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Disorders of the Thyroid Gland

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The thyroid gland produces two related hormones, thyroxine (T_4) and triiodothyronine (T_3) (Fig. 320-1). Acting through nuclear receptors, these hormones play a critical role in cell differentiation during development and help maintain thermogenic and metabolic homeostasis in the adult. Disorders of the thyroid gland result primarily from autoimmune processes that either stimulate the overproduction of thyroid hormones (*thyrotoxicosis*) or cause glandular destruction and hormone deficiency (*hypothyroidism*). In addition, benign nodules and various forms of thyroid cancer are relatively common and amenable to detection by physical examination.

FIGURE 320-1 Structures of thyroid hormones. Thyroxine (T_4) contains four iodine atoms. Deiodination leads to production of the potent hormone, triiodothyronine (T_3), or the inactive hormone, reverse T_3.

ANATOMY AND DEVELOPMENT

The thyroid gland is located in the neck, anterior to the trachea, between the cricoid cartilage and the suprasternal notch. The thyroid (Greek *thyreos*, shield, plus *eidos*, form) consists of two lobes that are connected by an isthmus. It is normally 12 to 20 g in size, highly vascular, and soft in consistency. Four parathyroid glands, which produce parathyroid hormone (Chap. 332), are located in the posterior region of each pole of the thyroid. The recurrent laryngeal nerves traverse the lateral borders of the thyroid gland and must be identified during thyroid surgery to avoid vocal cord paralysis.

The thyroid gland develops from the floor of the primitive pharynx during the third week of gestation. The gland migrates from the foramen cecum, at the base of the tongue, along the thyroglossal duct to reach its final location in the neck. This feature accounts for the rare ectopic location of thyroid tissue at the base of the tongue (lingual thyroid), as well as for the presence of thyroglossal duct cysts along this developmental tract. Thyroid hormone synthesis normally begins at about 11 weeks' gestation.

The parathyroid glands migrate from the third (inferior glands) and fourth (superior glands) pharyngeal pouches and become embedded in the thyroid gland. Neural crest derivatives from the ultimobranchial body give rise to thyroid medullary C cells that produce calcitonin, a calcium-lowering hormone. The C cells are interspersed throughout the thyroid gland, although their density is greatest in the juncture of the upper one-third and lower two-thirds of the gland.

Thyroid gland development is controlled by a series of developmental transcription factors. Thyroid transcription factor (TTF) 1 (also known as NKX2A), TTF-2 (also known as FKHL15), and paired homeobox-8 (PAX-8) are expressed selectively, but not exclusively, in the thyroid gland. In combination, they orchestrate thyroid cell development and the induction of thyroid-specific genes such as thyroglobulin (Tg), thyroid peroxidase (TPO), the sodium iodide symporter (NIS), and the thyroid-stimulating hormone receptor (TSH-R). Mutations in these developmental transcription factors or their downstream target genes are rare causes of thyroid agenesis or dyshormonogenesis and can cause congenital hypothyroidism (Table 320-1). Congenital hypothyroidism is common enough (approximately 1 in 4000 newborns) that neonatal screening is performed in most industrialized countries (see below). Though the underlying causes of most cases of congenital hypothyroidism are unknown, early treatment with thyroid hormone replacement precludes potentially severe developmental abnormalities.

TABLE 320-1 Genetic Causes of Congenital Hypothyroidism

Defective Gene Protein	Inheritance	Consequences
PROP-1	Autosomal recessive	Combined pituitary hormone deficiencies with preservation of adrenocorticotropic hormone
PIT-1	Autosomal recessive Autosomal dominant	Combined deficiencies of growth hormone, prolactin, thyroid-stimulating hormone (TSH)
TSHβ	Autosomal recessive	TSH deficiency
TTF-1	Autosomal dominant	Variable thyroid hypoplasia, choreoathetosis, pulmonary problems
TTF-2	Autosomal recessive	Thyroid agenesis, choanal atresia, spiky hair
PAX-8	Autosomal dominant	Thyroid dysgenesis

