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Thyroid and Antithyroid Drugs

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DRUG LIST

Three hormones, thyroxine (3,5,3′,5′-tetraiodothyronine, or T_4), triiodothyronine (3,5,3′-triiodothyronine, or T_3), and calcitonin (see Chapter 66) are secreted by the thyroid gland. The hormones T_4 and T_3 are iodine-containing amino acid derivatives and are unique in that they have no discrete target tissue. Every tissue in the body is affected in some way by thyroid hormones, and almost all cells appear to require constant optimal amounts for normal operation.

Thyroid hormones exert a wide variety of physiological actions through genomic and nongenomic mechanisms and influence the metabolism of proteins, carbohydrates, and lipids; cell morphology; membrane transport; ion homeostasis; oxygen consumption; heat production; and so on. Relatively constant circulating concentrations of T_4 and T_3 are required for normal growth and development and the proper functioning of the neural, reproductive, cardiovascular, gastrointestinal, and hematopoietic systems. Unlike most other hormones, whose circulating concentrations vary widely in response to external and internal stimuli, the circulating concentrations of thyroid hormones are usually held relatively constant over time.

In health, two negative feedback control systems operate to maintain circulating thyroid hormone levels. The first, the *hypothalamic–pituitary-thyroid axis* (HPTA), acts to regulate the concentration of thyroid hormones in the blood by controlling their synthesis and secretion by the thyroid gland. The second negative feedback control system is the *thyroid autoregulatory system*. It is intrinsic to the thyroid gland and acts to ensure that an adequate supply of iodide is extracted from the blood and made available for thyroid hormone synthesis despite variations in dietary iodine intake.

Worldwide, the most common thyroid disorder is hypothyroidism resulting from dietary iodine deficiency. In iodine-replete areas of the world, most thyroid disorders are the result of autoimmune disease. The symptoms manifested in hypothyroid and hyperthyroid states are largely independent of any underlying disorder of the thyroid gland itself; they are a function of the degree of hormone deficiency or excess.

A second dietary trace element, selenium, is also essential for normal thyroid hormone metabolism. Selenium in the form of selenocysteine is a required component for three enzymes that remove iodide from thyroid hormones. Deiodination is the major metabolic pathway by which T_4 and T_3 are cleared from the system. After secretion by the thyroid gland, T_4 may be deiodinated to yield either T_3 or the physiologically inactive reverse T_3 (3,3′,5′-triiodothyronine, or rT_3). T_3 and rT_3 are further deiodinated to form less active metabolites. Selenium, like iodine, is deficient in many areas of the world.

BIOSYNTHESIS, STORAGE, SECRETION, AND METABOLISM OF THYROID HORMONES

Thyroid epithelial cells synthesize and secrete T_4 and T_3 and make up the functional units of thyroid glandular tissue, the thyroid follicles. Thyroid follicles are hollow vesicles formed by a single layer of epithelial cells that are filled with *colloid*. T_4, T_3, and iodine are stored in the follicular colloid. T_4 and T_3 are derived from tyrosyl residues of the protein *thyroglobulin* (Tg). Thyroid follicular cells synthesize and secrete Tg into the follicular lumen. Thyroid follicular cells also remove iodide (I^-) from the blood and concentrate it within the follicular lumen. Within the follicles, some of the tyrosyl residues of Tg are iodinated, and a few specific pairs of iodotyrosyl residues may be coupled to form T_4 and T_3. Thus, T_4, T_3, and iodine (in the form of iodinated tyrosyl residues) are found within the peptide structure of the Tg that is stored in the follicular lumen.

The secretion of T_4 and T_3 requires the uptake of follicular contents across the follicular cell apical membrane, the enzymatic release of T_4 and T_3 from peptide linkage within Tg, and the transport of T_4 and T_3 across the follicular cell basal membrane to the blood. Several of the steps in synthesis and secretion of T_4 and T_3 may be compromised by iodine deficiency or disease and can be blocked selectively by a variety of chemicals and drugs.

Requirement for Iodine

A normal rate of thyroid hormone synthesis depends on an adequate dietary intake of iodine. Iodine is naturally present in water and soil, although some soils contain very low amounts. As a result, seafood is a more reliable source of iodine than crop plants. Approximately 1.6 billion people in more than 100 countries live in areas where natural sources of dietary iodine intake are marginal or insufficient. A minimum of 60 μg of elemental iodine is required each day for thyroid hormone synthesis, and at least 100 μg/day is required to eliminate thyroid follicular cell hyperplasia and thyroid enlargement (i.e., iodine deficiency goiter).

Subsequent to the ingestion of iodine in various forms, I^- is absorbed by the small intestine and enters the blood. Two competing pathways are involved in the clearance of I^- from the blood: renal filtration into urine and thyroidal uptake. The renal clearance rate for I^- (30–50 mL/minute) varies only with the glomerular filtration rate. However, the thyroidal I^- clearance rate is autoregulated to maintain an absolute thyroidal I^- uptake rate of approximately 100 μg I^- each day. To accomplish this, the thyroidal I^- clearance rate may vary (3 to 100 mL/minute) depending on the concentration of I^- in the blood.

Iodide Transport by Follicular Cells and Iodine Trapping Within Follicles

The thyroid follicular cells transport I^- across the cell and secrete the precursor protein, Tg, into the follicular lumen. In addition, these cells contain an apical membrane–bound enzyme, thyroperoxidase (TPO), and the enzymatic machinery to produce hydrogen peroxide (H_2O_2). In the presence of H_2O_2, TPO catalyzes the incorporation of I^- into tyrosyl residues of Tg to form monoiodotyrosine (MIT) and diiodotyrosine (DIT) and the coupling of these iodotyrosyl residues to form T_4 and T_3.

