYROCYTES

The basolateral membranes of thyrocytes facing the capillaries contain a **symporter** that transports two Na^+ ions and one I^- ion into the cell with each cycle, against the electrochemical gradient for I^-. This Na^+/I^- symporter **(NIS)** is capable of producing intracellular I^- concentrations that are 20–40 times as great as the concentration in plasma **(Figure 20–6)**. The process involved is secondary active transport (see Chapter 2), with the energy provided by active transport of Na^+ out of thyroid cells by Na, K ATPase. NIS is regulated both by transcriptional means and by active trafficking into and out of the thyrocyte basolateral membrane; in particular, TSH (see below) induces both NIS expression and the retention of NIS in the basolateral membrane, where it can mediate sustained iodide uptake.

FIGURE 20–6

Outline of thyroid hormone biosynthesis. Iodide (I^-) is transported vectorially from the plasma across the epithelial cells of the thyroid gland by specific transporters. The iodide is converted to iodine, which reacts with tyrosine residues exposed on the surface of thyroglobulin molecules resident in the colloid. Iodination of tyrosine takes place at the apical border of the thyroid cells while the tyrosine moieties remain bound to thyroglobulin via peptide linkages.



Iodide must also exit the thyrocyte across the apical membrane to access the colloid, where the initial steps of thyroid hormone synthesis occur. This transport step is believed to be mediated, at least in part, by a Cl^-/I^- exchanger known as **pendrin** (Figure 20–6). This protein was first identified as the product of the gene responsible for the Pendred syndrome, which causes thyroid dysfunction and deafness. Pendrin (SLC26A4) is one member of the larger family of SLC26 anion exchangers.

The relationship of thyroid function to iodide is unique. Iodide is essential for normal thyroid function, but iodide deficiency and iodide excess both inhibit thyroid function.

The salivary glands, the gastric mucosa, the placenta, the ciliary body of the eye, the choroid plexus, the mammary glands, and certain cancers derived from these tissues also express NIS and can transport iodide against a concentration gradient, but the transporter in these tissues is not affected by TSH. The physiologic significance of all these extrathyroidal iodide-concentrating mechanisms is obscure, but they may provide pathways for radioablation of NIS-expressing cancer cells using iodide radioisotopes. This approach is also useful for the ablation of thyroid cancers.

THYROID HORMONE SYNTHESIS & SECRETION

At the interface between the thyrocyte and the colloid, iodide undergoes a process referred to as organification. First, it is oxidized to iodine, and then incorporated into the carbon 3 position of tyrosine residues that are part of the thyroglobulin molecule in the colloid (Figure 20–6). **Thyroglobulin** is a glycoprotein made up of two subunits. It contains 123 tyrosine residues, but only 4–8 of these are normally incorporated into thyroid hormones. Thyroglobulin is synthesized in the thyrocytes and secreted into the colloid by exocytosis of granules. The oxidation and reaction of iodide with the secreted thyroglobulin is mediated by **thyroid peroxidase,** a membrane-bound enzyme found in the thyrocyte apical membrane. The thyroid hormones so produced remain part of the thyroglobulin molecule until needed. As such, colloid represents a reservoir of thyroid hormones, and humans can ingest a diet completely devoid of iodide for up to 2 months before a decline in circulating thyroid hormone levels is seen. When there is a need for thyroid hormone secretion, colloid is internalized by the thyrocytes by endocytosis, and directed toward lysosomal degradation. Thus, the peptide bonds of thyroglobulin are hydrolyzed, and free T_4 and T_3 are discharged into cytosol and thence to the capillaries (see below). Thyrocytes thus have four functions: They collect and transport iodine, they synthesize thyroglobulin and secrete it into the colloid, they fix iodine to the thyroglobulin to generate thyroid hormones, and they remove the thyroid hormones from thyroglobulin and secrete them into the circulation.

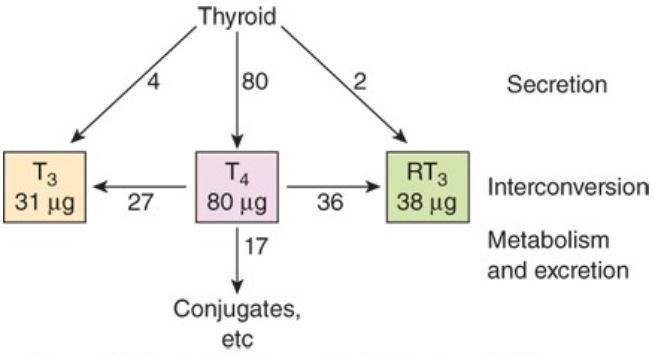
Thyroid hormone synthesis is a multistep process. Thyroid peroxidase generates reactive iodine species that can attack thyroglobulin. The first product is monoiodotyrosine (MIT). MIT is next iodinated on the carbon 5 position to form diiodotyrosine (DIT). Two DIT molecules then undergo an oxidative condensation to form T_4 with the elimination of the alanine side chain from the molecule that forms the outer ring. There are two theories of how this **coupling reaction** occurs. One holds that the coupling occurs with both DIT molecules attached to thyroglobulin (intramolecular coupling). The other holds that the DIT that forms the outer ring is first detached from thyroglobulin (intermolecular coupling). In either case, thyroid peroxidase is involved in coupling as well as iodination. T_3 is formed by condensation of MIT with DIT. RT_3 is likely formed by condensation of DIT with MIT. In the

normal human thyroid, the average distribution of iodinated compounds is 3% MIT, 33% DIT, 35% T_4, and 7% T_3. Only traces of RT_3 and other components are present.

