GOODMAN & GILMAN'S The PHARMACOLOGICAL BASIS OF THERAPEUTICS

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CHAPTER 56

THYROID AND ANTITHYROID DRUGS

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This chapter discusses the function of the thyroid hormones, thyroxine (T_4) and triiodothyronine (T_3), in growth and metabolism and the regulation of thyroid function by thyroid-stimulating hormone (TSH) secreted from the pituitary. Calcitonin, also secreted by the thyroid gland, is discussed in Chapter 61. Evaluation of free thyroxine and TSH levels as a means to assess thyroid function is provided as a prelude to the discussion of treatment of the hypothyroid patient with hormone replacement and of the hyperthyroid individual with one of a variety of antithyroid drugs, such as propylthiouracil and methimazole, and other thyroid inhibitors, including ionic inhibitors that interfere with the concentration of iodide by the thyroid gland and radioactive iodine, used both for diagnosis as well as treatment of hypothyroidism. Although disorders of the thyroid are common, effective treatment of most thyroid disorders is available.

Thyroid hormones, the only known iodine-containing compounds with biological activity, have two important functions. In developing animals and human beings, they are crucial determinants of normal development, especially in the central nervous system (CNS). In the adult, thyroid hormones act to maintain metabolic homeostasis, affecting the function of virtually all organ systems. To meet these requirements, there are large stores of preformed hormone within the thyroid gland. Metabolism of the thyroid hormones occurs primarily in the liver, although local metabolism within certain target tissues, such as the brain, also occurs. Serum concentrations of thyroid hormones are precisely regulated by the pituitary hormone, thyrotropin, in a classic negative-feedback system. The predominant actions of thyroid hormone are mediated *via* binding to nuclear thyroid hormone receptors and modulating transcription of specific genes. In this regard, thyroid hormones share a common mechanism of action with steroid hormones, vitamin D, and retinoids, whose receptors make up a superfamily of nuclear receptors (*see* Chapter 2).

Disorders of the thyroid are common. They consist of two general presentations: changes in the size or shape of the gland or changes in secretion of hormones from the gland. Thyroid nodules and goiter in the euthyroid patient are the most common endocrinopathies and can be caused by benign and malignant tumors. The presentation of overt hyper- or hypothyroidism often presents the clinician with dramatic clinical manifestations. While the diagnosis may be clinically obvious, subtle presentations require the use of biochemical tests of thyroid function. Screening of the newborn population for congenital hypothyroidism, followed by the institution of appropriate thyroid hormone replacement therapy, has dramatically decreased the incidence of mental retardation and cretinism in the United States. Worldwide, congenital hypothyroidism due to iodine deficiency remains the major preventable cause of mental retardation.

Effective treatment of most thyroid disorders is readily available. Treatment of the hypothyroid patient is straightforward and consists of hormone replacement. There are more options for treatment of the hyperthyroid patient, including the use of antithyroid drugs to decrease hormone synthesis and secretion by the gland and destruction of the gland by the administration of radioactive iodine or by surgical removal. Treatment of thyroid disorders in general is extremely satisfying, as most patients can be either cured or have their diseases controlled (*see* Braverman and Utiger, 1991; Braverman and Refetoff, 1994).

THYROID

The thyroid gland is the source of two fundamentally different types of hormones. The iodothyronine hormones include thyroxine and 3,5,3′-triiodothyronine; they are essential for normal growth and development and play an important role in energy metabolism. The other known

secretory product of the thyroid, calcitonin, is produced by the parafollicular (C−) cells and is discussed in Chapter 61.

History. The thyroid gland was first described by Galen and was named "glandulae thyroidaeae" by Wharton in 1656. Harington (1935) reviewed the many older opinions concerning the function of this gland. Wharton thought, for example, that the viscous fluid within the follicles lubricated the trachea. He also believed that the gland was larger in women to serve a cosmetic function in giving grace to the contour of the neck. Later observers, influenced by the liberal blood supply of the gland, believed that it provided a vascular shunt for the brain. With this function in mind, Rush in 1820 expressed the belief that the larger size of the gland in women was "necessary to guard the female system from the influence of the more numerous causes of irritation and vexation of mind to which they are exposed than the male sex." However, Hofrichter opposed this theory in the same year by pointing out that "If it were indeed true that the thyroid contains more blood at some times than at others, this effect would be visible to the naked eye; in this case women would certainly have long ceased to go about with bare necks, for husbands would have learned to recognize the swelling of this gland as a danger signal of threatening trouble from their better halves."

The thyroid was first recognized as an organ of importance when enlargement was observed to be associated with changes in the eyes and the heart in the condition we now call *hyperthyroidism*. It is of interest that this condition, the manifestations of which on occasion can be as striking as any in medicine, escaped description until Parry saw his first case in 1786. Parry's account was not published until 1825 and was followed in 1835 and 1840 by those of Graves and Basedow, whose names became applied to the disorder. In 1874 Gull first associated atrophy of the gland with the symptoms now known to be characteristic of thyroid deficiency, and hypofunction of the thyroid, *hypothyroidism*, in adults was known as *Gull's disease*. The term *myxedema* was applied to the clinical syndrome in 1878 by Ord in the belief that the characteristic thickening of the subcutaneous tissues was due to excessive formation of mucus.

Extirpation experiments to elucidate the function of the thyroid were at first misinterpreted because of the simultaneous removal of the parathyroids. However, the pioneer research in the late 19th century on the latter organs by Gley allowed the functional differentiation of these two endocrine glands. It was not until after calcitonin was discovered in 1961 that it was realized that the thyroid itself also was concerned with the regulation of Ca^{2+}. In 1891, Murray became the first to treat a case of hypothyroidism by injecting an extract of the thyroid gland; in the following year, Howitz, Mackenzie, and Fox independently discovered that thyroid tissue was fully effective when given by mouth.

Magnus-Levy discovered the effect of the thyroid on metabolic rate in 1895; he found that Gull's disease was characterized by a low rate of metabolism and that the administration of thyroid to hypothyroid or normal individuals increased oxygen consumption.

Chemistry of Thyroid Hormones. The principal hormones of the thyroid gland are the iodine-containing amino acid derivatives of thyronine—*thyroxine* (T_4) and T_3 (triiodothyronine; 3,5,3′-triiodothyronine; Figure 56–1). Thyroxine was first isolated in crystalline form from a hydrolysate of thyroid by Kendall in 1915; he found that the crystalline product exerted the same physiological effects as the extract from which it was obtained. Eleven years later the structural formula of thyroxine was elucidated by Harington, and in 1927 Harington and Barger synthesized the hormone.

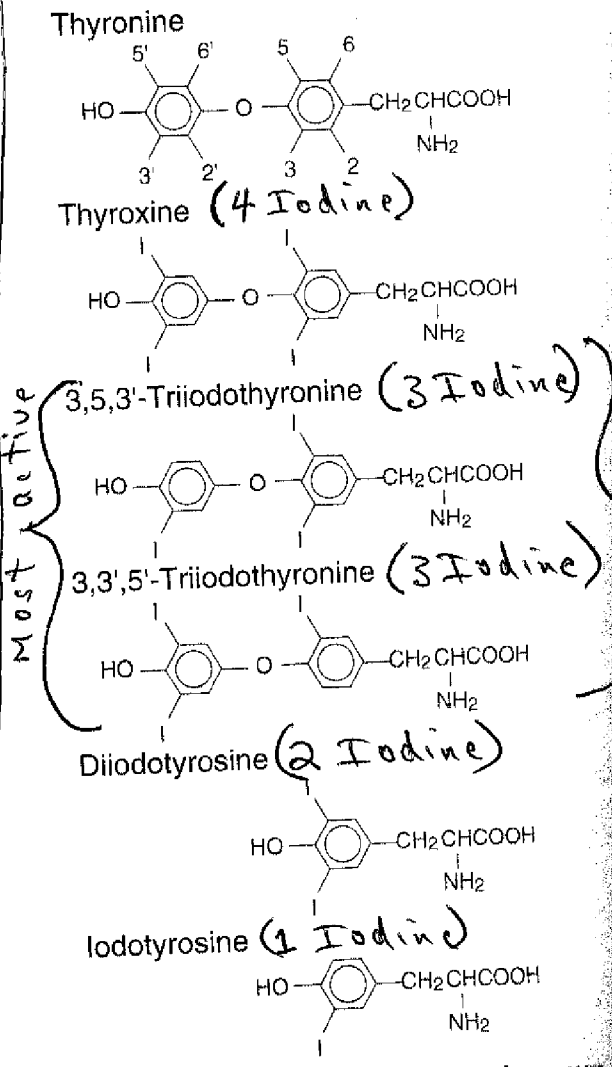


Figure 56–1. Thyronine, thyroid hormones, and precursors.