Thyroid follicular cells actively transport iodide into the cell against both a concentration gradient and a negative potential (Fig. 65.1). At the basal (blood side) follicular cell membrane, an iodide pump actively transports
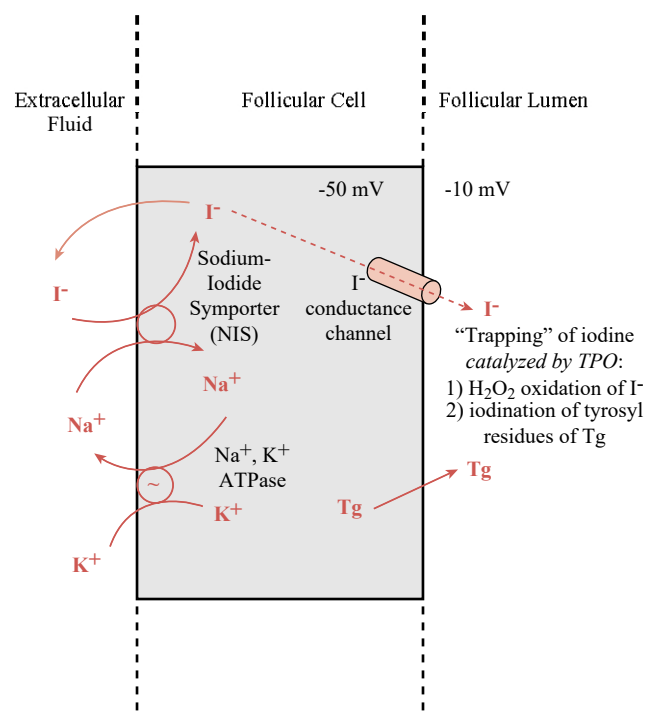

F I G U R E   6 5 . 1
Concentration of iodine within the thyroid follicular cell and follicular lumen.

I^- from the extracellular fluid (pertechnetate) into the cytoplasm and concentrates I^- within the follicular cell. The I^- concentration gradient between the thyroid gland and the blood normally ranges from 25 to 100 and is referred to as the thyroid–plasma or thyroid–serum ratio. During periods of active stimulation, the concentration of I^- within the follicle may be as high as 250 times that of the blood. On the luminal side of the apical membrane, the I^- is rapidly oxidized in the presence of H_2O_2 and TPO and incorporated into the tyrosyl residues in newly formed Tg to form MIT or DIT.

The thyroidal mechanism used for concentrating I^- may also concentrate other monovalent anions, including pertechnetate, perchlorate, and thiocyanate, within the follicular lumen. However, none of these anions become incorporated into Tg, although they may act as a competitive inhibitor of I^- transport. The ability of the thyroid gland to concentrate radioactive pertechnetate makes it a useful agent for thyroid imaging, since it is concentrated by the thyroid cells without further metabolism. The perchlorate and thiocyanate discharge tests make use of the ability of these anions to inhibit I^- transport to test for defects in the incorporation of I^- into Tg.

Coupling of Iodotyrosines to Form Iodothyronines

The final step in thyroid hormone synthesis is the coupling of two *iodotyrosines* within a single peptide chain of Tg to form the *iodothyronine* T_4 or T_3. Both the coupling of two DITs to form T_4 and the coupling of a MIT with a DIT to form T_3 are catalyzed by the enzyme TPO.

Storage of Thyroid Hormones and Iodine in Colloid

T_4, T_3, MIT, and DIT are stored outside the cell in the follicular colloid in peptide linkage within the Tg molecules. In normal humans on an iodine-sufficient diet, Tg makes up approximately 30% of the mass of the thyroid gland and represents a 2- to 3-month supply of hormone. The total amount of iodine contained as T_4, T_3, MIT, and DIT within Tg varies with the dietary iodine intake.

Secretion of Thyroid Hormones

The secretion of T_4 and T_3 is a relatively complex process because T_4 and T_3 are stored in the peptide structure of Tg within the follicular lumen and therefore are separated from the pertechnetate and the capillary endothelium by the thyroid follicular cells.

Endocytosis

The first step in the release of thyroid hormones from the thyroid gland is through *endocytosis* of colloid from the follicular lumen into the follicle cells. This may occur by macropinocytosis or micropinocytosis. Both processes are stimulated by TSH and result in the uptake of macropinocytotic or micropinocytotic vesicles that are limited by a single membrane and are filled with colloid inclusions. These endocytotic vesicles migrate from the follicular cell apical membrane toward the basal membrane. Within a few minutes of their formation, the colloid-containing endocytotic vesicles become surrounded by lysosomes containing glycoside hydrolases and proteases. The lysosomes eventually fuse with the endocytotic vesicles to form lysoendosomes. Within the lysoendosomes, Tg is hydrolyzed to yield peptide fragments, iodoamino acids (MIT and DIT), iodothyronines (T_4 and T_3), and other free amino acids. Once released from Tg, T_4 and T_3 rapidly diffuse across the basal plasma membrane into the pertechnetate and eventually into the circulation. During thyroidal secretion, only T_4, T_3 and a small amount of I^- normally reach the circulation; no Tg, MIT, or DIT escapes.

The T_4 and T_3 that are released from the thyroid gland are firmly but reversibly bound to several plasma proteins. More than 99% of the circulating thyroid hormone is protein bound, with only the free hormone available to enter cells (Table 65.1). The amount of T_4 or T_3 entering the cells and the ultimate physiological response are directly related to the plasma concentrations of free T_4 and free T_3. It is the concentrations of free T_4 and T_3 in the plasma that are regulated by the HPTA (Fig. 65.2) rather than the total (i.e., free plus protein-bound) plasma T_4 and T_3 concentrations.