The human thyroid secretes about 80 µg (103 nmol) of T_4, 4 µg (7 nmol) of T_3, and 2 µg (3.5 nmol) of RT_3 per day (**Figure 20–7**). MIT and DIT are not secreted. These iodinated tyrosines can be deiodinated by a microsomal **iodotyrosine deiodinase.** This represents a mechanism to recover iodine and bound tyrosines and recycle them for additional rounds of hormone synthesis. The iodine liberated by deiodination of MIT and DIT is reutilized in the gland and normally provides about twice as much iodide for hormone synthesis as NIS does. In patients with congenital absence of the iodotyrosine deiodinase, MIT and DIT appear in the urine and there are symptoms of iodine deficiency (see below). Iodinated thyronines are resistant to the activity of iodotyrosine deiodinase, thus allowing T_4 and T_3 to pass into the circulation.

FIGURE 20–7

Secretion and interconversion of thyroid hormones in normal adult humans. Figures are in micrograms per day. Note that most of the T_3 and RT_3 are formed from T_4 deiodination in the tissues and only small amounts are secreted by the thyroid. T_4 is also conjugated for subsequent excretion from the body.



Source: K.E. Barrett, S.M. Barman, H.L. Brooks, Jason X.J. Yuan: Ganong's Review of Medical Physiology, Twenty-Sixth Edition

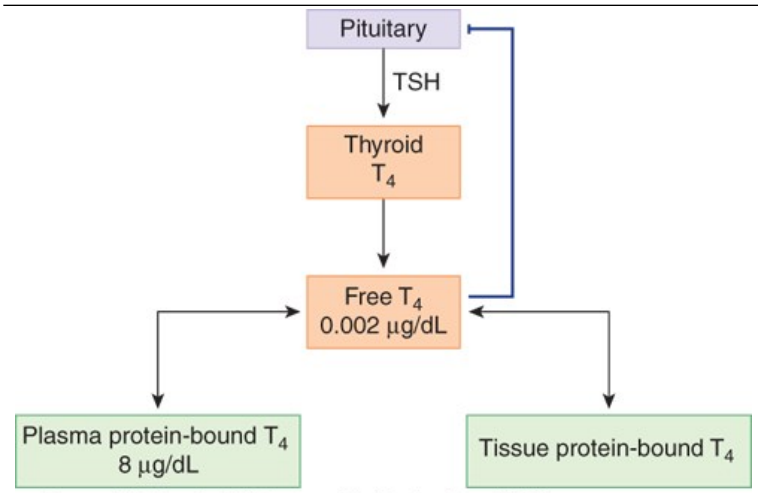
TRANSPORT & METABOLISM OF THYROID HORMONES

PROTEIN BINDING

The normal total **plasma T_4** level in adults is approximately 8 µg/dL (103 nmol/L), and the **plasma T_3** level is approximately 0.15 µg/dL (2.3 nmol/L). T_4 and T_3 are relatively lipophilic; thus, their free forms in plasma are in equilibrium with a much larger pool of protein-bound thyroid hormones in plasma and in tissues. Free thyroid hormones are added to the circulating pool by the thyroid. It is the free thyroid hormones in plasma that are physiologically active and that feed back to inhibit pituitary secretion of TSH (**Figure 20–8**). The function of protein-binding appears to be the maintenance of a large pool of hormone that can readily be mobilized as needed. In addition, at least for T_3, hormone-binding prevents excess uptake by the first cells encountered and promotes uniform tissue distribution. Total T_4 and T_3 can both be measured by radioimmunoassay. There are also direct assays that specifically measure only the free forms of the hormones. The latter are the more clinically relevant measures given that these are the active forms, and also due to both acquired and congenital variations in the concentrations of binding proteins between individuals.

FIGURE 20–8

Regulation of thyroid hormone synthesis. T_4 is secreted by the thyroid in response to TSH. Free T_4 secreted by the thyroid into the circulation is in equilibrium with T_4 bound to both plasma and tissue proteins. Free T_4 also feeds back to inhibit TSH secretion by the pituitary. Not shown, T_3 is also secreted (in small amounts) by the thyroid and produced (in larger amounts) from T_4 in the periphery by deiodination. T_3 also feeds back to reduce secretion of TSH from the pituitary.



Source: K.E. Barrett, S.M. Barman, H.L. Brooks, Jason X.J. Yuan: Ganong's Review of Medical Physiology, Twenty-Sixth Edition

The plasma proteins that bind thyroid hormones are **albumin, transthyretin** (formerly called **thyroxine-binding prealbumin),** and **thyroxine-binding globulin (TBG).** Of the three proteins, albumin has the largest **capacity** to bind T_4 (ie, it can bind the most T_4 before becoming saturated) and TBG has the smallest capacity. However, the **affinities** of the proteins for T_4 (ie, the avidity with which they bind T_4 under physiologic conditions) are such that most of the circulating T_4 is bound to TBG (**Table 20–1**). Smaller amounts of T_4 are bound to transthyretin and albumin.

TABLE 20–1

Binding of thyroid hormones to plasma proteins in normal adult humans.

Protein	Plasma Concentration (mg/dL)	Amounts of Circulating Hormone Bound (%)	
		T_4	T_3
Thyroxine-binding globulin (TBG)	2	67	46
Transthyretin (thyroxine-binding prealbumin, TBPA)	15	20	1
Albumin	3500	13	53

Normally, 99.98% of the T_4 in plasma is bound; the free T_4 level is only about 2 ng/dL. There is very little T_4 in the urine. Its biologic half-life is long (about 6–7 days), and its volume of distribution is less than that of ECF (10 L, or about 15% of body weight). All of these properties are characteristic of a substance that is strongly bound to protein.

T_3 is not bound to quite as great an extent; of the 0.15 µg/dLnormally found in plasma, 0.2% (0.3 ng/dL) is free. The remaining 99.8% is protein-bound, 46% to TBG and most of the remainder to albumin, with very little binding to transthyretin (Table 20–1). The lesser binding of T_3 correlates with the facts that T_3 has a shorter half-life than T_4 and that its action on the tissues is much more rapid. RT_3 also binds to TBG.