TSH-receptor	Autosomal recessive	Resistance to TSH
$G_{s\alpha}$ (Albright hereditary osteodystrophy)	Autosomal dominant	Resistance to TSH
Na^+/I^- symporter	Autosomal recessive	Inability to transport iodide
THOX2	Autosomal dominant	Organification defect
Thyroid peroxidase	Autosomal recessive	Defective organification of iodide
Thyroglobulin	Autosomal recessive	Defective synthesis of thyroid hormone
Pendrin	Autosomal recessive	Pendred's syndrome: sensorineural deafness and partial organification defect in thyroid
Dehalogenase	Autosomal recessive	Loss of iodide reutilization

The mature thyroid gland contains numerous spherical follicles composed of thyroid follicular cells that surround secreted colloid, a proteinaceous fluid that contains large amounts of thyroglobulin, the protein precursor of thyroid hormones (Fig. 320-2). The thyroid follicular cells are polarized—the basolateral surface is apposed to the bloodstream and an apical surface faces the follicular lumen. Increased demand for thyroid hormone, usually signaled by thyroid-stimulating hormone (TSH) binding to its receptor on the basolateral surface of the follicular cells, leads to Tg reabsorption from the follicular lumen and proteolysis within the cell to yield thyroid hormones for secretion into the bloodstream.

REGULATION OF THE THYROID AXIS

TSH, secreted by the thyrotrope cells of the anterior pituitary, plays a pivotal role in control of the thyroid axis and serves as the most useful physiologic marker of thyroid hormone action. TSH is a 31-kDa hormone composed of α and β subunits; the α subunit is common to the other glycoprotein hormones [luteinizing hormone, follicle-stimulating hormone,

human chorionic gonadotropin (hCG)], whereas the TSH β subunit is unique to TSH. The extent and nature of carbohydrate modification are modulated by thyrotropin-releasing hormone (TRH) stimulation and influence the biologic activity of the hormone.

The thyroid axis is a classic example of an endocrine feedback loop. Hypothalamic TRH stimulates pituitary production of TSH, which, in turn, stimulates thyroid hormone

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synthesis and secretion. Thyroid hormones feed back negatively to inhibit TRH and TSH production (Fig. 320-2). The "set-point" in this axis is established by TSH. TRH is the major positive regulator of TSH synthesis and secretion. Peak TSH secretion occurs ~15 min after administration of exogenous TRH. Dopamine, glucocorticoids, and somatostatin suppress TSH but are not of major physiologic importance except when these agents are administered in pharmacologic doses. Reduced levels of thyroid hormone increase basal TSH production and enhance TRH-mediated stimulation of TSH. High thyroid hormone levels rapidly and directly suppress TSH and inhibit TRH-mediated stimulation of TSH, indicating that thyroid hormones are the dominant regulator of TSH production. Like other pituitary hormones, TSH is released in a pulsatile manner and exhibits a diurnal rhythm; its highest levels occur at night. However, these TSH excursions are modest in comparison to those of other pituitary hormones, in part because TSH has a relatively long plasma half-life (50 min). Consequently, single measurements of TSH are adequate for assessing its circulating level. TSH is measured using immunoradiometric assays that are highly sensitive and specific. These assays readily distinguish between normal and suppressed TSH values; thus, TSH can be used for the diagnosis of hyperthyroidism (low TSH) as well as hypothyroidism (high TSH).

THYROID HORMONE SYNTHESIS, METABOLISM, AND ACTION

THYROID HORMONE SYNTHESIS

Thyroid hormones are derived from Tg, a large iodinated glycoprotein. After secretion into the thyroid follicle, Tg is iodinated on selected tyrosine residues that are subsequently coupled via an ether linkage. Reuptake of Tg into the thyroid follicular cell initiates proteolysis and the release of newly synthesized T_4 and T_3.