Thyroxine-binding globulin is the least abundant of the three major transport proteins. Nevertheless, it carries about 70% of the circulating T_4 and T_3 by virtue of its high affinity for the two hormones. *Transthyretin,* formerly known as thyroxine-binding prealbumin, binds only about 10 to 15% of the hormones. *Albumin,* a protein that has a binding affinity for a multitude of small molecules, has an even lower affinity for T_4 and T_3 than

TABLE 65.1   **Approximate Values for Thyroid Hormone Plasma Concentrations and Various Kinetic Parameters**

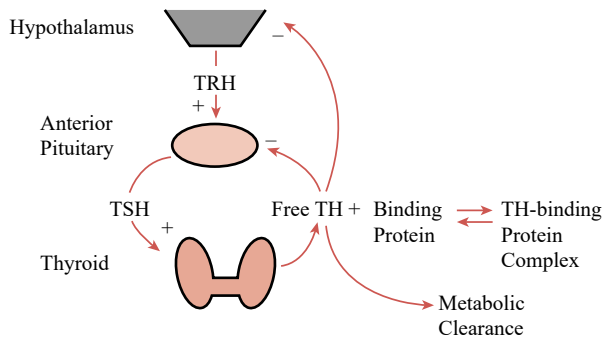|	T_4	T_3
Plasma concentration		
Total	7.77 mg/dL	0.14 mg/dL
Free	1.554 ng/dL	0.389 ng/dL
Total hormone in free form	0.02%	0.3%
Plasma half-life	6.7 days	0.75 days
Volume of distribution	10 L	40 L
Metabolic clearance rate	1.1 L/day	24 L/day
Total production rate	85.47 mg/day	33.6 mg/day
From thyroid secretion	100%	20%

FIGURE 65.2
The hypothalamic–pituitary–thyroid axis.

transthyretin, but the high plasma albumin concentration results in the binding of about 15 to 20% of the circulating thyroid hormones. Like T_4 and T_3 bound to transthyretin, the hormones may dissociate rapidly from albumin to generate free T_4 and free T_3. Circulating T_4 and T_3 are also bound by high-density lipoprotein (HDL). Plasma HDL may carry about 3% of the T_4 and 6% of the T_3. The physiological significance of this HDL binding is uncertain, but it may play a role in targeting thyroid hormone delivery to specific tissues.

The thyroid hormone transport proteins are not essential for hormone action. Rather, they participate in the maintenance of a steady supply of free hormone to tissues. Because of the presence of the binding proteins in the plasma, the size of the circulating thyroid hormone pool is quite large, and both T_4 and T_3 have very long half-lives in humans (Table 65.1). The total amount of thyroid hormone bound to plasma proteins is about three times that secreted and degraded in the course of a single day. Three functions can be postulated for the thyroid hormone transport proteins: (1) extrathyroidal storage of hormone, (2) a buffering action, such that effects of acute changes in rates of thyroid gland secretion or hormone metabolic clearance on plasma concentrations of free thyroid hormones are minimized, and (3) a hormone-releasing function that allows the very small free hormone pool to be continuously replenished and made available to cells as intracellular hormone is metabolized. Thus, the large pools of protein-bound T_4 and T_3 in the blood act to stabilize plasma free T_4 and free T_3 concentrations and consequently the intracellular concentrations of T_4 and T_3 and thyroid hormone receptor (TR) occupancy.

Cellular Uptake and Intracellular Binding of T_3 to Nuclear Thyroid Hormone Receptors

Free T_4 and T_3 can enter cells by carrier-mediated facilitated diffusion or active transport. After gaining access to the cell interior, T_4 may undergo 5′-monodeiodination to yield T_3. The T_3 thus mixes with T_3 entering the cell from the plasma and binds to nuclear TRs. The specific 5′-monodeiodinase enzyme and the level of activity vary from tissue to tissue, as does the contribution of plasma T_4 to nuclear TR-bound T_3.

Thyroid Hormone Activation and Inactivation by Selenodeiodinases

In humans, the major pathway in the metabolism of the thyroid hormones consists of the removal of iodine or deiodination. Three deiodinase isoenzymes, encoded on three distinct genes, catalyze the reductive deiodination. All three enzymes contain the rare amino acid selenocysteine. The essential trace element selenium therefore plays an important role in thyroid hormone economy.

The most important pathway for the metabolism of T_4 is monodeiodination. The removal of an iodide from the outer ring of T_4 yields T_3. Since the affinity of nuclear TRs is much higher for T_3 than T_4, outer ring monodeiodination of T_4 to yield T_3 produces a more active metabolite. Conversely, removal of an iodide from the inner ring of T_4 yields an inactive metabolite, rT_3. Both T_3 and rT_3 may undergo subsequent deiodinations to yield totally deiodinated thyronine (T_0).

Up to 80% of the circulating T_3 originates from deiodination of T_4. This is due mainly to a deiodinase (D1) activity in the liver, where most of the T_3 formed is exported into the circulation. Monodeiodination of T_4 to yield T_3 is catalyzed by another deiodinase (D2). It appears that D2 catalyzes T_3 from T_4 for local cellular demands independent of circulating T_3. The third enzyme involved in the reductive deiodination of T_4, T_3, and other iodothyronines is D3. The sole action of this enzyme is the removal of iodide from the inner ring of iodothyronines.

The three deiodinases have differing tissue distributions, substrate preferences, and K_m values. This arrangement allows for control of thyroid hormone action at the cellular level. The source and quantity of T_3

TABLE 65.2 TSH-Stimulated Events at the Thyroid Gland

Cyclic AMP–Mediated Events	Phospholipase C–Mediated Events
Sodium iodide symporter activity	H_2O_2 generation
Thyroglobulin synthesis	I^- conductance of the apical membrane
Thyroperoxidase synthesis	
Hormone synthesis	
Endocytosis and hydrolysis of colloid	
Hormone secretion	
Type 1 deiodinase activity	
Hypertrophy	

bound to nuclear TRs may vary among tissues depending on the distributions and relative activities of D1, D2, and D3.