FLUCTUATIONS IN BINDING

When a sudden, sustained increase in the concentration of thyroid-binding proteins in the plasma takes place, the concentration of free thyroid hormones falls. This change is temporary, however, because the decrease in the concentration of free thyroid hormones in the circulation stimulates TSH secretion, which in turn causes an increase in the production of free thyroid hormones. A new equilibrium is eventually reached at which the total quantity of thyroid hormones in the blood is elevated but the concentration of free hormones, the rate of their metabolism, and the rate of TSH

secretion are normal. Corresponding changes in the opposite direction occur when the concentration of thyroid-binding protein is reduced. Consequently, patients with elevated or decreased concentrations of binding proteins, particularly TBG, are typically neither hyperthyroid nor hypothyroid; that is, they are **euthyroid.**

TBG levels are elevated in estrogen-treated patients and during pregnancy, as well as after treatment with various drugs (**Table 20–2**). They are depressed by glucocorticoids, androgens, the weak androgen danazol, and the cancer chemotherapeutic agent L-asparaginase. A number of other drugs, including salicylates, the anticonvulsant phenytoin, and the cancer chemotherapeutic agents mitotane (o, p′-DDD) and 5-fluorouracil, inhibit binding of T_4 and T_3 to TBG and consequently produce changes similar to those produced by a decrease in TBG concentration. Changes in total plasma T_4 and T_3 can also be produced by changes in plasma concentrations of albumin and prealbumin.

TABLE 20–2

Effect of variations in the concentrations of thyroid hormone–binding proteins in the plasma on various parameters of thyroid function after equilibrium has been reached.

Condition	Concentrations of Binding Proteins	Total Plasma T_4, T_3, RT_3	Free Plasma T_4, T_3, RT_3	Plasma TSH	Clinical State
Hyperthyroidism	Normal	High	High	Low	Hyperthyroid
Hypothyroidism	Normal	Low	Low	High	Hypothyroid
Estrogens, methadone, heroin, antipsychotic drugs, clofibrate	High	High	Normal	Normal	Euthyroid
Glucocorticoids, androgens, danazol, asparaginase	Low	Low	Normal	Normal	Euthyroid

METABOLISM OF THYROID HORMONES

T_4 and T_3 are deiodinated in the liver, the kidneys, and many other tissues. These deiodination reactions serve not only to catabolize the hormones, but also to provide a local supply specifically of T_3, which is believed to be the primary mediator of the physiologic effects of thyroid secretion. One-third of the circulating T_4 is normally converted to T_3 in adult humans, and 45% is converted to RT_3. As shown in Figure 20–7, only about 13% of the circulating T_3 is secreted by the thyroid while 87% is formed by deiodination of T_4; similarly, only 5% of the circulating RT_3 is secreted by the thyroid and 95% is formed by deiodination of T_4. It should be noted as well that marked differences in the ratio of T_3 to T_4 occur in various tissues. Two tissues that have very high T_3/T_4 ratios are the pituitary and the cerebral cortex, due to the expression of specific deiodinases, as discussed below. In the brain, in particular, high levels of deiodinase activity ensure an ample supply of active T_3.

Three different deiodinases act on thyroid hormones: D_1, D_2, and D_3. All are unique in that they contain the rare amino acid selenocysteine, with selenium in place of sulfur, which is essential for their enzymatic activity. D_1 is present in high concentrations in the liver, kidneys, thyroid, and pituitary. It appears primarily to be responsible for maintaining the formation of T_3 from T_4 in the periphery. D_2 is present in the brain, pituitary, and brown fat. It also contributes to the formation of T_3. In the brain, it is located in astroglia and provides a supply of T_3 to neurons. D_3 is also present in the brain and in reproductive tissues. It acts only on the 5 position of T_4 and T_3 and is probably the main source of RT_3 in the blood and tissues.

Some of the T_4 and T_3 are further converted to deiodotyrosines by deiodinases. T_4 and T_3 are also conjugated in the liver to form sulfates and glucuronides. These conjugates enter the bile and pass into the intestine. The thyroid conjugates are hydrolyzed, and some are thereafter reabsorbed

(enterohepatic circulation), but others are excreted in the stool. In addition, some T_4 and T_3 pass directly from the circulation to the intestinal lumen. The iodide lost by these routes amounts to about 4% of the total daily iodide loss.

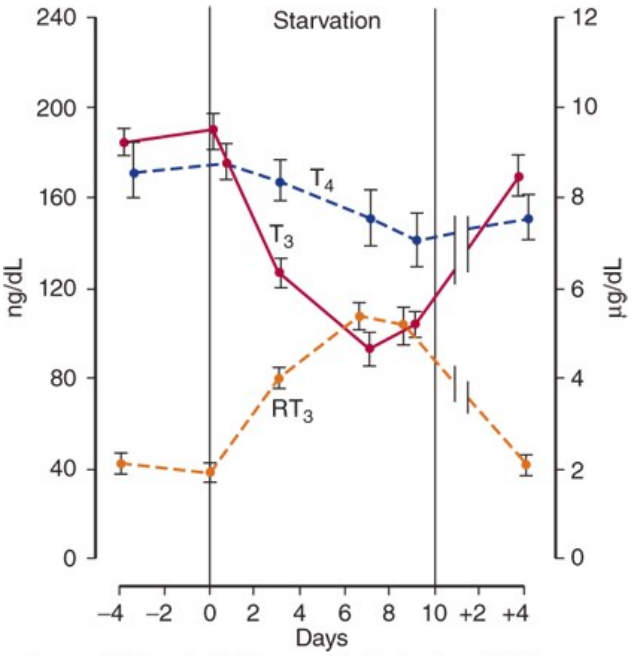
FLUCTUATIONS IN DEIODINATION

Much more RT_3 and much less T_3 are formed during fetal life, and the ratio shifts to that of adults about 6 weeks after birth. Various drugs inhibit deiodinases, producing a fall in plasma T_3 levels and a reciprocal rise in RT_3. Selenium deficiency has the same effect. A wide variety of nonthyroidal illnesses also suppress deiodinases. These include burns, trauma, advanced cancer, cirrhosis, chronic kidney disease, myocardial infarction, and febrile states. The low-T_3 state produced by these conditions disappears with recovery.