Following the isolation and the chemical identification of thyroxine, it was generally believed that all the hormonal activity of thyroid tissue could be accounted for by its content of thyroxine. However, careful studies revealed that crude thyroid preparations possessed greater calorigenic activity than could be accounted for by their thyroxine content. The enigma was resolved with the detection, isolation, and synthesis of triiodothyronine (Gross and Pitt-Rivers, 1952; Roche *et al.*, 1952a, 1952b). Further studies revealed that triiodothyronine is qualitatively similar to thyroxine in its biological action but that it is much more potent on a molar basis (Gross and Pitt-Rivers, 1953a, 1953b).

Structure–Activity Relationship. The stereochemical nature of the thyroid hormones plays an important role in defining hormone activity. A great many structural analogs of thyroxine have been synthesized in order to define the structure–activity relationship, to detect antagonists of thyroid hormones, or to find compounds exhibiting one desirable type of activity while not showing unwanted effects.

The only significant success has been the partial separation of the cholesterol-lowering action of thyroxine analogs from their calorigenic or cardiac effects. For example, introduction of specific arylmethyl groups at the 3′ position of triiodothyronine resulted in analogs that are liver-selective, cardiac-sparing thyromimetics (Leeson *et al.*, 1989). The D isomer of thyroxine was once used to lower the concentration of cholesterol in plasma, but cardiac side effects resulted in discontinuation of the clinical uses of this hormone. Newer analogs offer hope that more useful separation of these activities may yet be achievable (Underwood *et al.*, 1986; Sherman and Ladenson, 1992).

The structural requirements for a significant degree of thyroid hormone activity have been defined (*see* Jorgensen, 1964; Cody, 1980, 1991). The 3′-monosubstituted compounds are more active than the 3′,5′-disubstituted molecules. Thus, triiodothyronine is five times more potent than thyroxine, while 3′-isopropyl-3,5-diiodothyronine has seven times the activity.

Although the chemical nature of the 3, 5, 3′, and 5′ substituents is important, their effects on the conformation of the molecule are even more so. In thyronine, the two rings are angulated at about 120° at the ether oxygen and are free to rotate on their axes. As depicted schematically in Figure 56–2, when the 3,5 iodines are in place, rotation of the two rings is somewhat restricted, and they tend to take up positions perpendicular to one another. While not potent, even halogen-free derivatives possess some activity if they have the proper conformation. In general, the affinity of iodothyronines for the thyroid hormone receptor parallels their biological potency (Oppenheimer *et al.*, 1987), but additional factors including affinity for plasma proteins, rate of entry into cell nuclei, and rate of metabolism can affect therapeutic potency.

Recent structure–activity correlations indicate that certain plant flavonoids that are long-standing folk remedies can exhibit antihormonal properties, including inhibition of the enzyme that catalyzes 5′ (outer, or tyrosyl ring) deiodination of T_4 (type I iodothyronine 5′-deiodinase; Cody, 1991). These compounds are also potent competitors of thyroxine binding to transthyretin. Computer graphic modeling suggests that the best structural homology between thyroid hormones and flavonoids involves their respective phenolic rings.

Synthesis of Thyroid Hormones. The synthesis of the thyroid hormones is unique, complex, and seemingly grossly inefficient. The thyroid hormones are synthesized and stored as amino acid residues of thyroglobulin, a protein constituting the vast majority of the thyroid follicular colloid. The thyroid gland is unique in storing great quantities of potential hormone in this way, and extracellular thyroglobulin can represent a large portion of the mass of the gland. Thyroglobulin is a complex glycoprotein made up of two apparently identical subunits, each with a molecular mass of 330 kDa. Interestingly, molecular cloning has revealed that thyroglobulin belongs to a superfamily of serine hydrolases, including acetylcholinesterase (*see* Chapter 8).

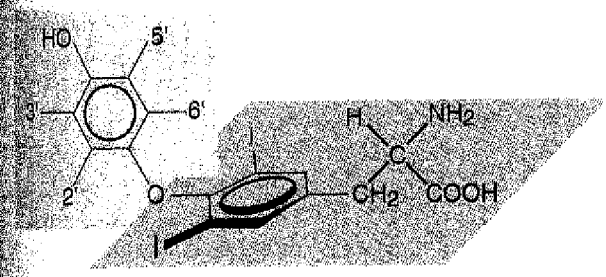
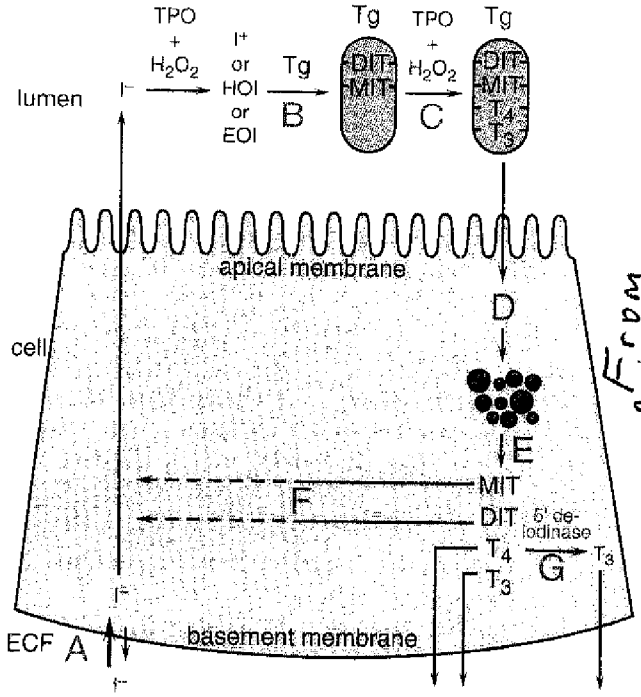


Figure 56–2. Structural formula of 3,5-diiodothyronine, drawn to show the conformation in which the planes of the aromatic rings are perpendicular to each other. (*Adapted from* Jorgensen, 1964. *See also* Cody, 1980.)

The major steps in the synthesis, storage, release, and interconversion of thyroid hormones are the following: (1) the uptake of iodide ion by the gland, (2) the oxidation of iodide and the iodination of tyrosyl groups of thyroglobulin, (3) coupling of iodotyrosine residues by ether linkage to generate the iodothyronines, (4) the proteolysis of thyroglobulin and the release of thyroxine and triiodothyronine into the blood, and (5) the conversion of thyroxine to triiodothyronine in peripheral tissues. These processes are summarized in Figure 56–3.

1. Uptake of Iodide. Iodine ingested in the diet reaches the circulation in the form of iodide. Under normal circumstances, its concentration in the blood is very low (0.2 to 0.4 μg/dl; about 15 to 30 nM), but the thyroid efficiently and actively transports the ion. As a result, the ratio of thyroid to plasma iodide concentration is usually between 20 and 50 and can far exceed 100 when the gland is stimulated. The iodide transport mechanism is inhibited by a number of ions such as thiocyanate and perchlorate (Figure 56–3). The transport system is stimulated by thyrotropin [thyroid-stimulating hormone (TSH); *see* below] and also is controlled by an autoregulatory mechanism. Thus, decreased stores of thyroid iodine enhance iodide uptake, and the administration of iodide can reverse this situation.

If the further metabolism of iodide is blocked by antithyroid drugs, the iodide-concentrating mechanism can be more easily studied. Thus isolated, the mechanism resembles those found in other structures that concentrate iodide, including the salivary glands, gastric mucosa, midportion of the small intestine, choroid plexus, skin, mammary gland, and perhaps the placenta, all of which maintain a concentration of iodide greater than that of the blood. It has been suggested that the accumulation of iodide by the placenta and the mammary gland may be of importance in providing adequate supplies for the fetus and infant, but no obvious purpose is served by the accumulation of iodide at the other sites. It is evident that the iodide-accumulating system of the thyroid is not unique to the gland and does not account for the specific function of synthesizing thyroid hormone.



METABOLIC STEP		INHIBITOR
A	Iodide transport	ClO_4^-, SCN^-
B	Iodination	PTU, MMI
C	Coupling	PTU, MMI
D	Colloid resorption	Colchicine, Li^{2+}, I^- Cytochalasin B
E	Proteolysis	I^-
F	Deiodination of DIT + MIT	Dinitrotyrosine
G	Deiodination of T_4	PTU

Figure 56–3. Major pathways of thyroid hormone biosynthesis and release.

Abbreviations are as follows: Tg, thyroglobulin; DIT, diiodotyrosine; MIT, monoiodotyrosine; TPO, thyroid peroxidase; HOI, hypoiodous acid; EOI, enzyme-linked species; PTU, propylthiouracil; MMI, methimazole; ECF, extracellular fluid. (Adapted from Taurog, 1991, *with permission.*)

2. Oxidation and Iodination. Consistent with the conditions generally necessary for halogenation of aromatic rings, the iodination of tyrosine residues requires the iodinating species to be in a higher state of oxidation than is the anion. The exact nature of the iodinating species was uncertain for many years. However, Magnusson and coworkers (1984) have provided convincing evidence that it is hypoiodate, either as hypoiodous acid (HOI) or as an enzyme-linked species (E-OI).