MECHANISMS OF ACTION OF THYROID HORMONES

Thyroid hormone mechanisms of action can be classified into two types: (1) genomic or nuclear and (2) nongenomic, including effects at the plasma membrane and mitochondria. Genomic effects involve modification of gene transcription, are mediated only by T_3, and require at least several hours to detect. Nongenomic actions are generally rapid in onset and occur in response to T_4 and some T_4 metabolites (e.g., rT_3, T_3, and T_2).

Genomic Actions of Thyroid Hormones

Thyroid hormone receptors are members of a superfamily of nuclear receptors that includes receptors for estrogen, glucocorticoid, mineralocorticoid, retinoic acid, 9-cis-retinoic acid (retinoid X), and vitamin D. Similar to the mechanism of action of lipophilic steroid hormones, the lipophilic T_3 binds to a protein receptor to form a complex and the hormone–receptor complex binds to an appropriate hormone response element on DNA to alter the transcription of specific genes. The current view of the mechanism of thyroid hormone action differs from that for steroid hormones, however, in three major ways: (1) There are apparently no cytosolic receptors for thyroid hormones. (2) The nuclear TRs can bind to DNA nucleotide sequences in the regulatory region of thyroid hormone–responsive genes in the absence of thyroid hormone binding. (3) In the absence of T_3 binding, TR bound to these specific areas of DNA may repress or promote the transcription of the associated thyroid hormone-responsive gene.

Nongenomic Actions of Thyroid Hormone

The nongenomic actions of thyroid hormone are increasingly recognized as physiologically significant. Nongenomic actions may be observed within minutes of stimulation and respond to a range of thyroid hormone metabolites (T_4, T_3, rT_3, T_2). The magnitude of nongenomic actions is usually only a few fold in contrast to the multifold genomic actions. The nongenomic actions (Table 65.2) may involve interactions with components of the cellular signal transduction pathways, such as cyclic adenosine monophosphate (cAMP), phosphatidyl inositol, and protein kinases. Examples include effects on cellular respiration, cell morphology, vascular tone, and ion homeostasis. Possible nongenomic targets of thyroid hormone include the plasma membrane, cy-

toskeleton, sarcoplasmic reticulum, mitochondria, and contractile elements of vascular smooth muscle.

PHYSIOLOGICAL EFFECTS OF THYROID HORMONES

There is no discrete target tissue for thyroid hormones; virtually every cell in the body is affected by thyroid hormones in some way. These hormones are intimately involved in the maintenance of normal function in virtually every cell type, including cellular responsiveness to other hormones, to the availability of metabolic substrates, to growth factors, and so on. Thyroid dysfunction can produce dramatic changes in the metabolism of proteins, carbohydrates, and lipids at the cellular level that can have repercussions for the operation of the cardiovascular, gastrointestinal, musculoskeletal, reproductive, and nervous systems. Some of the clinical manifestations of thyroid dysfunction are presented next in the discussions of hypothyroid and hyperthyroid states.

HYPOTHYROID STATES

Hypothyroidism refers to the exposure of body tissues to a subnormal amount of thyroid hormone. This can result from a defect anywhere in the HPTA. As a consequence of the lack of thyroid hormone, a wide variety of physiological and clinical disturbances involving virtually every organ system may result.

Primary hypothyroidism results from an inability of the thyroid gland itself to produce and secrete sufficient quantities of T_4 and T_3 and accounts for most cases of hypothyroidism. In iodine-sufficient areas of the world, the most common cause of primary hypothyroidism is *chronic autoimmune thyroiditis (*Hashimoto's thyroiditis). Other causes of primary hypothyroidism include spontaneous degeneration of glandular tissue (idiopathic hypothyroidism), thyroid ablation with radioactive iodine uptake (^{131}I), and total or subtotal surgical thyroidectomy. Primary hypothyroidism is accompanied by an elevation in pituitary TSH secretion and circulating TSH levels. An enlargement of the thyroid, or goiter, usually develops with increasing duration of the primary hypothyroidism.

Biosynthetic defects in thyroid hormonogenesis may also result in an inability of the thyroid gland to produce sufficient hormone and may be due to inherited enzymatic deficiencies or the ingestion of natural or therapeutically administered antithyroid agents. An example in the latter category is lithium, widely used to treat psychiatric disorders and associated with the development of hypothyroidism and goiter. It is concentrated by the thyroid, where it inhibits thyroidal I^- uptake, incorpora-

tion of I⁻ into Tg, coupling of iodotyrosine, and, eventually, thyroid hormone secretion.

Secondary hypothyroidism, or pituitary hypothyroidism, is the consequence of impaired thyroid-stimulating hormone (TSH) secretion and is less common than primary hypothyroidism. It may result from any of the causes of hypopituitarism (e.g., pituitary tumor, postpartum pituitary necrosis, trauma). Patients with secondary hypothyroidism exhibit undetectable or inappropriately low serum TSH concentrations. In secondary hypothyroidism, a normal thyroid gland lacks the normal level of TSH stimulation necessary to synthesize and secrete thyroid hormones. Such patients usually also have impaired secretion of TSH in response to exogenous thyrotropin-releasing hormone (TRH) administration.

Tertiary hypothyroidism, or hypothalamic hypothyroidism, results from impaired TRH stimulation of pituitary TSH. This may be due to a disorder that damages the hypothalamus or interferes with hypothalamic–pituitary portal blood flow, thereby preventing delivery of TRH to the pituitary. Tumors, trauma, radiation therapy, or infiltrative disease of the hypothalamus can cause such damage. This relatively rare form of hypothyroidism is also characterized by inappropriately low levels of serum TSH.