Diet also has a clear-cut effect on conversion of T_4 to T_3. In fasted individuals, plasma T_3 is reduced by 10–20% within 24 h and by about 50% in 3–7 days, with a corresponding rise in RT_3 (**Figure 20–9**). Free and bound T_4 levels remain essentially normal. During more prolonged starvation, RT_3 returns to normal but T_3 remains depressed. At the same time, the basal metabolic rate (BMR) falls and urinary nitrogen excretion, an index of protein breakdown, is decreased. Thus, the decline in T_3 conserves calories and protein. Conversely, overfeeding increases T_3 and reduces RT_3.

FIGURE 20–9

Effect of starvation on plasma levels of T_4, T_3, and RT_3 in humans. The scale for T_3 and RT_3 is on the left and the scale for T_4 is on the right. The most pronounced effect is a reduction in T_3 levels with a reciprocal rise in RT_3. The changes, which conserve calories by reducing tissue metabolism, are reversed promptly by refeeding. Similar changes occur in wasting diseases. (Reproduced with permission from Burger AG: New aspects of the peripheral action of thyroid hormones. Triangle 1983;22:175. Copyright © 1983 Sandoz Ltd., Basel, Switzerland.)



REGULATION OF THYROID SECRETION

Thyroid function is regulated primarily by variations in the circulating level of pituitary TSH (Figure 20–8). TSH secretion is increased by the hypothalamic hormone TRH (see Chapter 17) and inhibited in a negative feedback manner by circulating free T_4 and T_3. The effect of T_4 is enhanced by production of T_3 in the cytoplasm of the pituitary cells by the D_2 they contain. TSH secretion is also inhibited by stress, and in experimental animals it is

increased by cold and decreased by warmth.

CHEMISTRY & METABOLISM OF TSH

Human TSH is a glycoprotein made up of α and β subunits that become noncovalently linked in the pituitary thyrotropes. TSH-α is identical to the α subunit of luteinizing hormone, follicle-stimulating hormone, and human chorionic gonadotropin (hCG) (see Chapters 18 and 22). The functional specificity of TSH is therefore conferred by the β subunit.

The biologic half-life of human TSH is about 60 min. TSH is degraded for the most part in the kidneys and to a lesser extent in the liver. Secretion is pulsatile, and mean output starts to rise at about 9:00 PM, peaks at midnight, and then declines thereafter. The normal secretion rate is about 110 µg/day. The average plasma level is about 2 µg/mL.

Because the α subunit in hCG is the same as that in TSH, large amounts of hCG can activate TSH receptors nonspecifically. In some patients with benign or malignant tumors of placental origin, plasma hCG levels can rise so high that they produce mild hyperthyroidism.

EFFECTS OF TSH ON THE THYROID

When the pituitary is removed, thyroid function is depressed and the gland atrophies; when TSH is administered, thyroid function is stimulated. TSH acts via its receptor, a typical G-protein-coupled, seven-transmembrane receptor that activates adenylyl cyclase through G_s. It also activates phospholipase C (PLC). Within a few minutes after the injection of TSH, there are increases in iodide binding, synthesis of T_3, T_4, and iodotyrosines, secretion of thyroglobulin into the colloid, and endocytosis of colloid. Iodide trapping is increased in a few hours; blood flow increases; and, with long-term TSH treatment, the thyrocytes hypertrophy and the weight of the gland increases.

Whenever TSH stimulation is prolonged, the thyroid becomes detectably enlarged. Enlargement of the thyroid is called a **goiter.**

OTHER FACTORS AFFECTING THYROID GROWTH

In addition to TSH receptors, thyrocytes express receptors for insulin-like growth factor I (IGF-I) and epidermal growth factor (EGF). IGF-I and EGF promote growth, whereas interferon-γ and tumor necrosis factor-α inhibit growth. The effect of the cytokines implies that thyroid function might be inhibited in the setting of chronic inflammation, which could contribute to cachexia, or weight loss.

CONTROL MECHANISMS

The mechanisms regulating thyroid secretion are summarized in Figure 20–8. The negative feedback effect of thyroid hormones on TSH secretion is exerted in part at the hypothalamic level, but it is also due in large part to an action on the pituitary, since T_4 and T_3 block the increase in TSH secretion produced by TRH. Infusion of either T_4 or T_3 reduces circulating TSH, which declines measurably within 1 h. The day-to-day maintenance of thyroid secretion depends on the feedback interplay of thyroid hormones with TSH and TRH (Figure 20–8). The adjustments that appear to be mediated via TRH include the increased secretion of thyroid hormones produced by cold and, presumably, the decrease produced by heat. It is worth noting that although cold produces clear-cut increases in circulating TSH in human infants, the rise produced by cold in adults is negligible. Consequently, in adults, increased heat production due to increased thyroid hormone secretion **(thyroid hormone thermogenesis)** plays little if any role in the response to cold. Stress has an inhibitory effect on TRH secretion. Glucocorticoids also inhibit TSH secretion.

EFFECTS OF THYROID HORMONES

Some of the widespread effects of thyroid hormones in the body are secondary to stimulation of O_2 consumption **(calorigenic action),** although the hormones also affect growth and development in mammals, help regulate lipid metabolism, and increase the absorption of carbohydrates from the intestine **(Table 20–3)**. They also increase the dissociation of oxygen from hemoglobin by increasing red cell 2,3-diphosphoglycerate (DPG) (see Chapter 35).

TABLE 20–3

Physiologic effects of thyroid hormones.