The oxidation of iodide to its active form is accomplished by thyroid peroxidase, a heme-containing enzyme that utilizes hydrogen peroxide (H_2O_2) as the oxidant (Taurog, 1991; Magnusson *et al.*, 1987). Thyroid peroxidase has been cloned and identified as an autoantigen in autoimmune thyroid disease (McLachlan and Rapoport, 1992). The peroxidase is membrane-bound and appears to be concentrated at or near the apical surface of the thyroid cell. The reaction results in the formation of monoiodotyrosyl and diiodotyrosyl residues in thyroglobulin just prior to its storage in the lumen of the thyroid follicle. It is thought that the formation of the H_2O_2 that serves as a substrate for the peroxidase occurs in close proximity to its site of utilization and involves the oxidation of reduced nicotinamide adenine di-nucleotide phosphate (NADPH). An increase in the generation of H_2O_2 may be an important facet of the mechanism by which TSH stimulates the organification of iodide in thyroid cells. This hypothesis has arisen from observations that TSH stimulates the synthesis of inositol trisphosphate and elevates cytosolic concentrations of Ca^{2+} in thyroid follicular cells (Corda *et al.*, 1985; Field *et al.*, 1987; Laurent *et al.*, 1987); the formation of H_2O_2 is stimulated by a rise in cytosolic Ca^{2+} (Takasu *et al.*, 1987).

3. Formation of Thyroxine and Triiodothyronine from Iodotyrosines. The remaining synthetic step is the coupling of two diiodotyrosyl residues to form thyroxine or of monoiodotyrosyl and diiodotyrosyl residues to form triiodothyronine. These are also oxidative reactions and appear to be catalyzed by the same peroxidase discussed above. The mechanism involves the enzymatic transfer of groups, perhaps as iodotyrosyl free radicals or positively charged ions, within thyroglobulin. Although many other proteins can serve as substrates for the peroxidase, none is as efficient as thyroglobulin in yielding thyroxine. The configuration of the protein is thus presumed to be important in facilitating this coupling reaction. Thyroxine formation occurs primarily at a location near the amino terminus of the protein, while most of the triiodotyrosine is synthesized near the carboxy terminus (Dunn *et al.*, 1987). The relative rates of synthetic activity at the various sites depend on the concentration of TSH and the availability of iodide. This may account, at least in part, for the long-known relationship between the proportion of thyroxine and triiodothyronine formed in the thyroid and the availability of iodide or the relative quantities of the two iodotyrosines. For example, when there is a deficiency of iodine in rat thyroid, the ratio of thyroxine to triiodothyronine decreases from 4:1 to 1:3 (Greer *et al.*, 1968). Because triiodothyronine is at least five times as active as thyroxine and contains only/ three-fourths as much iodine, a decrease in the quantity of available iodine need have little impact on the effective amount of thyroid hormone elaborated by the gland. Although a decrease in the availability of iodide and

thiol: Glutathione di-thiol: Alpha Lipoic Acid

the associated increase in the proportion of monoiodotyrosine favor the formation of triiodothyronine over thyroxine, a deficiency in diiodotyrosine ultimately can impair the formation of both forms of the hormone. In addition to the coupling reaction, intrathyroidal and secreted triiodothyronine is generated by the 5′-deiodination of thyroxine (Chanoine *et al.*, 1993).

4. Secretion of Thyroid Hormones. Since thyroxine and triiodothyronine are synthesized and stored within thyroglobulin, proteolysis is an important part of the secretory process. This process is initiated by endocytosis of colloid from the follicular lumen at the apical surface of the cell. This "ingested" thyroglobulin appears as intracellular colloid droplets, which apparently then fuse with lysosomes containing the requisite proteolytic enzymes. It is generally believed that thyroglobulin must be completely broken down into its constituent amino acids for the hormones to be released. As the molecular mass of thyroglobulin is 660 kDa, and the protein is made up of about 300 carbohydrate residues and 5500 amino acid residues, only two to five of which are thyroxine, this is an extravagant process. TSH appears to enhance the degradation of thyroglobulin by increasing the activity of several thiol endopeptidases of the lysosomes (Dunn and Dunn, 1988). The endopeptidases selectively cleave thyroglobulin, yielding hormone-containing intermediates that are subsequently processed by exopeptidases (Dunn *et al.*, 1991). The liberated hormones then exit the cell, presumably at its basal membrane. When thyroglobulin is hydrolyzed, monoiodotyrosine and diiodotyrosine also are liberated, but they usually do not leave the thyroid. Instead, they are selectively metabolized, and the iodine, liberated in the form of iodide, is reincorporated into protein. Normally, all this iodide is reused; however, when proteolysis is activated intensely by TSH, some of the iodide reaches the circulation, at times accompanied by trace amounts of the iodotyrosines.

5x More Active

5. Conversion of Thyroxine to Triiodothyronine in Peripheral Tissues. The normal daily production of thyroxine has been estimated to range between 70 and 90 μg, while that of triiodothyronine is between 15 and 30 μg. Although triiodothyronine is secreted by the thyroid, metabolism of thyroxine by sequential monodeiodination in the peripheral tissues accounts for about 80% of circulating triiodothyronine (Figure 56–4). Removal of the 5′-, or outer ring, iodine leads to the formation of triiodothyronine and is the "activating" metabolic pathway. The major site of conversion of thyroxine to triiodothyronine outside the thyroid is the liver. Thus, when thyroxine is given to hypothyroid patients in doses that pro-

80% Outside Thyroid

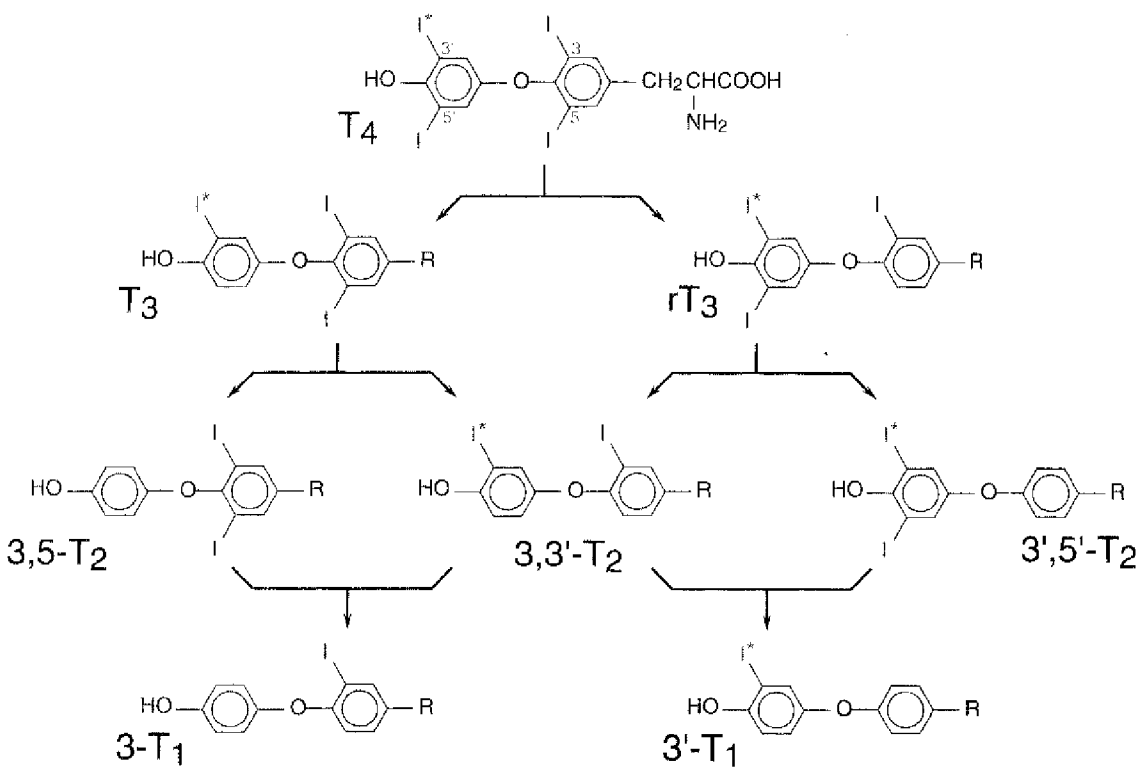


Figure 56–4. Pathways of iodothyronine deiodination.

duce normal concentrations of thyroxine in plasma, the plasma concentration of triiodothyronine also reaches the normal range. Most peripheral target tissues utilize triiodothyronine that is derived from the circulating hormone. Notable exceptions are the brain and pituitary, for which local generation of triiodothyronine is a major source for the intracellular hormone. Removal of the iodine on position 5 of the inner ring produces the metabolically inactive 3,3′,5′-triiodothyronine (reverse T_3, rT_3; Figure 56–1). Under normal conditions, about 41% of thyroxine is converted to triiodothyronine, about 38% is converted to reverse T_3, and about 21% is metabolized via other pathways, such as conjugation in the liver and excretion in the bile. Normal circulating concentrations of thyroxine in plasma range from 4.5 to 11.0 μg/dl, while those of triiodothyronine are about 100-fold less (60 to 180 ng/dl).