Clinical Manifestations of Hypothyroidism

During the perinatal period, there is an absolute requirement for thyroid hormone for the development and maturation of the nervous and musculoskeletal systems. In the perinatal nervous system, thyroid hormone plays a critical role in normal growth of the cerebral and cerebellar cortices, the proliferation of axons, the branching of dendrites, synaptogenesis, myelination, cell migration, and so on.

Thyroid hormone also plays a major role in the maturation of bone. A deficiency of thyroid hormone in early life leads to both delay in and abnormal development of epiphyseal centers of ossification (epiphyseal dysgenesis). Hypothyroidism-induced impairment of linear growth can lead to dwarfism in which the limbs are disproportionately short in relation to the trunk with the apparent bone age retarded in relation to chronological age.

The hallmarks of infantile hypothyroidism (e.g., retardation of mental development and growth) become manifest only in later infancy and are largely irreversible. Consequently, early recognition and initiation of replacement therapy are crucial. In the absence of thyroid hormone therapy, the symptoms of infantile hypothyroidism include feeding problems, failure to thrive, constipation, a hoarse cry, and somnolence. In succeeding months, especially in severe cases, protuberance of the abdomen, dry skin, poor growth of hair and nails, delayed eruption of the deciduous teeth, and delay in reaching the normal milestones of development (e.g., holding up the head, sitting, walking, and talking) become evident.

In adults, the signs and symptoms of hypothyroidism include somnolence, slow mentation, dryness and loss of hair, increased fluid in body cavities (e.g., the pericardial sac), low metabolic rate, tendency to gain weight, hyperlipidemia, subnormal temperature, cold intolerance, bradycardia, reduced systolic and increased diastolic pulse pressure, hoarseness, muscle weakness, slow return of muscle to the neutral position after a tendon jerk, constipation, menstrual abnormalities, infertility, and sometimes myxedema (hard edema of subcutaneous tissue with increased content of proteoglycans in the fluid). A goiter (i.e., enlargement of the thyroid gland) may be present.

Juvenile or adult patients with primary hypothyroidism (as indicated by low serum free T_4 and high serum TSH concentrations) are usually treated with thyroxine with the aim of relieving symptoms and reducing the serum TSH concentration into the normal reference range. If the primary hypothyroidism is the result of iodine deficiency, then gradually increasing dietary iodine supplementation may also be instituted in addition to the thyroxine replacement therapy. Iodine supplementation alone may lead to the development of acute hyperthyroidism.

Patients with secondary or tertiary hypothyroidism are also usually treated with thyroxine, but the serum TSH concentration is not a reliable guide to therapy. The efficacy of thyroid hormone replacement in these patients must be assessed clinically and by measurement of the serum T_4 concentration.

The most extreme manifestation of untreated hypothyroidism is *myxedema coma,* which even if detected early and appropriately treated, carries a mortality rate of 30 to 60%. Myxedema coma is a misnomer. Most patients exhibit neither the myxedema nor coma. Patients with myxedema coma usually have longstanding hypothyroidism with the classic symptoms of hypothyroidism. Decompensation into myxedema coma may occur when the homeostatic mechanisms of the severely hypothyroid patient are subject to a stressful precipitating event (e.g., infection, trauma, some medications, stroke, surgery). The principal manifestation of myxedema coma is a deterioration of mental status (apathy, confusion, psychosis, but rarely coma). Other common clinical features include hypothermia, diastolic hypertension (early), hypotension (late), hypoventilation, hypoglycemia, and hyponatremia. If myxedema coma is suspected, the patient is usually admitted to an intensive care unit for pulmonary and cardiovascular support

and treated with intravenous T_4 (or sometimes T_3). Until coexisting adrenal insufficiency is ruled out, hydrocortisone should also be administered.

DRUGS USED IN THE TREATMENT OF HYPOTHYROIDISM

Levothyroxine Sodium

Levothyroxine sodium (*Levothroid, Synthroid, Levoxine*) is the sodium salt of the naturally occurring levorotatory isomer of T_4. It is the preparation of choice for maintenance of plasma T_4 and T_3 concentrations for thyroid hormone replacement therapy in hypothyroid patients. It is absorbed intact from the gastrointestinal tract, and its long half-life allows for convenient once-daily administration. Since much of the T_4 is deiodinated to T_3, it is usually unnecessary to use more expensive preparations containing both T_4 and T_3. The aim is to establish euthyroidism with measured serum concentrations of T_4, T_3, and TSH within the normal range.

The TSH-suppressive effects of exogenous T_4 also prove useful in removing the stimulatory effects of TSH on the thyroid gland in the management of simple nonendemic goiter, chronic thyroiditis, and TSH-dependent thyroid carcinoma.

Liothyronine Sodium

Liothyronine sodium (*Cytomel*) is the sodium salt of the naturally occurring levorotatory isomer of T_3. Liothyronine is generally not used for maintenance thyroid hormone replacement therapy because of its short plasma half-life and duration of action. The use of T_3 alone is recommended only in special situations, such as in the initial therapy of myxedema and myxedema coma and the short-term suppression of TSH in patients undergoing surgery for thyroid cancer. The use of T_3 alone may also be useful in patients with the rare condition of $5'$-deiodinase deficiency who cannot convert T_4 to T_3.

Liotrix

Liotrix (*Euthroid, Thyrolar*) is a 4:1 mixture of levothyroxine sodium and liothyronine sodium. Like levothyroxine, liotrix is used for thyroid hormone replacement therapy in hypothyroid patients. Although the idea of combining T_4 and T_3 in replacement therapy so as to mimic the normal ratio secreted by the thyroid gland is not new, it does not appear that liotrix offers any therapeutic advantage over levothyroxine alone.