Iodine Metabolism And Transport

Iodide uptake is a critical first step in thyroid hormone synthesis. Ingested iodine is bound to serum proteins, particularly albumin. Unbound iodine is excreted in the urine. The thyroid gland extracts iodine from the circulation in a highly efficient manner. For example, 10 to 25% of radioactive tracer (e.g., ^{123}I) is taken up by the normal thyroid gland over 24 h; this value can rise to 70 to 90% in Graves' disease. Iodide uptake is mediated by the Na^+/I^- symporter (NIS), which is expressed at the basolateral membrane of thyroid follicular cells. NIS is most highly expressed in the thyroid gland but low levels are present in the salivary glands, lactating breast, and placenta. The iodide transport mechanism is highly regulated, allowing adaptation to variations in dietary supply. Low iodine levels increase the amount of NIS and stimulate uptake, whereas high iodine levels suppress NIS

expression and uptake. The selective expression of the NIS in the thyroid allows isotopic scanning, treatment of hyperthyroidism, and ablation of thyroid cancer with radioisotopes of iodine, without significant effects on other organs. Mutation of the *NIS*gene is a rare cause of congenital hypothyroidism, underscoring its importance in thyroid hormone synthesis. Another iodine transporter, pendrin, is located on the apical surface of thyroid cells and mediates iodine efflux into the lumen. Mutation of the *PENDRIN*gene causes *Pendred syndrome*, a disorder characterized by defective organification of iodine, goiter, and sensorineural deafness.

Iodine deficiency is prevalent in many mountainous regions and in central Africa, central South America, and northern Asia. In areas of relative iodine deficiency, there is an increased prevalence of goiter and, when deficiency is severe, hypothyroidism and cretinism. *Cretinism* is characterized by mental and growth retardation and occurs when children who live in iodine-deficient regions are not treated with iodine or thyroid hormone to restore normal thyroid hormone levels during early childhood. These children are often born to mothers with iodine deficiency, and it is likely that maternal thyroid hormone deficiency worsens the condition. Concomitant selenium deficiency may also contribute to the neurologic manifestations of cretinism. Iodine supplementation of salt, bread, and other food substances has markedly reduced the prevalence of cretinism. Unfortunately, however, iodine deficiency remains the most common cause of preventable mental deficiency, often because of resistance to the use of food additives or the cost of supplementation. In addition to overt cretinism, mild iodine deficiency can lead to subtle reduction of IQ. Oversupply of iodine,

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through supplements or foods enriched in iodine (e.g., shellfish, kelp), is associated with an increased incidence of autoimmune thyroid disease. The recommended average daily intake of iodine is 150 µg/d for adults, 90 to 120 µg/d for children, and 200 µg/d for pregnant women. Urinary iodine is >10 µg/dL in iodine-sufficient populations.

FIGURE 320-2 Regulation of thyroid hormone synthesis. *Left*. Thyroid hormones T_4 and T_3 feed back to inhibit hypothalamic production of thyrotropin-releasing hormone (TRH) and pituitary production of thyroid-stimulating hormone (TSH). TSH stimulates thyroid gland production of T_4 and T_3. *Right*. Thyroid follicles are formed by thyroid epithelial cells surrounding proteinaceous colloid, which contains thyroglobulin. Follicular cells, which are polarized, synthesize thyroglobulin and carry out thyroid hormone biosynthesis (see text for details). TSH-R, thyroid-stimulating hormone receptor; Tg, thyroglobulin; NIS, sodium-iodide symporter; TPO, thyroid peroxidase; DIT, di-iodotyrosine; MIT, monoiodotyrosine

Organification, Coupling, Storage, Release

After iodide enters the thyroid, it is trapped and transported to the apical membrane of thyroid follicular cells where it is oxidized in an organification reaction that involves TPO and hydrogen peroxide. The reactive iodine atom is added to selected tyrosyl residues within Tg, a large (660 kDa) dimeric protein that consists of 2769 amino acids. The iodotyrosines in Tg are then coupled via an ether linkage in a reaction that is also catalyzed by TPO. Either T_4 or T_3 can be produced by this reaction, depending on the

number of iodine atoms present in the iodotyrosines. After coupling, Tg is taken back into the thyroid cell where it is processed in lysosomes to release T_4 and T_3. Uncoupled mono- and diiodotyrosines (MIT, DIT) are deiodinated by the enzyme dehalogenase, thereby recycling any iodide that is not converted into thyroid hormones.