The enzyme responsible for the conversion of thyroxine to triiodothyronine is iodothyronine 5′-deiodinase, which exists as two distinct isozymes that are differentially expressed and regulated in peripheral tissues (Figure 56–5; Leonard and Visser, 1986). Type I 5′-deiodinase (5′D-I) is found in the liver, kidney, and thyroid and generates circulating triiodothyronine that is utilized by most peripheral target tissues. Although 5′-deiodination is the major function of this isozyme, 5′D-I also catalyzes 5-deiodination. 5′D-I is inhibited by a variety of factors (Table 56–1), including the antithyroid drug, *propylthiouracil*. The decreased plasma triiodothyronine concentrations observed in nonthyroidal illnesses are a result of inhibition of 5′D-I (Kaptein, 1986) and decreased entrance of thyroxine into cells. 5′D-I is "up-regulated" in hyperthyroidism and "down-regulated" in hypothyroidism. The cloning of 5′D-I has identified the enzyme as a selenoprotein and demonstrated the presence of a selenocystine at the active site (Berry *et al.*, 1991; Berry and Larsen, 1992). Type II 5′-deiodinase (5′D-II) is limited in distribution to the brain, pituitary, and, in the rat, brown fat and functions to supply intracellular triiodothyronine to these tissues (Visser *et al.*, 1982). 5′D-II has a much lower K_m for thyroxine than does 5′D-I (nM *vs.* μM

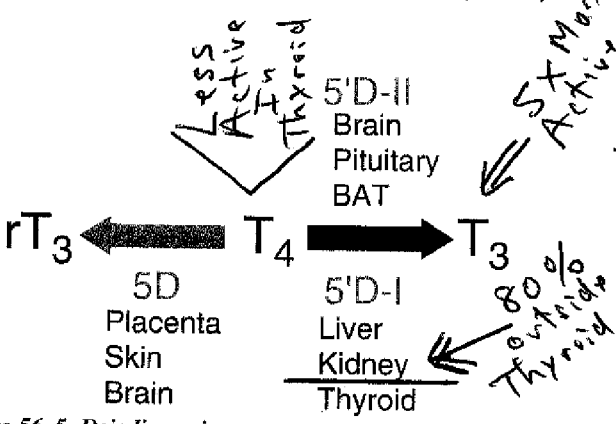


Figure 56–5. Deiodinase isozymes.

Abbreviations are as follows: 5′D-I, type I iodothyronine 5′-deiodinase; 5′D-II, type II iodothyronine 5′-deiodinase; 5D, type III iodothyronine 5-deiodinase; BAT, brown adipose tissue.

Table 56–1
Conditions and Factors That Inhibit Type I 5′-Deiodinase Activity

Acute and chronic illness
Caloric deprivation (especially carbohydrate)
Malnutrition
Glucocorticoids
β-Adrenergic blocking drugs (*e.g.*, propranolol in high doses)
Oral cholecystographic agents (*e.g.*, iopanoic acid, sodium ipodate)
Amiodarone
Propylthiouracil
Fatty acids
Fetal/neonatal period
Selenium deficiency

K_m values), and its activity is unaffected by propylthiouracil. 5′D-II is dynamically regulated by its substrate, thyroxine, such that elevated levels of the enzyme are found in hypothyroidism and suppressed levels are found in hyperthyroidism (Leonard *et al.*, 1981). Thus, 5′D-II appears to autoregulate the intracellular supply of triiodothyronine in the brain and pituitary. 5′D-II is a multimeric protein and is not a selenoenzyme (Safran *et al.*, 1991). Inner ring deiodination, or 5-deiodination, is primarily catalyzed by type III iodothyronine deiodinase (5D), which is found in the placenta, skin, and brain. Whether or not 5D is a selenoprotein is controversial.

Transport of Thyroid Hormones in the Blood. Iodine in the circulation is normally present in several forms, with 95% as organic iodine and approximately 5% as iodide. Most of the organic iodine is thyroxine (90% to 95%), while triiodothyronine represents a relatively minor fraction (about 5%). The thyroid hormones are transported in the blood in strong but noncovalent association with certain plasma proteins.

Thyroxine-binding globulin is the major carrier of thyroid hormones. It is an acidic glycoprotein with a molecular mass of approximately 63 kDa, and it binds one molecule of thyroxine per molecule of protein with a very high affinity (the equilibration association constant, K_a, is about 10^{10} M^{-1}). Triiodothyronine is bound less avidly. Thyroxine, but not triiodothyronine, also is bound by transthyretin (also called thyroxine-binding prealbumin). This protein is present in higher concentration than is the thyroxine-binding globulin, but it binds thyroxine and triiodothyronine with equilibrium association constants near 10^7 M^{-1} and 10^6 M^{-1}, respectively. Transthyretin has four apparently identical subunits, but has only a single high-affinity binding site. Albumin also can serve as a carrier for thyroxine when the more avid carriers are saturated. It

is difficult, however, to estimate its quantitative or physiological importance, with the exception of the syndrome known as *familial dysalbuminemic hyperthyroxinemia.* This is an autosomal dominant hereditary disorder characterized by the increased affinity of albumin for thyroxine (Ruiz *et al.,* 1982). Thyroxine binds also to the apolipoproteins of the high density lipoproteins, HDL_2 and HDL_3, the significance of which is unclear at present (Benevenga *et al.,* 1992).

Binding of thyroid hormones to plasma proteins protects the hormones from metabolism and excretion, resulting in their long half-lives in the circulation. The free (unbound) hormone is a small percentage (about 0.03% of thyroxine and about 0.3% of triiodothyronine) of the total hormone in plasma (Larsen *et al.,* 1981). The differential binding affinity for serum proteins also is reflected in the 10- to 100-fold difference in circulating hormone concentrations and half-lives of thyroxine and triiodothyronine.

Essential to understanding the regulation of thyroid function is the "free hormone" concept: only the unbound hormone has metabolic activity (Mendel, 1989). Thus, because of the high degree of binding of thyroid hormones to plasma proteins, changes in either the concentrations of these proteins or the binding affinity of the hormones for the proteins would have major effects on the total serum hormone levels. Certain drugs and a variety of pathological and physiological conditions, such as the changes in circulating concentrations of estrogens during the menstrual cycle, can alter both the binding of thyroid hormones to plasma proteins and the amounts of these proteins (Table 56–2).

Table 56–2
Factors That Alter Binding of Thyroxine to Thyroxine-Binding Globulin

INCREASE BINDING	DECREASE BINDING
Drugs	
Estrogens	Glucocorticoids
Methadone	Androgens
Clofibrate	L-Asparaginase
5-Fluorouracil	Salicylates
Heroin	Mefenamic Acid
Tamoxifen	Antiseizure medications (phenytoin, carbamazepine)
	Furosemide
Systemic Factors	
Liver disease	Inheritance
Porphyria	Acute and chronic illness
HIV infection	
Inheritance	

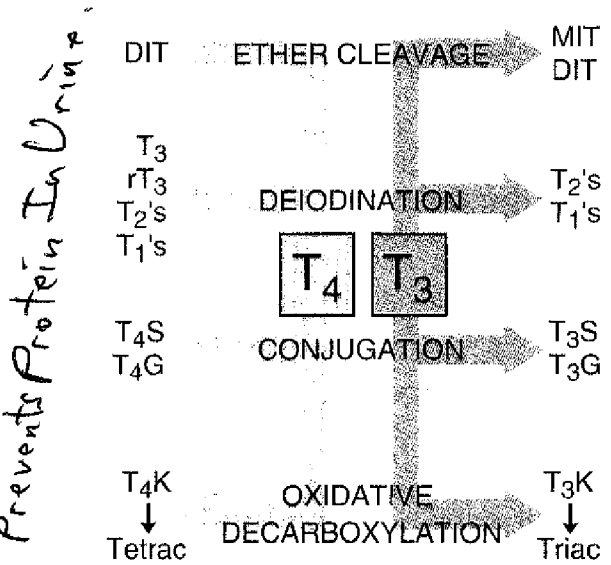


Figure 56–6. Pathways of metabolism of thyroxine (T_4 and triiodothyronine (T_3).

Abbreviations are as follows: DIT, diiodotyrosine; MIT, monoiodotyrosine; T_4S, T_4 sulfate; T_4G, T_4 glucuronide; T_3S, T_3 sulfate; T_3G, T_3 glucuronide; T_4K, T_4 pyruvic acid; T_3K, T_3 pyruvic acid; Tetrac, tetraiodothyroacetic acid. Triac, triiodothyroacetic.

However, since the pituitary responds to and regulates circulating free hormone levels, minimal changes in free hormone concentrations are seen. Laboratory tests that measure only total hormone levels, therefore, can be subject to misinterpretation. Appropriate tests of thyroid function are discussed later in this chapter.