Target Tissue	Effect	Mechanism
Heart	Chronotropic and inotropic	Increased number of β-adrenergic receptors Enhanced responses to circulating catecholamines Increased proportion of α-myosin heavy chain (with higher ATPase activity)
Adipose tissue	Catabolic	Stimulated lipolysis
Muscle	Catabolic	Increased protein breakdown
Bone	Developmental	Promote normal growth and skeletal development
Nervous system	Developmental	Promote normal brain development
Gut	Metabolic	Increased rate of carbohydrate absorption
Lipoprotein	Metabolic	Formation of LDL receptors
Other	Calorigenic	Stimulated oxygen consumption by metabolically active tissues (exceptions: testes, uterus, lymph nodes, spleen, anterior pituitary) Increased metabolic rate

Modified with permission from McPhee SJ, Lingarra VR, Ganong WF (editors): *Pathophysiology of Disease*, 6th ed. New York, NY: McGraw-Hill; 2010.

MECHANISM OF ACTION

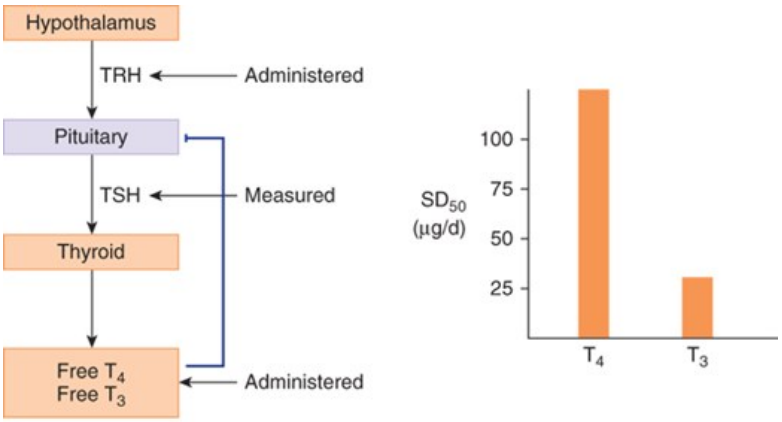
Thyroid hormones enter cells and T_3 binds to thyroid hormone receptors **(TRs),** members of the superfamily of hormone-sensitive nuclear transcription factors. T_4 can also bind, but not as avidly. The hormone–receptor complex then migrates to the nucleus and binds to DNA via zinc fingers and increases (or in some cases, decreases) the expression of a variety of different genes that code for proteins regulating cell function (see Chapters 1 and 16).

There are two human TR genes: an α receptor gene on chromosome 17 and a β receptor gene on chromosome 3. By alternative splicing, each forms at least two different mRNAs and therefore two different receptor proteins. TRβ2 is found only in the brain, but TRα1, TRα2, and TRβ1 are widely distributed. TRα2 differs from the other three in that it does not bind thyroid hormones due to a unique C-terminus, and may actually antagonize the activity of the other TRs. TRs bind to DNA as monomers, homodimers, and heterodimers with other nuclear receptors, particularly the retinoid X receptor **(RXR).** The TR/RXR heterodimer does not bind to 9-*cis* retinoic acid, the usual ligand for RXR, but TR binding to DNA is greatly enhanced in response to thyroid hormones when the receptor is in the form of this heterodimer. There are also coactivator and corepressor proteins that affect the actions of TRs. Presumably, this complexity underlies the ability of thyroid hormones to produce many different effects in the body.

In most of its actions, T_3 acts more rapidly and is three to five times more potent than T_4 **(Figure 20–10)**. This is because T_3 is less tightly bound to plasma proteins than is T_4, but binds more avidly to thyroid hormone receptors. As previously noted, RT_3 is inert.

FIGURE 20–10

Experiment demonstrating the relative potency of T_4 and T_3. Healthy male volunteers were given TRH to stimulate TSH production in the absence or presence of various doses of T_3 or T_4. The left hand portion of the figure shows the relationships between the hormones that were administered or measured. On the right, the calculated doses of T_3 and T_4 needed to reduce the TSH response induced by TRH by 50% (SD_{50}) are shown. Note the substantially greater potency of T_3. (Data from Sawin CT, Hershman JM, Chopra IJ: The comparative effect of T4 and T3 on the TSH response to TRH in young adult men. J Clin Endo Metab 1977; 44:273–278.)



CALORIGENIC ACTION

T_4 and T_3 increase O_2 consumption by almost all metabolically active tissues. The exceptions are the adult brain, testes, uterus, lymph nodes, spleen, and anterior pituitary. T_4 actually depresses the O_2 consumption of the anterior pituitary, presumably because it inhibits TSH secretion. The increase in metabolic rate produced by a single dose of T_4 becomes measurable after a latent period of several hours and lasts 6 days or more.

Some of the calorigenic effect of thyroid hormones is due to metabolism of the fatty acids they mobilize. In addition, thyroid hormones increase the activity of the membrane-bound Na, K ATPase in many tissues.

EFFECTS SECONDARY TO CALORIGENESIS

When the metabolic rate is increased by T_4 and T_3 in adults, nitrogen excretion is increased; if food intake is not increased, endogenous protein and fat stores are catabolized and weight is lost. In hypothyroid children, small doses of thyroid hormones cause a positive nitrogen balance because they stimulate growth, but large doses cause protein catabolism similar to that produced in the adult. The potassium liberated during protein catabolism appears in the urine, and there is also an increase in urinary hexosamine and uric acid excretion.

When the metabolic rate is increased, the need for all vitamins is increased and vitamin deficiency syndromes may be precipitated. Thyroid hormones are necessary for hepatic conversion of carotene to vitamin A, and the accumulation of carotene in the bloodstream **(carotenemia)** in hypothyroidism is responsible for the yellowish tint of the skin. Carotenemia can be distinguished from jaundice because in the former condition the sclera are not yellow.