Disorders of thyroid hormone synthesis are rare causes of congenital hypothyroidism. The vast majority of these disorders are due to recessive mutations in TPO or Tg, but defects have also been identified in the TSH-R, NIS, pendrin, hydrogen peroxide generation, and in dehalogenase. Because of the biosynthetic defect, the gland is incapable of synthesizing adequate amounts of hormone, leading to increased TSH and a large goiter.

TSH Action

TSH regulates thyroid gland function through the TSH-R, a seven-transmembrane G protein–coupled receptor (GPCR). The TSH-R is coupled to the α subunit of stimulatory G protein ($G_{s\alpha}$), which activates adenylyl cyclase, leading to increased production of cyclic AMP. TSH also stimulates phosphatidylinositol turnover by activating phospholipase C. The functional roles of the TSH-R are exemplifiedby the consequences of naturally occurring mutations. Recessive loss-of-function mutations are a rare cause of thyroid hypoplasia and congenital hypothyroidism. Dominant gain-of-function mutations cause sporadic or familial nonautoimmune hyperthyroidism that is characterized by goiter, thyroid cell hyperplasia, and autonomous function. Most of these activating mutations occur in the transmembrane domain of the receptor. They are thought to mimic conformational changes similar to those induced by TSHbinding or the interactions of thyroid-stimulating immunoglobulins (TSI) in Graves' disease. Activating TSH-R mutations also occur as somatic events and lead to clonal selection and expansion of the affected thyroid follicular cell (see below).

Other Factors that Influence Hormone Synthesis and Release

Although TSH is the dominant hormonal regulator of thyroid gland growth and function, a variety of growth factors, most produced locally in the thyroid gland, also influence thyroid hormone synthesis. These include insulin-like growth factor I (IGF-I), epidermal growth factor, transforming growth factor β (TGF-β), endothelins, and various cytokines. The quantitative roles of these factors are not well understood, but they are important in selected disease states. In acromegaly, for example, increased levels of growth hormone and IGF-I are associated with goiter and predisposition to multinodular goiter. Certain cytokines and interleukins (ILs) produced in association with autoimmune thyroid disease induce thyroid growth, whereas others lead to apoptosis. Iodine deficiency increases thyroid blood flow and upregulates the NIS, stimulating more efficient uptake. Excess iodide transiently inhibits thyroid iodide organification, a phenomenon known as the *Wolff-Chaikoff effect*. In individuals with a normal thyroid, the gland escapes from this inhibitory effect and iodide organification resumes; the suppressive action of high iodide may persist, however, in patients with underlying autoimmune thyroid disease.

THYROID HORMONE TRANSPORT AND METABOLISM

Serum Binding Proteins

T_4 is secreted from the thyroid gland in at least 20-fold excess over T_3 (Table 320-2). Both hormones are bound to plasma proteins, including thyroxine-binding globulin (TBG), transthyretin (TTR), formerly known as thyroxine-binding prealbumin, or TBPA), and albumin. The plasma-binding proteins increase the pool of circulating hormone, delay hormone clearance, and may modulate hormone delivery to selected tissue sites. The concentration of TBG is relatively low (1 to 2 mg/dL), but because of its high affinity for thyroid hormones ($T_4 > T_3$), it carries about 80% of the bound hormones. Albumin has relatively low affinity for thyroid hormones but has a high plasma concentration (~3.5 g/dL), and it binds up to 10% of T_4 and 30% of T_3. TTR carries about 10% of T_4 but little T_3.