Thyroid USP and Thyroglobulin

Thyroid USP (*Thyrar, Thyroid Strong, S-P-T*) is derived from dried and defatted thyroid glands of domestic animals (bovine, ovine, or porcine), while Tg (*Proloid*) is a partially purified extract of frozen porcine thyroid glands. Although used extensively in the past, these preparations are rarely used today.

The total thyroid hormone content of thyroid glands and the ratio of T_3 to T_4 vary somewhat from one species to another. Thyroid USP preparations are therefore standardized on the basis of their iodine content. Much of the iodine in these preparations is in the metabolically inactive form of iodotyrosines. Thus, a given preparation may satisfy the USP iodine assay requirements and yet contain low amounts of T_4 and T_3. *Thyrar* (a beef extract) and *Armour Thyroid* tablets (a pork extract) are evaluated by additional biological assays to ensure consistent potency from one batch to another.

The production of *Proloid,* which is a partially purified frozen porcine Tg preparation, is an attempt to avoid the variability in desiccated thyroid preparations. It is also assayed and standardized for biological potency. Thyroglobulin is slightly more expensive and offers no particular therapeutic advantage over Thyroid USP. These two preparations have a higher ratio of T_3 to T_4 than that found in human thyroid secretion, so supraphysiological levels of T_3 may occur in the immediate postabsorptive period because of the rapid release of T_3 from ingested Tg, its immediate absorption, and the relatively long period (1 day) required for T_3 to equilibrate in its volume of distribution.

ADVERSE EFFECTS OF TREATMENT WITH THYROID HORMONE

The most common adverse effects (i.e., symptoms of hyperthyroidism) are the result of a drug overdose; they include cardiac palpitation and arrhythmias, tachycardia, weight loss, tremor, headache, insomnia, and heat intolerance. Symptoms subside if medication is withheld for several days.

In patients with longstanding hypothyroidism and those with ischemic heart disease, rapid correction of hypothyroidism may precipitate angina, cardiac arrhythmias, or other adverse effects. For these patients, replacement therapy should be started at low initial doses, followed by slow titration to full replacement as tolerated over several months. If hypothyroidism and some degree of adrenal insufficiency coexist, an appropriate adjustment of the corticosteroid replacement must be initiated prior to thyroid hormone replacement therapy. This prevents acute adrenocortical insufficiency that could otherwise arise from a thyroid hormone–induced increase in the metabolic clearance rate of adrenocortical hormones.

DRUG INTERACTIONS

Administration of sympathomimetic agents and thyroid hormone to patients with coronary artery disease may increase the risk of coronary insufficiency. Since thyroid hormones increase the catabolism of vitamin K–dependent clotting factors, the effects of coumarin anticoagulants may be enhanced. During concomitant therapy, the dosage of the anticoagulant may have to be reduced. Conversely, initiation of thyroid hormone therapy in patients with diabetes mellitus may increase the requirement for insulin or oral hypoglycemic agents. Similarly, a larger dose of cardiac glycosides (e.g., digitoxin, digoxin) may be required in digitalized patients.

THYROTOXICOSIS

Thyrotoxicosis is any condition in which the body tissues are exposed to supraphysiological concentrations of thyroid hormones. This designation is preferred to the term *hyperthyroidism* to describe this disorder because its origin may not result from excessive thyroid gland secretion. Thyrotoxicosis factitia arises from the ingestion of excessive quantities of thyroid hormone rather than from overactivity of the thyroid gland. The term hyperthyroidism is reserved for disorders that result from overproduction of hormone by the thyroid itself. This distinction is important because only conditions caused by hyperthyroidism respond to treatment with agents that decrease iodine uptake, thyroid hormone production, and the release of thyroid hormone, and only these conditions may require permanent radioactive or surgical ablation of the gland.

The manifestations of hyperthyroidism depend on the severity of the disease, the age of the patient, the presence or absence of extrathyroidal manifestations, and the specific disorder producing the thyrotoxicosis. Of the various types of hyperthyroidism, only two are common: Graves' disease and toxic multinodular goiter. Less common causes include toxic adenoma and postpartum thyroiditis, among others.

Graves' disease, the most common type of hyperthyroidism, is an autoimmune disease that is characterized by the presence of TSH receptor–stimulating antibodies (TSAB) that bind to the TSH receptors (TSHR) on thyroid follicular cells. These TSABs mimic TSH in stimulating growth of the thyroid gland (diffuse goiter) and by causing an increase in synthesis and secretion of T_4 and T_3. In these patients, serum concentrations of T_4, T_3, and TSAB are elevated, while TSH levels are suppressed. Additional symptoms of Graves' disease may include infiltrative ophthalmopathy (*exophthalmos*) and occasionally infiltrative dermopathy. Both of these are also thought to result from an autoimmune process.

In older patients *toxic multinodular goiter* typically presents as longstanding asymptomatic multinodular goiters. Functional autonomy of the nodules develops over time by an unknown mechanism and causes the disease to move from the nontoxic to the toxic phase. The onset of hyperthyroidism is gradual, and the symptoms are usually milder than those of Graves' disease.

Toxic adenoma (Plummer's disease) is less common and is caused by one or more autonomous adenomas of the thyroid gland. These autonomously secreting tumors occur in an intrinsically normal thyroid gland and result from point mutations in the TSHRs on thyroid follicular cells. These point mutations lead to constitutive activation of the TSHR in the absence of TSH. Tumor growth is progressive over many years, and with growth, a progressively larger share of thyroid hormone secretion is assumed by the adenoma; TSH secretion is inhibited, while the remainder of the gland is unstimulated and may atrophy. Continued autonomous growth results in excessive secretion of T_4 and T_3 and thyrotoxicosis.