The skin normally contains a variety of proteins combined with polysaccharides, hyaluronic acid, and chondroitin sulfuric acid. In hypothyroidism, these complexes accumulate, promoting water retention and the characteristic puffiness of the skin (myxedema). When thyroid hormones are administered, the proteins are metabolized, and diuresis continues until the myxedema is cleared.

Milk secretion is decreased in hypothyroidism and stimulated by thyroid hormones, a fact sometimes put to practical use in the dairy industry. Thyroid hormones do not stimulate the metabolism of the uterus but are essential for normal menstrual cycles and fertility.

EFFECTS ON THE CARDIOVASCULAR SYSTEM

Large doses of thyroid hormones cause enough extra heat production to lead to a slight rise in body temperature (Chapter 17), which in turn activates heat-dissipating mechanisms. Peripheral resistance decreases because of cutaneous vasodilation, and this increases levels of renal Na^+ and water absorption, expanding blood volume. Cardiac output is increased by the direct action of thyroid hormones, as well as that of catecholamines, on the heart, so that pulse pressure and cardiac rate are increased and circulation time is shortened.

T_3 is not formed from T_4 in cardiac myocytes, but circulating T_3 enters myocytes, combines with its receptors, and enters the nucleus, where the complex promotes the expression of some genes and inhibits the expression of others. Those that are enhanced include the genes for α-myosin heavy chain, sarcoplasmic reticulum Ca^{2+} ATPase, β-adrenergic receptors, G-proteins, Na, K ATPase, and certain K^+ channels. Those that are inhibited include the genes for β-myosin heavy chain, phospholamban, two types of adenylyl cyclase, TRs, and NCX, the Na^+–Ca^{2+} exchanger. The net result is increased heart rate and force of contraction.

The two myosin heavy chain (MHC) isoforms, α-MHC and β-MHC, produced by the heart are encoded by two highly homologous genes located on the short arm of chromosome 17. Each myosin molecule consists of two heavy chains and two pairs of light chains (see Chapter 5). The myosin containing β-MHC has less ATPase activity than the myosin containing α-MHC. α-MHC predominates in the atria in adults, and its level is increased by treatment with thyroid hormone. This increases the speed of cardiac contraction. Conversely, expression of the α-MHC gene is depressed and that of the β-MHC gene is enhanced in hypothyroidism.

EFFECTS ON THE NERVOUS SYSTEM

In hypothyroidism, mentation is slow and the cerebrospinal fluid (CSF) protein level is elevated. Thyroid hormones reverse these changes, and large doses cause rapid mentation, irritability, and restlessness. Overall, cerebral blood flow and glucose and O_2 consumption by the brain are normal in adult hypothyroidism and hyperthyroidism. However, thyroid hormones enter the brain in adults and are found in gray matter in numerous different locations. In addition, astrocytes in the brain convert T_4 to T_3, and there is a sharp increase in brain D_2 activity after thyroidectomy that is reversed within 4 h by a single intravenous dose of T_3. Some of the effects of thyroid hormones on the brain are probably secondary to increased responsiveness to catecholamines, with consequent increased activation of the reticular activating system (see Chapter 14). In addition, thyroid hormones have marked effects on brain development. The parts of the central nervous system (CNS) most affected are the cerebral cortex and the basal ganglia. In addition, the cochlea is also affected. Consequently, thyroid hormone deficiency during development causes mental retardation, motor rigidity, and deaf–mutism. Deficiencies in thyroid hormone synthesis secondary to a failure of thyrocytes to transport iodide presumably also contribute to deafness in Pendred syndrome, discussed above.

Thyroid hormones also exert effects on reflexes. The reaction time of stretch reflexes (see Chapter 12) is shortened in hyperthyroidism and prolonged in hypothyroidism. Measurement of the reaction time of the ankle jerk (Achilles reflex) once attracted attention as a clinical test for evaluating thyroid function, but this reaction time is also affected by other diseases and thus is not a specific assessment of thyroid activity.

RELATION TO CATECHOLAMINES

The actions of thyroid hormones and the catecholamines norepinephrine and epinephrine are intimately interrelated. Epinephrine increases the metabolic rate, stimulates the nervous system, and produces cardiovascular effects similar to those of thyroid hormones, although the duration of these actions is brief. Norepinephrine has generally similar actions. The toxicity of the catecholamines is markedly increased in rats treated with T_4.

Although plasma catecholamine levels are normal in hyperthyroidism, the cardiovascular effects, tremulousness, and sweating that are seen in the setting of excess thyroid hormones can be reduced or abolished by sympathectomy. They can also be reduced by drugs such as propranolol that block β-adrenergic receptors. Indeed, propranolol and other β-blockers are used extensively in the treatment of thyrotoxicosis and in the treatment of the severe exacerbations of hyperthyroidism called **thyroid storms.** However, even though β-blockers can weakly inhibit extrathyroidal conversion of T_4 to T_3, and consequently may produce a small fall in plasma T_3, they have little effect on the other actions of thyroid hormones. Presumably, the functional synergism observed between catecholamines and thyroid hormones, particularly in pathologic settings, arises from their overlapping biologic functions as well as the ability of thyroid hormones to increase expression of catecholamine receptors and the signaling effectors to which they are linked.

EFFECTS ON SKELETAL MUSCLE

Muscle weakness occurs in most patients with hyperthyroidism **(thyrotoxic myopathy),** and when the hyperthyroidism is severe and prolonged, the myopathy may be severe. The muscle weakness may be due in part to increased protein catabolism. Thyroid hormones affect the expression of the MHC genes in skeletal as well as cardiac muscle (see Chapter 5). However, the effects produced are complex and their relation to the myopathy is not established. Hypothyroidism is also associated with muscle weakness, cramps, and stiffness.

EFFECTS ON CARBOHYDRATE METABOLISM

Thyroid hormones increase the rate of absorption of carbohydrates from the gastrointestinal tract, an action that is probably independent of their calorigenic action. In hyperthyroidism, therefore, the plasma glucose level rises rapidly after a carbohydrate meal, sometimes exceeding the renal threshold. However, it falls again at a rapid rate.