Degradation and Excretion (Figure 56–6). Thyroxine is eliminated slowly from the body, with a half-life of 6 to 7 days. In hyperthyroidism, the half-life is shortened to 3 or 4 days, whereas in hypothyroidism it may be 9 to 10 days. These changes presumably are due to altered rates of metabolism of the hormone. In conditions associated with increased binding to plasma proteins, such as pregnancy, clearance is retarded; the reverse is observed when there is reduced protein binding of thyroid hormones or when binding to protein is inhibited by certain drugs (Table 56–2). Triiodothyronine, which is less avidly bound to protein, has a half-life of approximately 1 day.

The liver is the major site of nondeiodinative degradation of thyroid hormones; thyroxine and triiodothyronine are conjugated with glucuronic and sulfuric acids through the phenolic hydroxyl group and excreted in the bile. There is an enterohepatic circulation of the thyroid hormones; they are liberated by hydrolysis of the conjugates in the intestine and reabsorbed. A portion of the conjugated material reaches the colon unchanged, is hydrolyzed there, and is eliminated

in feces as the free compounds. In human beings, approximately 20% of thyroxine is eliminated in the stool.

As discussed above, the major route of metabolism of thyroxine is deiodination to either triiodothyronine or reverse T_3. Triiodothyronine and reverse T_3 are deiodinated to three different diiodothyronines (*see* Figure 56–4), inactive metabolites that are normal constituents of human plasma. Additional metabolites (monoiodotyrosine and diiodotyrosine) in which the diphenyl ether linkage is cleaved have been detected both *in vitro* and *in vivo*.

Regulation of Thyroid Function. During the past century, it was appreciated that cellular changes occur in the anterior pituitary in association with endemic goiter or following thyroidectomy. The classical experimental observations of Cushing (1912) and the clinical observations of Simmonds (1914) established that ablation or disease of the pituitary causes thyroid hypoplasia. It eventually was determined that thyrotropes of the anterior pituitary secrete *thyrotropin*, or TSH. TSH is a glycoprotein hormone with α and β subunits analogous to those of the gonadotropins. Its structure is discussed with those of other glycoprotein hormones in Chapter 55. Although there was evidence that thyroid hormone or lack of it causes cellular changes in the pituitary, the control of secretion of TSH by the negative-feedback action of thyroid hormone was not appreciated fully until its central role in the pathogenesis of goiter was elucidated in the early 1940s. TSH is secreted in a pulsatile manner and circadian pattern, its levels in the circulation being highest during sleep at night. It is now recognized that the rate of secretion of TSH is delicately controlled by thyrotropin-releasing hormone (TRH) and the quantity of free thyroid hormones in the circulation. If extra thyroid hormone is given, transcription of the thyrotropin gene is decreased (*see* Samuels *et al.*, 1988), the secretion of TSH is suppressed, and the thyroid becomes inactive and regresses. Any decrease in the normal rate of secretion of the thyroid evokes an enhanced secretion of TSH in an attempt to stimulate the thyroid to secrete more hormone. Additional mechanisms of the effect of thyroid hormone on TSH secretion appear to be a reduction in TRH secretion by the hypothalamus and a reduction in the number of receptors for TRH on pituitary cells.

Thyrotropin-Releasing Hormone (TRH). TRH stimulates the release of preformed TSH from secretory granules and also stimulates the subsequent synthesis of both α and β subunits of TSH. Somatostatin, dopamine, and pharmacological doses of glucocorticoids inhibit TRH-stimulated TSH secretion.

TRH is a tripeptide with both terminal amino and carboxyl groups blocked (L-pyroglutamyl-L-histidyl-L-proline amide). The mature hormone is derived from a precursor protein that contains six copies of the tripeptide flanked by dibasic residues. TRH is synthesized by the hypothalamus and is released into the hypophysioportal circulation, where it is brought into contact with TRH receptors on thyrotropes. The binding of TRH to its receptor, a G protein–coupled receptor, elicits stimulation of the hydrolysis of polyphosphatidylinositols and activation of protein kinase C (Gershenghorn, 1986). Ultimately, TRH stimulates the synthesis and release of TSH by the thyrotrope.

TRH also has been localized in the CNS in regions of the cerebral cortex, circumventricular structures, neurohypophysis, pineal gland, and spinal cord. These findings, as well as its localization in nerve endings, suggest that TRH may act as a neurotransmitter or neuromodulator outside of the hypothalamus. Administration of TRH to animals produces CNS mediated effects on behavior, thermoregulation, autonomic tone, and cardiovascular function, including increases in blood pressure and heart rate. TRH also has been identified in pancreatic islet cells and in certain parts of the gastrointestinal tract. Its physiological role there is not known.

Actions of TSH on the Thyroid. When TSH is given to experimental animals, the first effect on thyroid hormone metabolism that can be measured is increased secretion, which can be seen within minutes. All phases of hormone synthesis and release are eventually stimulated: iodide uptake and organification, hormone synthesis, endocytosis, and proteolysis of colloid. There is increased vascularity of the gland and hypertrophy and hyperplasia of thyroid cells. These effects follow the binding of TSH to its receptor on the plasma membrane of thyroid cells.

The TSH receptor is a member of the family of G protein–coupled receptors and is structurally similar to the receptors for luteinizing hormone (LH) and follicle-stimulating hormone (FSH) (*see* Chapter 55; Parmentier *et al.*, 1989; Vassart and Dumont, 1992; Nagayama and Rapoport, 1992). These receptors share significant amino acid sequences and have large extracellular domains that are involved in binding of hormone.

When TSH binds to its receptor, adenylyl cyclase is stimulated and cyclic AMP levels in the cells increase. At higher concentrations than are required to stimulate cyclic AMP formation, TSH causes activation of phospholipase C, with a resultant hydrolysis of polyphosphatidylinositols, increased cytoplasmic Ca^{2+}, and activation of protein kinase C (Manley *et al.*, 1988; Van Sande *et al.*, 1990). Both the adenylyl cyclase and the phospholipase C signaling pathways appear to mediate effects of TSH on thyroid function in human beings, although the adenylyl cyclase pathway may be the sole mediating pathway in other species (*see* Vassart and Dumont, 1992).

Testosterone Peaks At 4 AM. (Androgens)

Somatostatin = Growth Hormone Inhibitor

Growth Hormone Peaks 30-60 minutes After Night Time Sleep.

Relation of Iodine to Thyroid Function. Normal thyroid function obviously requires an adequate intake of iodine; without it, normal amounts of hormone cannot be made, TSH is secreted in excess, and the thyroid becomes hyperplastic and hypertrophies. The enlarged and stimulated thyroid becomes remarkably efficient at extracting the residual traces of iodide from the blood. The iodide-concentrating mechanism develops a gradient for the ion that may be ten times normal, and in mild to moderate iodine deficiency, the thyroid usually succeeds in producing sufficient hormone. Adult hypothyroidism and cretinism may occur in more severe iodine deficiency.

In some areas of the world, simple or nontoxic goiter is prevalent because dietary iodine is not sufficient (Delange *et al.*, 1993). Significant regions of iodine deficiency are present in Central and South America, Africa, Europe, southeast Asia, and China. The daily requirement for iodine in adults is 1 to 2 μg/kg body weight. The United States recommended daily allowance for iodine is in the range of 40 to 120 μg for children and 150 μg for adults, with the addition of 25 μg and 50 μg recommended during pregnancy and lactation, respectively. Vegetables, meat, and poultry contain minimal amounts of iodine, whereas dairy products and fish are relatively high in iodine content (Table 56–3; Braverman, 1994). Potable water usually contains negligible amounts of iodine.

Iodine has been used empirically for the treatment of iodine-deficiency goiter for 150 years. However, its modern use was the outgrowth of the extensive studies of Marine, which culminated in the use of iodine to prevent goiter in school children in Akron, Ohio, a region where endemic iodine deficiency goiter was prevalent (Marine and Kimball, 1917). The success of these experiments led to the adoption of iodine prophylaxis and therapy in many regions throughout the world where iodine-deficiency goiter is endemic.

The most practicable method for providing small supplements of iodine for large segments of the population is the addition of iodide or iodate to table salt; iodate is now preferred. In some countries, the use of iodized salt is required by law; in others, including the United States, the use is optional. In the United States, iodized salt provides 100 μg of iodine per gram. Other vehicles for supplying iodine to large populations who are iodine-deficient include oral or intramuscular injection of iodized oil (Thilly *et al.*, 1973), iodized drinking water supplies, iodized irrigation systems, and iodized animal feed.

Table 56–3
Iodine Content in Some Foodstuffs in the United States (1982–1989)

FOOD	IODINE/SERVING, μg
Ready-to-eat cereals	87
Dairy-based desserts	70
Fish	57
Milk	56
Dairy products	49
Eggs	27
Bread	27
Beans, peas, tuber	17
Meat	16
Poultry	15

SOURCE: Adapted from Braverman, 1994.