Clinical Manifestations of Thyrotoxicosis

The signs and symptoms of thyrotoxicosis, regardless of the cause, may include the following: increased basal metabolic rate, heat intolerance, tachycardia, widened pulse pressure, cardiac arrhythmias, skeletal muscle weakness, muscle wasting, tremor, hyperreflexia, emotional instability, nervousness, insomnia, change in menstrual pattern, frequent bowel movements (occasionally diarrhea), and weight loss despite an increased appetite. In addition, very frequent manifestations of all forms of thyrotoxicosis, irrespective of the underlying cause, are retraction of the upper eyelid (evident as the presence of a rim of sclera between the lid and the limbus) and lid lag. These ocular manifestations appear to be due largely to increased adrenergic stimulation and are ameliorated by adrenergic antagonists and reversed promptly upon successful treatment of the thyrotoxicosis. These eye signs do not indicate Graves' infiltrative ophthalmopathy and are not accompanied by protrusion of the eyes.

In Graves' disease, the autoimmune processes mediate the enlargement of the thyroid gland, the infiltrative ophthalmopathy with exophthalmos, and the dermopathy and thereby distinguish Graves' disease from other causes of thyrotoxicosis.

Thyrotoxic Crisis, or Thyroid Storm

Thyrotoxic crisis, thyroid storm, or accelerated hyperthyroidism is an extreme accentuation of thyrotoxicosis. Although uncommon, this serious complication of hyperthyroidism usually occurs in association with Grave's disease and occasionally with toxic multinodular goiter.

If unrecognized, it is invariably fatal. Thyroid storm is usually abrupt in onset and occurs in patients whose preexisting thyrotoxicosis has been treated incompletely or not at all. Thyrotoxic crisis may be related to cytokine release and an acute immunological disturbance caused by a precipitating condition, such as trauma, surgery, diabetic ketoacidosis, toxemia of pregnancy, or parturition. Although the serum thyroid hormone levels may not be appreciably greater than those in uncomplicated thyrotoxicosis, the clinical picture is severe hypermetabolism with fever, profuse sweating, tachycardia, arrhythmias, and so on. Pulmonary edema or congestive heart failure may also develop. With progression of the disorder, apathy, stupor, and coma may supervene, and hypotension can develop. There are no foolproof criteria by which severe thyrotoxicosis complicated by some other serious disease can be distinguished from thyrotoxic crisis induced by that disease. In any event, the differentiation between these alternatives is of no great significance because treatment of the two is the same, directed at systemic support and amelioration of the thyrotoxicosis.

DRUGS USED IN THE TREATMENT OF HYPERTHYROIDISM

Treatment of hyperthyroidism is directed at reducing the excessive synthesis and secretion of thyroid hormones. This may be accomplished by inhibiting thyroidal synthesis and secretion with antithyroid drugs, by reducing the amount of functional thyroid tissue, or by both. Unfortunately, only a small proportion of patients treated with antithyroid drugs obtain long-term remission of their hyperthyroidism. Ablative therapy is often necessary. Since many of the signs and symptoms of hyperthyroidism reflect increased cellular sensitivity to adrenergic stimulation, a β-adrenergic antagonist is often used adjunctively. Propranolol (*Inderal*), the most widely used β-adrenoceptor blocker, is effective in ameliorating many of the manifestations of thyrotoxicosis. It may reduce thyrotoxicosis-induced tachycardia, palpitations, tremor, sweating, heat intolerance, and anxiety, which are largely mediated through the adrenergic nervous system. Propranolol may also impair the conversion of T_4 to T_3. The use of propranolol is contraindicated in thyrotoxic patients with asthma or chronic obstructive pulmonary disease because it impairs bronchodilation. It is also contraindicated in patients with heart block and those with congestive heart failure, unless severe tachycardia is a contributory factor.

Thionamides

Thionamides are the primary drugs used to decrease thyroid hormone production. They do not inhibit secretion of stored thyroid hormone, and therefore, when they are used alone, their clinical effects are not apparent until the preexisting intrathyroidal store of thyroid hormone is depleted. This may take several weeks. Propylthiouracil and methylthiouracil (methimazole; *Tapazole*) are the most commonly used preparations in the United States.

Thionamide drugs interfere with peroxidase-catalyzed reactions. In the thyroid gland, they inhibit the activity of the enzyme TPO, which is required for the intrathyroidal oxidation of I^-, the incorporation of I^- into Tg, and the coupling of iodotyrosyl residues to form thyroid hormones. Thus, these drugs inhibit thyroid hormone synthesis and with time, also secretion. Propylthiouracil, but not methimazole, also inhibits D1, which deiodinates T_4 to T_3. Because of this additional action, propylthiouracil is often used to provide a rapid alleviation of severe thyrotoxicosis.

In patients with autoimmune thyroid disease, thionamide drugs may also exert an immunosuppressive effect. As the drug is concentrated in thyroid follicular cells, the expression of thyroid antigen and the release of prostaglandins and cytokines are decreased. Subsequently, the autoimmune response is impaired. Thionamides also inhibit the generation of oxygen radicals in T cells, B cells, and particularly the antigen-presenting cells within the thyroid gland. Thus, thionamides may cause a decline in thyroid autoantibody titers, although the clinical importance of immunosuppression is unclear.

Thionamide drugs are well absorbed from the gastrointestinal tract. Although they have short plasma half-lives (propylthiouracil 1.5 hours; methimazole 6 hours), they accumulate in the thyroid gland, and a single daily dose may exert effects for greater than 24 hours. Thionamides undergo hepatic conjugation to form glucuronides and are excreted in the bile and urine. Nevertheless, few glucuronide conjugates are found in the feces because they are absorbed from the gastrointestinal tract.