EFFECTS ON CHOLESTEROL METABOLISM

Thyroid hormones lower circulating cholesterol levels. The plasma cholesterol level drops before the metabolic rate rises, which indicates that this action is independent of the stimulation of O_2 consumption. The decrease in plasma cholesterol concentration is due to increased formation of low-density lipoprotein (LDL) receptors in the liver, resulting in increased hepatic removal of cholesterol from the circulation. Despite considerable effort, however, it has not been possible to produce a clinically useful thyroid hormone analog that lowers plasma cholesterol without increasing metabolism.

EFFECTS ON GROWTH

Thyroid hormones are essential for normal growth and skeletal maturation (see Chapter 21). In hypothyroid children, bone growth is slowed and epiphysial closure delayed. In the absence of thyroid hormones, growth hormone secretion is also depressed. This further impairs growth and development, since thyroid hormones normally potentiate the effect of growth hormone on tissues.

DISORDERS OF THYROID FUNCTION

Based on the foregoing, some of the causes and effects of either under- or overactive thyroid function (hypo- and hyperthyroid conditions, respectively) should be predictable (**Clinical Boxes 20–1** and **20–2**). Altered regulation of thyroid-responsive physiological systems can also be seen in the setting of thyroid hormone resistance, most commonly attributed to mutations in TRβ (**Clinical Box 20–3**).

CLINICAL BOX 20–1

Reduced Thyroid Function

The syndrome of adult **hypothyroidism** is generally called **myxedema,** although this term is also used to refer specifically to the skin changes in the syndrome. Hypothyroidism may be the end result of a number of diseases of the thyroid gland, or it may be secondary to pituitary or hypothalamic failure. In the latter two conditions, the thyroid remains able to respond to TSH. Thyroid function may be reduced by a number of conditions **(Table 20–4)**. For example, when the dietary iodine intake falls below 50 µg/day, thyroid hormone synthesis is inadequate and secretion declines. As a result of increased TSH secretion, the thyroid hypertrophies, producing an **iodine deficiency goiter** that may become very large. Such "endemic goiters" have been substantially reduced by the practice of adding iodide to table salt. Drugs may also inhibit thyroid function. Most do so either by interfering with the iodide-trapping mechanism or by blocking the organic binding of iodine. In either case, TSH secretion is stimulated by the decline in circulating thyroid hormones, and a goiter is produced. Paradoxically, another substance that inhibits thyroid function under certain conditions is iodide itself. In normal individuals, large doses of iodide act directly on the thyroid to produce a mild and transient inhibition of organic binding of iodide and hence of hormone synthesis. This inhibition is known as the **Wolff–Chaikoff effect.**

In completely athyreotic adults, the BMR falls to about 40%. The hair is coarse and sparse, the skin is dry and yellowish (carotenemia), and cold is poorly tolerated. Mentation is slow, memory is poor, and in some patients there are severe mental symptoms ("myxedema madness"). Plasma cholesterol is elevated. Children who are hypothyroid from birth or before are called **cretins.** They are dwarfed and mentally retarded. Worldwide, congenital hypothyroidism is one of the most common causes of preventable mental retardation. The main causes are included in Table 20–4. They include not only maternal iodine deficiency and various congenital abnormalities of the fetal hypothalamo–pituitary–thyroid axis, but also maternal antithyroid antibodies that cross the placenta and damage the fetal thyroid. T_4 also crosses the placenta, and unless the mother is hypothyroid, growth and development are normal until birth. If treatment is started at birth, the prognosis for normal growth and development is good, and mental retardation can generally be avoided; for this reason, screening tests for congenital hypothyroidism are becoming routine. When the mother is hypothyroid as well, as in the case of iodine deficiency, the mental deficiency is more severe and less responsive to treatment after birth. It has been estimated that 20 million people in the world now have various degrees of brain damage caused by iodine deficiency in utero.

Uptake of tracer doses of radioactive iodine can be used to assess thyroid function (contrast this with the use of large doses to ablate thyroid tissue in cases of hyperthyroidism (Clinical Box 20–2)).

THERAPEUTIC HIGHLIGHTS

The treatment of hypothyroidism depends on the underlying mechanisms. Iodide deficiency can be addressed by adding it to the diet, as is done routinely in developed countries. In congenital hypothyroidism, levothyroxine—a synthetic form of the thyroid hormone T_4—can be given. It is important that this take place as soon as possible after birth, with levels regularly monitored, to minimize long-term adverse effects.

TABLE 20–4

Causes of congenital hypothyroidism.

Maternal iodine deficiency
Fetal thyroid dysgenesis
Inborn errors of thyroid hormone synthesis
Maternal antithyroid antibodies that cross the placenta
Fetal hypopituitary hypothyroidism

CLINICAL BOX 20–2

Hyperthyroidism

The symptoms of an overactive thyroid gland follow logically from the actions of thyroid hormone discussed in this chapter. Thus, hyperthyroidism is characterized by nervousness; weight loss; hyperphagia; heat intolerance; increased pulse pressure; a fine tremor of the outstretched fingers; warm, soft skin; sweating; and a BMR from +10 to as high as +100. It has various causes **(Table 20–5);** however, the most common cause is **Graves disease (Graves hyperthyroidism),** which accounts for 60–80% of the cases. This is an autoimmune disease, more common in women, in which antibodies to the TSH receptor stimulate the receptor. This produces marked T_4 and T_3 secretion and enlargement of the thyroid gland (goiter). However, due to the feedback effects of T_4 and T_3, plasma TSH is low, not high. Another hallmark of Graves disease is the occurrence of swelling of tissues in the orbits, producing protrusion of the eyeballs **(exophthalmos).** This occurs in 50% of patients and often precedes the development of obvious hyperthyroidism. Other antithyroid antibodies are present in Graves disease, including antibodies to thyroglobulin and thyroid peroxidase. In Hashimoto thyroiditis, autoimmune antibodies and infiltrating cytotoxic T cells ultimately destroy the thyroid, but during the early stage the inflammation of the gland causes excess thyroid hormone secretion and thyrotoxicosis similar to that seen in Graves disease.