Actions of Thyroid Hormones. Whereas the precise biochemical mechanisms through which thyroid hormones exert their developmental and tissue-specific effects are only beginning to be understood, the concept that most of the actions of thyroid hormones are mediated by nuclear receptors has been well accepted since the mid-1980s (for review, *see* Oppenheimer *et al.*, 1987; Brent, 1994). In this model, triiodothyronine binds to high-affinity nuclear receptors, which then bind to a specific DNA sequence (thyroid hormone response element) in the promoter/regulatory region of specific genes. In this fashion, triiodothyronine modulates gene transcription and, ultimately, protein synthesis. In general, the receptor without hormone is bound to the thyroid response element in the basal state. Typically, this results in repressed gene transcription, although there are some examples of constitutive gene activation. Binding by triiodothyronine may activate gene transcription by releasing the repression. Hormone-associated receptors also may have direct activation or repressive actions. Thyroxine also binds to these receptors, but it does so with a much lower affinity than triiodothyronine. It is likely that thyroxine serves principally as a "prohormone," with essentially all actions of thyroid hormone at the transcriptional level being caused by triiodothyronine.

Nuclear thyroid hormone receptors were cloned in 1986 by several laboratories (Weinberger *et al.*, 1986; Sap *et al.*, 1986). They were discovered to be the cellular homologs of an avian retroviral oncoprotein, denoted c-*erb* A. There is considerable homology between the thyroid hormone receptors and the steroid nuclear receptors, and together they make up a gene superfamily that also includes the retinoic acid and vitamin D nuclear receptors (*see* Chapters 2 and 63; Mangelsdorf *et al.*, 1994). The thyroid hormone receptors are derived from two genes, c-*erb* A α (TRα) and c-*erb* A β (TRβ), with multiple isoforms identified (Figure 56–7; Lazar, 1993). TRα$_1$ and TRβ$_1$ are found in virtually all tissues that respond to thyroid hormone, whereas the other isoforms exhibit a more tissue-specific distribution. TRβ$_2$, for example, is expressed solely in the anterior

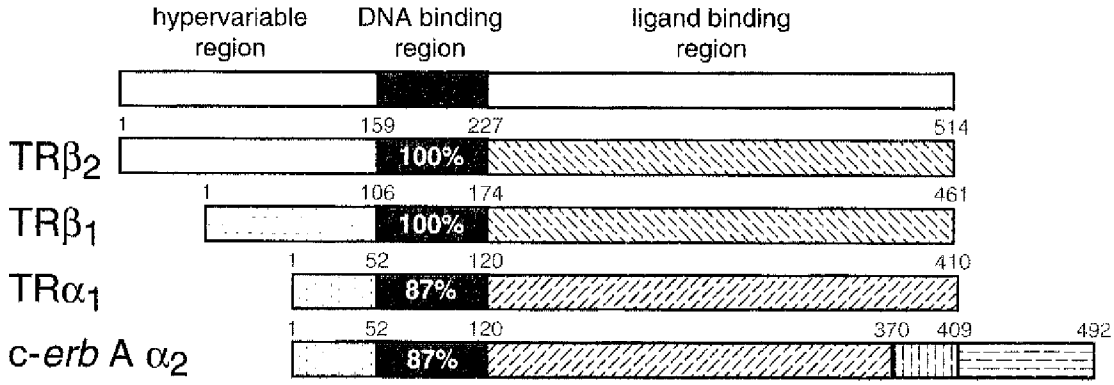


Figure 56–7. Thyroid hormone receptor isoforms.

The percent of amino acid identity in the DNA binding region is indicated. Identical patterns in the hypervariable and ligand binding regions indicate 100% homology. Three thyroid hormone receptor (TR) isoforms bind thyroid hormone (TRβ_1, TRβ_2, and TRα_1); c-*erb* A α_2 does not.

pituitary, c-*erb* A α_2, an isoform that binds to the thyroid response element but does not bind triiodothyronine, is the most abundant isoform in brain (Strait *et al.*, 1990).

In addition to nuclear receptor–mediated actions, there are several well-characterized, nongenomic actions of thyroid hormones, including those occurring at the level of the plasma membrane (Davis *et al.*, 1989) and on the cellular cytoarchitecture (Farwell *et al*, 1990; Siegrist-Kaiser *et al.*, 1990). In addition, there are well-characterized thyroid hormone binding sites on the mitochondria (Sterling, 1989). In several of these processes, thyroxine is the hormone that produces the response. The overall contribution of the extranuclear sites to cellular regulation by thyroid hormones is likely to be minor.

Growth and Development. As discussed above, it is generally believed that the thyroid hormones exert most if not all of their effects through control of DNA transcription and, ultimately, protein synthesis. This is certainly true for the actions of the hormones on the normal growth and development of the organism. Perhaps the most dramatic example is found in the tadpole, which is almost magically transformed into a frog by thyroid hormone. Not only does the animal grow limbs, lungs, and other terrestrial accoutrements, but the hormone also stimulates the synthesis of a host of enzymes and so influences the tail that it is digested away and used to build new tissue elsewhere.

Thyroid hormone plays a critical role in brain development (Dussault and Ruel, 1987; Porterfield and Hendrich, 1993). The appearance of functional, chromatin-bound receptors for thyroid hormone coincides with neurogenesis in the brain (Strait *et al.*, 1990). The absence of thyroid hormone during the period of active neurogenesis (up to 6 months postpartum) leads to irreversible mental retardation (cretinism) and is accompanied by multiple morphological alterations in the brain (Legrand, 1979). These severe morphological alterations result from disturbed neuronal migration, deranged axonal projections, and decreased synaptogenesis. Thyroid hormone supplementation during the first 2 weeks of life prevents the development of these disturbed morphological changes.

Myelin basic protein, a major component of myelin, is the product of a specific gene that is regulated by thyroid hormone during development (Farsetti *et al.*, 1991). Decreased expression of myelin basic protein results in defective myelinization in the hypothyroid brain. Several other minor brain-specific genes have been reported to be developmentally regulated by thyroid hormone (Porterfield and Hendrich, 1993). A common characteristic of these proteins is that their expression appears to be merely delayed in the hypothyroid animal; normal levels are eventually achieved in the adult.

The actions of thyroid hormones on protein synthesis and enzymatic activity are certainly not limited to the brain, and a large number of tissues are affected by the administration of thyroid hormone or by its deficiency. The extensive defects in growth and development that are found in cretins provide a vivid reminder of the pervasive effects of thyroid hormones in normal individuals.

Cretinism is usually classified as endemic or sporadic. *Endemic cretinism* is encountered in regions of endemic goiter and is usually caused by extreme deficiency of iodine. Goiter may or may not be present. *Sporadic cretinism* is a consequence of failure of the thyroid to develop normally or the result of a defect in the synthesis of thyroid hormone. Goiter is present if a synthetic defect is at fault.

While detectable at birth, cretinism often is not recognized until 3 to 5 months of age. When untreated, the condition eventually leads to such gross changes as to be unmistakable. The child is dwarfed, with short extremities, and is mentally retarded, inactive, uncomplaining, and listless. The face is puffy and expressionless, and the enlarged tongue may protrude through the thickened lips of the half-opened mouth. The skin may have a yellowish hue and feel doughy, and it is dry and cool to the touch. The heart rate is slow, the body temperature may be low, closure of the fontanels is delayed, and the teeth erupt late. Appetite is poor, feeding is slow and interrupted by choking, constipation is frequent, and there may be an umbilical hernia.

For treatment to be fully effective, the diagnosis must be made long before these obvious changes have come about. Screening of newborn infants for deficient function of the thyroid is carried out in the United States and in most industrialized countries. Concentrations of TSH and thyroxine are measured in blood from the umbilical cord or from a heel stick. The incidence of congenital dysfunction of the thyroid is about 1 per 4000 births (Fisher, 1991).

Calorigenic Effect. A characteristic response of homeothermic animals to thyroid hormone is increased oxygen consumption (Oppenheimer, 1991). Most peripheral tissues contribute to this response; heart, skeletal muscle, liver, and kidney are stimulated markedly by thyroid hormone. Indeed, 30% to 40% of the thyroid hormone–dependent increase in oxygen consumption can be attributed to stimulation of cardiac contractility. Several organs, including brain, gonads, and spleen, are unresponsive to the calorigenic effects of thyroid hormone. The mechanism of the calorigenic effect of thyroid hormone has been elusive. At one time, it was erroneously believed that thyroid hormone uncoupled mitochondrial oxidative phosphorylation. Thyroid hormone–dependent lipogenesis may constitute a quantitatively important energy sink, and studies in rats have demonstrated that about 4% of the increased caloric expenditure induced by thyroid hormone is accounted for by lipogenesis. A link between lipogenesis and thermogenesis is the stimulation of lipolysis by triiodothyronine. Further, thyroid hormone induces expression of several lipogenic enzymes, including malic enzyme and fatty acid synthetase. Although the entire picture is not clear, there appears to be an integrated thyroid hormone response program for regulating the set-point of energy expenditure and maintaining the metabolic machinery necessary to sustain it.

Cardiovascular Effects. Thyroid hormone influences cardiac function by direct and indirect actions; changes in the cardiovascular system are prominent clinical consequences in thyroid dysfunctional states. In hyperthyroidism, there is tachycardia, increased stroke volume, increased cardiac index, cardiac hypertrophy, decreased peripheral vascular resistance, and increased pulse pressure. In hypothyroidism, there is bradycardia, decreased cardiac index, pericardial effusion, increased peripheral vascular resistance, decreased pulse pressure, and elevations of mean arterial pressure. (For a review of the effects of thyroid hormone on the heart, *see* Braverman *et al.*, 1994.)