The thionamide drugs are used in the management of hyperthyroidism and thyrotoxic crisis and in the preparation of patients for surgical subtotal thyroidectomy. Although the use of thionamides alone may restore euthyroidism, it is difficult to adjust the dosage in some patients. This has led to the development of block-and-replace regimens in which a full blocking dose of thionamide plus a levothyroxine supplement is prescribed. Although thionamides may be used to treat hyperthyroidism during pregnancy, they should be given in minimally effective doses to avoid inducing infantile hypothyroidism and thyroid enlargement in the developing fetus.

If given in excessive amounts over a long period, thionamides may cause hypothyroidism and enlargement of the thyroid gland. The most serious adverse effects are granulocytopenia and agranulocytosis, which occur in about 0.5% of patients and usually within 3 months of starting therapy. The most frequently observed adverse

effect is rash. Arthralgia, myalgia, cholestatic jaundice, lymphadenopathy, drug fever, psychosis, and a lupuslike syndrome have also been reported.

Iodine and Iodine-Containing Agents
Iodides

The effects of iodide on the thyroid gland are complex. When administered in pharmacological amounts, potassium iodide (KI) causes a transient inhibition of the uptake and incorporation of I^- into Tg (Wolff-Chaikoff effect). In addition, high doses of KI also inhibit the secretion of thyroid hormone and thyroid blood flow. These effects make KI an ideal agent for treating severe thyrotoxicosis or thyroid crisis when a rapid decrease in plasma T_4 and T_3 is desirable. As the thyroid gland escapes from Wolff-Chaikoff effect, I^- accumulates within the gland and hormone synthesis resumes. With continued treatment with KI alone, the inhibition of thyroid secretion may also diminish. Hypersecretion of thyroid hormone and thyrotoxicosis may return at the previous or a more severe intensity. For this reason, iodide alone is not used for the management of hyperthyroidism. Nevertheless, KI has long been used in combination with propylthiouracil in the management of thyrotoxic crisis to rapidly inhibit thyroid hormone secretion. Iodide plus a thionamide has also been used in the immediate preoperative preparation of patients about to undergo total or subtotal surgical thyroidectomy.

The ability of KI to block the thyroidal uptake of I^- and its incorporation into Tg would prove useful in the event of an accident at a nuclear power plant. In such an event, large quantities of radionuclides, including isotopes of radioiodine, could be released into the atmosphere. Administration of KI (*Thyro-Block*) to inhibit the uptake and incorporation of radioiodine would be the most effective means of limiting the potential damage to the thyroid gland.

Adverse reactions to iodine can be divided into intrathyroidal and extrathyroidal reactions. Among the intrathyroidal reactions is iodine-induced thyrotoxicosis (Jod-Basedow's phenomenon), which may occur in patients with nontoxic nodular goiter given low doses (<25 mg/day) of potassium or sodium iodide. At higher doses (50–500 mg/day), iodide goiter or hypothyroidism or both may develop, but this usually requires long exposure. Extrathyroidal adverse reactions to iodine are relatively rare and generally not serious. These include rash, which may be acneiform; drug fever; sialadenitis (inflammation of the salivary glands); conjunctivitis and rhinitis; vasculitis; and a leukemoid eosinophilic granulocytosis.

Oral Cholecystographic Agents

The iodine-containing oral cholecystographic contrast agents (OCAs) include sodium ipodate (*Oragrafin*), iopanoic acid (*Telepaque*), tyropanoic acid (*Bilopaque*), and iocetamic acid (*Cholebrine*). They all inhibit D1 and D2. These actions make OCAs useful as adjunctive therapy with other antithyroid drugs by promoting a rapid fall in the plasma T_3 concentration of the seriously thyrotoxic patient.

In addition, the metabolism of OCAs results in the release of large amounts of I^- into the circulation. As described for KI, I^- released from OCAs may have effects at the thyroid gland and if used alone to treat hyperthyroidism, OCAs carry the same potential to induce increased secretion of thyroid hormone and exacerbation of thyrotoxicosis. When an OCA is used in the treatment of hyperthyroidism, large doses of antithyroid agents are usually administered concomitantly. However, the combination of OCAs and antithyroid drugs may cause resistance to the antithyroid drugs with time, presumably because of the elevation in intrathyroidal I^- content. Thus, it is recommended that the use of OCAs be reserved for short-term treatment of patients with severe thyrotoxicosis and significant comorbidity (e.g., myocardial infarction, sepsis, stroke) for rapid control of plasma T_3 concentrations.

When the OCAs are used for these purposes, they are administered at much lower doses than when used for cholecystography. At the higher doses, the major adverse effects of these compounds are acute renal failure, thrombocytopenia, and athrombocytosis; possible minor adverse reactions include diarrhea, nausea, vomiting, and dysuria.

Radioiodine

Millicurie amounts of ^{131}I (*Iodotope I-131*) are used for thyroid ablation in the management of hyperthyroidism. ^{131}I is taken up and trapped in the same manner as I^-. The ablative effect is exerted primarily through β-particle emissions, which destroy thyroid tissue. The major disadvantage associated with this therapy is the development of hypothyroidism after thyroid ablation. Microcurie amounts of radioiodine also are used for the diagnostic evaluation of thyroid function.

Potassium Perchlorate

The perchlorate ion of potassium perchlorate, $KClO_4$, is a competitive inhibitor of thyroidal I^- transport via the Sodium Iodide Symporter (NIS). This drug can cause fatal aplastic anemia and gastric ulcers and is now rarely used. If administered with careful supervision, in limited low doses and for only brief periods, serious toxic effects can be avoided. The compound is especially effective in treating iodine-induced hyperthyroidism, which may occur, for example, in patients treated with the antiarrhythmic compound amiodarone. Perchlorate ion can also be used in a diagnostic test of I^- incorporation into Tg, the so-called perchlorate discharge test.