TABLE 320-2 Characteristics of Circulating T_4 and T_3

Hormone Property	T_4	T_3
Serum concentrations		
Total hormone	8 µg/dL	0.14 µg/dL
Fraction of total hormone in the free form	0.02%	0.3%
Free (unbound) hormone	21×10^{-12} M	6×10^{-12} M
Serum half-life	7 d	0.75 d
Fraction directly from the thyroid	100%	20%
Production rate, including peripheral conversion	90 µg/d	32 µg/d
Intracellular hormone fraction	~20%	~70%
Relative metabolic potency	0.3	1
Receptor binding	10^{-10} M	10^{-11} M

When the effects of the various binding proteins are combined, approximately 99.98% of T_4 and 99.7% of T_3 are protein-bound. Because T_3 is less tightly bound than T_4, the amount of unbound T_3 is greater than unbound T_4, even though there is less total T_3 in the circulation. The unbound, or free, concentrations of the hormones are ~2×10^{-11} M for T_4 and ~6×10^{-12} M for T_3, which roughly correspond to the thyroid hormone receptor binding constants for these hormones (see below). Only the unbound hormone is biologically available to tissues. Therefore, homeostatic mechanisms that regulate the thyroid axis are directed towards maintenance of normal concentrations of unbound hormones.

Dysalbuminemic Hyperthyroxinemia

A number of inherited and acquired abnormalities affect thyroid hormone binding proteins. X-linked TBG deficiency is associated with very low levels of total T_4 and T_3. However, because unbound hormone levels are normal, patients are euthyroid and TSH levels are normal. The importance of recognizing this disorder is to avoid efforts to normalize total T_4 levels, as this leads to thyrotoxicosis and is futile because of rapid hormone clearance in the absence of TBG. TBG levels are elevated by estrogen, which increases sialylation and delays TBG clearance. Consequently, in women who are pregnant or taking estrogen-containing contraceptives, elevated TBG increases total T_4 and T_3 levels; however, unbound T_4 and T_3 levels are normal. Mutations in TBG, TTR, and albumin that increase binding affinity for T_4 and/or T_3 cause disorders known as *euthyroid hyperthyroxinemia* or *familial dysalbuminemic hyperthyroxinemia* (FDH) (Table 320-3). These disorders result in increased total T_4 and/or T_3, but unbound hormone levels are normal. The familial nature of the disorders, and the fact that TSH levels are normal rather than suppressed, suggest this diagnosis. Unbound hormone levels (ideally measured by dialysis) are normal in FDH. The diagnosis can be confirmed by using tests that measure the affinities of radiolabeled hormone binding to specific transport proteins or by performing DNA sequence analyses of the abnormal transport protein genes.

TABLE 320-3 Conditions Associated with Euthyroid Hyperthyroxinemia

Disorder	Cause	Transmission	Characteristics

Familial dysalbuminemic hyperthyroxinemia (FDH)	Albumin mutations, usually R218H	AD	Increased T_4 Normal unbound T_4 Rarely increased T_3
TBG			
Familial excess	Increased TBG production	XL	Increased total T_4, T_3 Normal unbound T_4, T_3
Acquired excess	Medications (estrogen), pregnancy, cirrhosis, hepatitis	Acquired	Increased total T_4, T_3 Normal unbound T_4, T_3
Transthyretin[a]			
Excess	Islet tumors	Acquired	Usually normal T_4, T_3
Mutations	Increased affinity for T_4 or T_3	AD	Increased total T_4, T_3 Normal unbound T_4, T_3
Medications: propranolol, ipodate, iopanoic acid, amiodarone	Decreased $T_4 \rightarrow T_3$ conversion	Acquired	Increased T_4 Decreased T_3 Normal or increased TSH
Sick-euthyroid syndrome	Acute illness, especially psychiatric disorders	Acquired	Transiently increased unbound T_4 Decreased TSH T_4 and T_3 may also be decreased (see text)
Resistance to thyroid hormone (RTH)	Thyroid hormone receptor β	AD	Increased unbound T_4, T_3

	mutations		Normal or increased TSH Some patients clinically thyrotoxic

[a] Also known as thyroxine-binding prealbumin, TBPA.