Thyroid hormones play a direct role in regulating myocardial gene expression. Triiodothyronine regulates genes encoding the isoforms of the sarcomeric myosin heavy chains by increasing the expression of the α gene and decreasing the expression of the β gene (Everett *et al.*, 1986). A thyroid hormone response element has been located in the 5′ upstream region of the α myosin heavy chain gene. Triiodothyronine also upregulates the gene encoding myosin Ca^{2+}-ATPase, which plays a critical role in myocardial contraction (Rohrer and Dillman, 1989). Regulation of these two genes results in the changes in contractility observed in hyper- and hypothyroidism.

Thyroid hormones also indirectly influence cardiac function. The sensitivity of the cardiac myocyte to catecholamines is enhanced in hyperthyroidism and depressed in hypothyroidism, possibly due to changes in expression of myocardial β-adrenergic receptors; this is the basis for the use of β-adrenergic receptor antagonists in relieving some of the cardiac manifestations of hyperthyroidism. Electrical impulse generation and conduction are increased in hyperthyroidism and decreased in hypothyroidism. These two actions likely account for the chronotropic effects of triiodothyronine. Finally, triiodothyronine causes hemodynamic alterations in the periphery that result in alterations in the chronotropic and ionotropic state of the myocardium.

Metabolic Effects. Thyroid hormones stimulate metabolism of cholesterol to bile acids, and hypercholesterolemia is a characteristic feature of hypothyroid states. Thyroid hormones have been shown to increase the specific binding of low density lipoprotein (LDL) by liver cells (Salter *et al.*, 1988), and the concentration of hepatic receptors for LDL is decreased in hypothyroidism (Scarabottolo *et al.*, 1986; Gross *et al.*, 1987). The number of LDL receptors available on the surface of hepatocytes is a strong determinant of the plasma cholesterol concentration (*see* Chapter 36).

Thyroid hormones enhance the lipolytic responses of fat cells to other hormones, for example, catecholamines, and elevated plasma free fatty acid concentrations are seen in hyperthyroidism. In contrast to other lipolytic hormones, thyroid hormones do not directly increase the accumulation of cyclic AMP. They may, however, regulate the capacity of other hormones to enhance the accumulation of the cyclic nucleotide by decreasing the activity of a microsomal phosphodiesterase that hydrolyzes cyclic AMP (Nunez and Correze, 1981). There also is evidence that thyroid hormones act to maintain normal coupling of the β-adrenergic receptor to the catalytic subunit of adenylyl cyclase in fat cells. Fat cells from hypothyroid rats have increased concentrations of guanine nucleotide–binding regulatory proteins (G proteins) that mediate the inhibitory control of adenylyl cyclase (*see* Chapter 2). This can account for both the decreased response to lipolytic hormones and the increased sensitivity to inhibitory regulators, such as adenosine, that are found in hypothyroidism (Ros *et al.*, 1988).

Thyrotoxicosis is an insulin-resistant state (Gottlieb and Braverman, 1994). Postreceptor defects in the liver and peripheral tissues, manifested by depleted glycogen stores and enhanced glucogenesis, lead to insulin insensitivity. In addition, there is increased absorption of glucose from the gut. Compensatory increases in insulin secretion result in order to maintain euglycemia. This may result in the "unmasking" of clinical diabetes in previously undiagnosed patients and an increase in the insulin requirements of diabetic patients already on insulin. Hypothyroidism results in decreased absorption of glucose from the gut and decreased insulin secretion. Peripheral glucose uptake also is slowed in hypothyroidism, although glucose utilization by the brain is unaffected. Insulin requirements are decreased in the hypothyroid patient with diabetes.

Thyroid Hyperfunction. Thyrotoxicosis is a condition caused by elevated concentrations of circulating free thyroid hormones. Various disorders of different etiologies can result in this syndrome. The term *hyperthyroidism* is restricted to those conditions in which thyroid hormones are excessively released due to gland hyperfunction. Iodine up-

Iodide

Iodide is the oldest remedy for disorders of the thyroid gland. Before the antithyroid drugs were used, it was the only substance available for control of the signs and symptoms of hyperthyroidism. Its use in this way is indeed paradoxical, and the explanation for this paradox is still incomplete.

Mechanism of Action. High concentrations of iodide appear to influence almost all important aspects of iodine metabolism by the thyroid gland (*see* Ingbar, 1972). The capacity of iodide to limit its own transport has been mentioned above. Acute inhibition of the synthesis of iodotyrosines and iodothyronines by iodide also is well known (the *Wolff-Chaikoff effect*). This transient, 2-day inhibition is observed only above critical concentrations of intracellular rather than extracellular concentration of iodide. With time there is "escape" from this inhibition that is associated with an adaptive decrease in iodide transport and a lowered intracellular iodide concentration (Braverman and Ingbar, 1963). The mechanism of the Wolff-Chaikoff effect may involve inhibition of inositol phosphate signaling pathways within the thyrocyte (Corvilain *et al.*, 1994).

A very important clinical effect of high plasma iodide concentration is an inhibition of the release of thyroid hormone. This action is rapid and efficacious in severe thyrotoxicosis. The effect is exerted directly on the thyroid gland, and it can be demonstrated in the euthyroid subject and experimental animals as well as in the hyperthyroid patient. Recent studies in a cultured thyroid cell line suggest that some of the inhibitory effects of iodide on thyrocyte proliferation may be mediated by actions of iodide on crucial regulatory points in the cell cycle (Smerdely *et al.*, 1993).

In euthyroid individuals, the administration of doses of iodide from 1.5 to 150 mg daily results in small decreases in plasma thyroxine and triiodothyronine concentrations and small compensatory increases in serum TSH values, with all values remaining in the normal range. However, euthyroid patients with a history of a wide variety of underlying thyroid disorders may develop iodine-induced hypothyroidism when exposed to large amounts of iodine present in many commonly prescribed drugs (Table 56–6), and these patients do not escape from the acute Wolff-Chaikoff effect (Braverman, 1994). Among the disorders that predispose patients to iodine-induced hypothyroidism are: treated Graves' disease, Hashimoto's thyroiditis, postpartum lymphocytic thyroiditis, subacute painful thyroiditis, and lobectomy for benign nodules. The most commonly prescribed iodine-containing drugs are certain expectorants, topical antiseptics, and radiology contrast agents.

Response to Iodide in Hyperthyroidism. The response to iodides in patients with hyperthyroidism is often striking and rapid. The effect is usually discernible within 24 hours, and the basal metabolic rate may fall at a rate comparable to that following thyroidectomy. This provides evidence that the release of hormone into the circulation is rapidly blocked. Furthermore, thyroid hormone synthesis also may be decreased. The maximal effect is attained after 10 to 15 days of continuous therapy, when the signs and symptoms of hyperthyroidism may have greatly improved.

The changes in the thyroid gland have been studied in detail; vascularity is reduced, the gland becomes much firmer, the cells become smaller, colloid reaccumulates in the follicles, and the quantity of bound iodine increases. The changes are those that would be expected if the excessive stimulus to the gland had somehow been removed or antagonized.

Unfortunately, iodide therapy usually does not completely control the manifestations of hyperthyroidism, and after a variable period of time, the beneficial effect disappears. With continued treatment, the hyperthyroidism may return in its initial intensity or may become even more severe than it was at first. It is for this reason that, when iodide was the only agent available for the treatment of hyperthyroidism, it use was usually restricted to preparation of the patient for thyroidectomy.

Therapeutic Uses. The uses of iodide in the treatment of hyperthyroidism are in the preoperative period in preparation for thyroidectomy and, in conjunction with antithyroid drugs and propranolol, in the treatment of thyrotoxic crisis. Prior to surgery, iodide is sometimes employed alone, but more frequently it is used after the hyperthyroidism has been controlled by an antithyroid drug. It is then given during the 7 to 10 days immediately preceding the operation. Optimal control of hyperthyroidism is achieved if antithyroid drugs are first given alone. If iodine also is given from the beginning, variable responses are observed; sometimes the effect of iodide predominates, storage of hormone is promoted, and prolonged antithyroid treatment is required before the hyperthyroidism is controlled. These clinical observations may be explained by the ability of iodide to prevent the inactivation of thyroid peroxidase by antithyroid drugs (Taurog, 1991).

Another use of iodine is to protect the thyroid from radioactive iodine fallout following a nuclear accident. Because the uptake of radioactive iodine is inversely proportional to the serum concentration of stable iodine, the administration of 30 to 100 mg of iodide daily will markedly decrease the thyroid uptake of radioisotopes of iodine. Following the Chernobyl nuclear reactor accident in 1986, approximately 10 million children and adults in Poland were given stable iodide to block the thyroid exposure to radioactive iodine from the atmosphere and from dairy products from cows that ate contaminated grass (Naumann and Wolf, 1993).