THERAPEUTIC HIGHLIGHTS

Some of the symptoms of hyperthyroidism can be controlled by the **thioureylenes.** These are a group of compounds related to thiourea, which inhibit the iodination of monoiodotyrosine and block the coupling reaction. The two used clinically are propylthiouracil and methimazole. Iodination of tyrosine is inhibited because propylthiouracil and methimazole compete with tyrosine residues for iodine and become iodinated. In addition, propylthiouracil but not methimazole inhibits D_2 deiodinase, reducing the conversion of T_4 to T_3 in many extrathyroidal tissues. In severe cases, hyperthyroidism can also be treated by the infusion of radioactive iodine, which accumulates in the gland and then partially destroys it. Surgery is also considered if the thyroid becomes so large that it affects swallowing and/or breathing.

TABLE 20–5

Causes of hyperthyroidism.

Thyroid overactivity
Graves disease
Solitary toxic adenoma
Toxic multinodular goiter
Early stages of Hashimoto thyroiditis[a]
TSH-secreting pituitary tumor
Mutations causing constitutive activation of TSH receptor
Other rare causes
Extrathyroidal
Administration of T_3 or T_4 (factitious or iatrogenic hyperthyroidism)
Ectopic thyroid tissue

[a]Note that ultimately the thyroid will be destroyed in Hashimoto disease, resulting in hypothyroidism. Many patients only present after they become hypothyroid, and do not recall a transient phase of hyperthyroidism.

CLINICAL BOX 20–3

Thyroid Hormone Resistance

Some mutations in the gene that codes for TRβ are associated with resistance to the effects of T_3 and T_4. Most commonly, there is resistance to thyroid hormones in the peripheral tissues and the anterior pituitary gland. Patients with this abnormality are usually not clinically hypothyroid, because they maintain plasma levels of T_3 and T_4 that are high enough to overcome the resistance, and hTRα is unaffected. However, plasma TSH is inappropriately high relative to the high circulating T_3 and T_4 levels and is difficult to suppress with exogenous thyroid hormone. Some patients have thyroid hormone resistance only in the pituitary. They have hypermetabolism and elevated plasma T_3 and T_4 levels with normal, nonsuppressible levels of TSH. A few patients apparently have peripheral resistance with normal pituitary sensitivity. They have hypometabolism despite normal plasma levels of T_3, T_4, and TSH. An interesting finding is that **attention deficit hyperactivity disorder,** a condition frequently diagnosed in children who are overactive and impulsive, is much more common in individuals with thyroid hormone resistance than in the general population. This suggests that hTRβ may play a special role in brain development.

THERAPEUTIC HIGHLIGHTS

Most patients remain euthyroid in this condition, even in the face of a goiter. It is important to consider thyroid hormone resistance in the differential diagnosis of Graves disease to avoid the inappropriate use of antithyroid medications or even thyroid ablation. Isolated peripheral resistance to thyroid hormones can be treated by supplying large doses of synthetic T_4 exogenously. These are sufficient to overcome the resistance and increase the metabolic rate.

The amount of thyroid hormone required to maintain normal function in thyroidectomized individuals is defined as the amount necessary to return plasma TSH to normal. Indeed, measurement of TSH is regarded as one of the best tests of thyroid function. The amount of T_4 that normalizes plasma TSH in individuals lacking a functional thyroid gland (**athyreotic**) averages 112 µg of T_4 by mouth per day in adults. About 80% of this dose is absorbed from the gastrointestinal tract. It produces a slightly greater than normal level of free T_4 but a normal level of free T_3, indicating that circulating T_3 may be the principal feedback regulator of TSH secretion in humans.

CHAPTER SUMMARY

- The thyroid gland straddles the trachea in the front of the neck and consists of multiple acini (follicles). Each follicle is surrounded by a single layer of epithelial cells and is filled with colloid, consisting predominantly of thyroglobulin. When the gland is active, areas where the colloid is being reabsorbed are visible (reabsorption lacunae).
- The gland transports and fixes iodide to amino acids present in thyroglobulin to generate the thyroid hormones thyroxine (T_4) and triiodothyronine (T_3). Iodide is transported into the follicle epithelial cells via the Na^+/I^- symporter (NIS) and from there to the colloid via the chloride/iodide exchanger, pendrin. Thyroid peroxidase converts iodide to iodine then incorporates this into the carbon 3 position of tyrosine residues in thyroglobulin in the process of organification.
- Thyroid hormones circulate in the plasma predominantly in protein-bound forms. Only the free hormones are biologically active, and both feed back to reduce secretion of TSH.
- Synthesis and secretion of thyroid hormones is stimulated by thyroid-stimulating hormone (TSH) from the pituitary, which in turn is released in response to thyrotropin-releasing hormone (TRH) from the hypothalamus. These releasing factors are controlled by changes in whole body status (eg, exposure to cold or stress).
- Thyroid hormones exert their effects by entering cells and binding to thyroid receptors. The liganded forms of thyroid receptors are nuclear transcription factors that alter gene expression.
- Thyroid hormones stimulate metabolic rate, calorigenesis, cardiac function, and normal mentation, and interact synergistically with catecholamines. Thyroid hormones also play critical roles in development, particularly of the nervous system, and growth.
- Disease results with both underactivity and overactivity of the thyroid gland. Hypothyroidism is accompanied by mental and physical slowing in adults, and by mental retardation and dwarfism if it occurs in neonatal life. Overactivity of the thyroid gland, which most commonly is caused by autoantibodies that trigger secretion (Graves disease), results in body wasting, nervousness, and tachycardia.