Note: AD, autosomal dominant; TBG, thyroxine-binding globulin; TSH, thyroid-stimulating hormone; XL, X-linked.

Certain medications, such as salicylates and salsalate, can displace thyroid hormones from circulating binding proteins. Although these drugs transiently perturb the thyroid axis by increasing free thyroid hormone levels, TSH is suppressed until a new steady state is reached, thereby restoring euthyroidism. Circulating factors associated with acute illness may also displace thyroid hormone from binding proteins (see "Sick Euthyroid Syndrome," below).

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Deiodinases

T_4 may be thought of as a precursor for the more potent T_3. T_4 is converted to T_3 by the deiodinase enzymes (Fig. 320-1). Type I deiodinase, which is located primarily in thyroid, liver, and kidney, has a relatively low affinity for T_4. Type II deiodinase has a higher affinity for T_4 and is found primarily in the pituitary gland, brain, brown fat, and thyroid gland. The presence of type II deiodinase allows it to regulate T_3 concentrations locally, a property that may be important in the context of levothyroxine (T_4) replacement. Type II deiodinase is also regulated by thyroid hormone—hypothyroidism induces the enzyme, resulting in enhanced $T_4 \rightarrow T_3$ conversion in tissues such as brain and pituitary. $T_4 \rightarrow T_3$ conversion is impaired by fasting, systemic illness or acute trauma, oral contrast agents, and a variety of medications (e.g., propylthiouracil, propranolol, amiodarone, glucocorticoids). Type III deiodinase inactivates T_4 and T_3 and is the most important source of reverse T_3 (rT_3). Massive hemangiomas that express type III deiodinase are a rare cause of hypothyroidism in infants.

THYROID HORMONE ACTION

Nuclear Thyroid Hormone Receptors

Thyroid hormones act by binding to nuclear *thyroid hormone receptors* (TRs) α and β. Both TRα and TRβ are expressed in most tissues, but their relative levels of expression vary among organs; TRα is particularly abundant in brain, kidney, gonads, muscle, and heart,

whereas TRβ expression is relatively high in the pituitary and liver. Both receptors are variably spliced to form unique isoforms. The TRβ2 isoform, which has a unique amino terminus, is selectively expressed in the hypothalamus and pituitary, where it plays a role in feedback control of the thyroid axis. The TRα2 isoform contains a unique carboxy terminus that prevents thyroid hormone binding; it may function to block the action of other TR isoforms.

The TRs contain a central DNA-binding domain and a C-terminal ligand-binding domain. They bind to specific DNA sequences, termed *thyroid response elements* (TREs), in the promoter regions of target genes (Fig. 320-3). The receptors bind as homodimers or as heterodimers with retinoic acid X receptors (RXRs) (Chap. 317). The activated receptor can either stimulate gene transcription (e.g., myosin heavy chain α) or inhibit transcription (e.g., TSH β-subunit gene), depending on the nature of the regulatory elements in the target gene.

Thyroid hormones bind with similar affinities to TRα and TRβ. However, T_3 is bound with 10 to 15 times greater affinity than T_4, which explains its increased hormonal potency. Though T_4 is produced in excess of T_3, receptors are occupied mainly by T_3, reflecting $T_4 \rightarrow T_3$ conversion by peripheral tissues, greater T_3 bioavailability in the plasma, and receptors' greater affinity for T_3. After binding to TRs, thyroid hormone induces conformational changes in the receptors that modify its interactions with accessory transcription factors. In the absence of thyroid hormone binding, the aporeceptors bind to co-repressor proteins that inhibit gene transcription. Hormone binding dissociates the co-repressors and allows the recruitment of coactivators that enhance transcription. The discovery of TR interactions with co-repressors explains the fact that TR silences gene expression in the absence of hormone binding. Consequently, hormone deficiency has a profound effect on gene expression because it causes gene repression as well as loss of hormone-induced stimulation. This concept has been corroborated by the finding that targeted deletion of the TR genes in mice has a less pronounced phenotypic effect than hormone deficiency.