The dosage or form in which iodide is administered bears little relationship to the response achieved in hyperthyroidism, provided not less than the minimal effective amount is given; this dosage is

Table 56–6
Commonly Used Iodine-Containing Drugs

DRUGS	IODINE CONTENT
Oral or local	
Amiodarone	75 mg/tablet
Calcium iodide (*e.g.*, CALCIDRINE SYRUP)	26 mg/ml
Iodoquinol (diiodohydroxyquin)	134–416 mg/tablet
Echothiophate iodide ophthalmic solution	5–41 μg/drop
Hydriodic acid syrup	13–15 mg/ml
Iodochlohydroxyquin	104 mg/tablet
Iodine-containing vitamins	0.15 mg/tablet
Iodinated glycerol	15 mg/tablet
Idoxuridine ophthalmic solution	18 μg/drop
Kelp	0.15 mg/tablet
Potassium iodide (*e.g.*, QUADRINAL)	145 mg/tablet
Lugol's solution	6.3 mg/drop
Niacinamide hydroiodide + potassium iodide (*e.g.*, IODO-NIACIN)	115 mg/tablet
PONARIS nasal emollient	5 mg/0.8 ml
Saturated solution of potassium iodide	38 mg/drop
Parenteral preparations	
Sodium iodide, 10% solution	85 mg/ml
Topical antiseptics	
Iodoquinol (diiodohydroxyquin) cream	6 mg/g
Iodine tincture	40 mg/ml
Iodochlorhydroxyquin cream	12 mg/g
Iodoform gauze	4.8 mg/100 mg gauze
Povidone iodine	10 mg/ml
Radiology contrast agents	
Diatrizoate meglumine sodium	370 mg/ml
Propyliodone	340 mg/ml
Iopanoic acid	333 mg/tablet
Ipodate	308 mg/capsule
Iothalamate	480 mg/ml
Metrizamide	483 mg/ml before dilution
Iohexol	463 mg/ml

SOURCE: Adapted from Braverman, 1994.

6 mg per day in most, but not all, patients. *Strong iodine solution* (Lugol's solution) is widely used and consists of 5% iodine and 10% potassium iodide, which yields a dose of 6.3 mg of iodine per drop. The iodine is reduced to iodide in the intestine before absorption. Saturated solution of potassium iodide also is available, containing 38 mg per drop. Typical doses include 3 to 5 drops of Lugol's solution or 1 to 3 drops of saturated solution of potassium iodide 3 times a day. These doses have been determined empirically and are far in excess of that needed.

Untoward Reactions. Occasional individuals show marked sensitivity to iodide or to organic preparations that contain iodine when they are administered intravenously. The onset of an acute reaction may occur immediately or several hours after administration. Angioedema is the outstanding symptom, and swelling of the larynx may lead to suffocation. Multiple cutaneous hemorrhages may be present. Also, manifestations of the serum-sickness type of hypersensitivity, such as fever, arthralgia, lymph node enlargement, and eosinophilia, may appear. Thrombotic thrombocytopenic purpura and fatal periarteritis nodosa attributed to hypersensitivity to iodide have also been described.

The severity of symptoms of chronic intoxication with iodide (*iodism*) is related to the dose. The symptoms start with an unpleasant brassy taste and burning in the mouth and throat, as well as soreness of the teeth and gums. Increased salivation is noted. Coryza, sneezing, and irritation of the eyes with swelling of the eyelids are

commonly observed. Mild iodism simulates a "head cold." The patient often complains of a severe headache that originates in the frontal sinuses. Irritation of the mucous glands of the respiratory tract causes a productive cough. Excess transudation into the bronchial tree may lead to pulmonary edema. In addition, the parotid and submaxillary glands may become enlarged and tender, and the syndrome may be mistaken for mumps parotitis. There also may be inflammation of the pharynx, larynx, and tonsils. Skin lesions are common, and vary in type and intensity. They usually are mildly acneform and distributed in the seborrheic areas. Rarely, severe and sometimes fatal eruptions (ioderma) may occur after the prolonged use of iodides. The lesions are bizarre, resemble those caused by bromism, a rare problem, and, as a rule, involute quickly when iodide is withdrawn. Symptoms of gastric irritation are common; and diarrhea, which is sometimes bloody, may occur. Fever is occasionally observed, and anorexia and depression may be present. The mechanisms involved in the production of these derangements remain unknown.

Fortunately, the symptoms of iodism disappear spontaneously within a few days after stopping the administration of iodide. The renal excretion of I^- can be increased by procedures that promote Cl^- excretion (*e.g.*, osmotic diuresis, chloruretic diuretics, and salt loading). These procedures may be useful when the symptoms of iodism are severe.

Radioactive Iodine

Chemical and Physical Properties. Although iodine has several radioactive isotopes, greatest use has been made of ^{131}I. It has a half-life of 8 days, and, therefore, over 99% of its radiation is expended within 56 days. Its radioactive emissions include both γ rays and β particles. The short-lived radionuclide of iodine, ^{123}I, is primarily a γ-emitter with a half-life of only 13 hours. This permits a relatively brief exposure to radiation during thyroid scans.

Effects on the Thyroid Gland. The chemical behavior of the radioactive isotopes of iodine is identical to that of the stable isotope, ^{127}I. ^{131}I is rapidly and efficiently trapped by the thyroid, incorporated into the iodoamino acids, and deposited in the colloid of the follicles, from which it is slowly liberated. Thus, the destructive β particles originate within the follicle and act almost exclusively upon the parenchymal cells of the thyroid with little or no damage to surrounding tissue. The γ radiation passes through the tissue and can be quantified by external detection. The effects of the radiation depend upon the dosage. When small tracer doses of ^{131}I are administered, thyroid function is not disturbed. However, when large amounts of radioactive iodine gain access to the gland, the characteristic cytotoxic actions of ionizing radiation are observed. Pyknosis and necrosis of the follicular cells are followed by disappearance of colloid and fibrosis of the gland. With properly selected doses of ^{131}I, it is possible to destroy the thyroid gland completely without detectable injury to adjacent tissues. After smaller doses, some of the follicles, usually in the periphery of the gland, retain their function.

Therapeutic Uses. *Sodium iodide I 131* (IODOTOPE THERAPEUTIC) is available as a solution or in capsules containing essentially carrier-free ^{131}I suitable for oral administration. *Sodium iodide I 123* is available for scanning procedures. Radioactive iodine finds its widest use in the treatment of hyperthyroidism and in the diagnosis of disorders of thyroid function. Discussion will be limited to the uses of ^{131}I.

Hyperthyroidism. Radioactive iodine is highly useful in the treatment of hyperthyroidism, and in many circumstances it is regarded as the therapeutic procedure of choice for this condition (Soloman *et al.*, 1990; for review, *see* Farrar and Toff, 1991). The use of iodide as treatment for hyperthyroidism, however, may preclude, for months, treatment and certain imaging studies with radioactive iodine.

Dosage and Technique. ^{131}I is administered orally, and the effective dose differs for individual patients. It depends primarily upon the size of the thyroid, the iodine uptake of the gland, and the rate of release of radioactive iodine from the gland subsequent to its deposition in the colloid. To determine these variables insofar as possible, many investigators administer a tracer dose of ^{131}I and calculate the ^{131}I accumulated by the gland and the rate of loss therefrom. The weight of the gland is estimated by palpation. From these data, the dose of isotope necessary to provide from 7000 to 10,000 rad per gram of thyroid tissue is determined. Even when dosage is controlled in this manner, it is difficult to predict the response of an individual to a given amount of the isotope. For these reasons, the optimal dose of ^{131}I, expressed in terms of microcuries taken up per gram of thyroid tissue, varies in different laboratories from 80 to 150 μCi. The usual total dose is 4 to 15 mCi. Lower-dosage ^{131}I therapy (80 μCi/g thyroid) has been advocated to reduce the incidence of subsequent hypothyroidism. While the incidence of hypothyroidism in the early years after such therapy is lower, many patients with late hypothyroidism may go undetected, and the ultimate incidence of hypothyroidism is probably no less than with the larger doses (Glennon *et al.*, 1972). In addition, relapse of the hyperthyroid state, or initial failure to alleviate the hyperthyroid state, is increased in patients receiving lower doses of ^{131}I.

Course of Disease. The course of hyperthyroidism in a patient who has received an optimal dose of ^{131}I is characterized by progressive recovery. It is very unusual for any tenderness to be noted in the thyroid region, and most observers have failed to detect any exacerbation of hyperthyroidism from loss of hormone from the damaged gland in patients whose preformed hormone stores have been depleted by antithyroid drug therapy. Beginning a few weeks after treatment, the symptoms of hyperthyroidism gradually abate over a period of 2 to 3 months. If therapy has been inadequate, the necessity for further treatment is apparent within 6 to 12 months.

Depending to some extent upon the dosage schedule adopted, one-half to two-thirds of patients are cured by a single dose, one-third to one-fifth require two doses, and the remainder require three or more doses before the disorder is controlled. Patients treated with larger doses of ^{131}I almost always develop hypothyroidism within a few months.