FIGURE 320-3 Mechanism of thyroid hormone receptor action. The thyroid hormone receptor (TR) and retinoid X receptor (RXR) form heterodimers that bind specifically to thyroid hormone response elements (TRE) in the promoter regions of target genes. In the absence of hormone, TR binds co-repressor (CoR) proteins that silence gene expression. The numbers refer to a series of ordered reactions that occur in response to thyroid hormone: (1) T_4 or T_3 enters the nucleus; (2) T_3 binding dissociates CoR from TR; (3) Coactivators (CoA) are recruited to the T_3-bound receptor; (4) gene expression is altered.

Thyroid Hormone Resistance

Resistance to thyroid hormone (RTH) is an autosomal dominant disorder characterized by elevated thyroid hormone levels and inappropriately normal or elevated TSH. Individuals with RTH do not, in general, exhibit signs and symptoms that are typical of hypothyroidism because hormone resistance is partial and is compensated by increased levels of thyroid hormone. The clinical features of RTH can include goiter, attention deficit disorder, mild reduction in IQ, delayed skeletal maturation, tachycardia, and impaired metabolic

responses to thyroid hormone.

The disorder is caused by mutations in the TRβ receptor gene. These mutations, located in restricted regions of the ligand-binding domain, cause loss of receptor function. However, because the mutant receptors retain the capacity to dimerize with RXRs, bind to DNA, and recruit co-repressor proteins, they function as antagonists of the remaining, normal TRβ and TRα receptors. This property, referred to

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as "dominant negative" activity, explains the autosomal dominant mode of transmission. The diagnosis is suspected when unbound thyroid hormone levels are increased without suppression of TSH. Similar hormonal abnormalities are found in other affected family members, although the TRβ mutation arises de novo in about 20% of patients. DNA sequence analysis of the TRβ gene provides a definitive diagnosis. RTH must be distinguished from other causes of euthyroid hyperthyroxinemia (e.g., FDH) and inappropriate secretion of TSH by TSH-secreting pituitary adenomas (Chap. 318). In most patients, no treatment is indicated; the importance of making the diagnosis is to avoid inappropriate treatment of mistaken hyperthyroidism and to provide genetic counseling.

PHYSICAL EXAMINATION

In addition to the examination of the thyroid itself, the physical examination should include a search for signs of abnormal thyroid function and the extrathyroidal features of ophthalmopathy and dermopathy (see below). Examination of the neck begins by inspecting the seated patient from the front and side, and noting any surgical scars, obvious masses, or distended veins. The thyroid can be palpated with both hands from behind or while facing the patient, using the thumbs to palpate each lobe. It is best to use a combination of these methods, especially when the nodules are small. The patient's neck should be slightly flexed to relax the neck muscles. After locating the cricoid cartilage, the isthmus can be identified and followed laterally to locate either lobe (normally the right lobe is slightly larger than the left). By asking the patient to swallow sips of water, thyroid consistency can be better appreciated as the gland moves beneath the examiner's fingers.

Features to be noted include thyroid size, consistency, nodularity, and any tenderness or fixation. An estimate of thyroid size (normally 12 to 20 g) should be made, and a drawing is often the best way to record findings. However, ultrasound is the method of choice when it is important to determine thyroid size accurately. The size, location, and consistency of any nodules should also be defined. A bruit over the gland indicates increased vascularity, as occurs in hyperthyroidism. If the lower borders of the thyroid lobes are not clearly felt, a goiter may be retrosternal. Large retrosternal goiters can cause venous distention over the neck and difficulty breathing, especially when the arms are raised (Pemberton's sign). With any central mass above the thyroid, the tongue should be extended, as thyroglossal cysts then move upward. The thyroid examination is not complete without assessment for lymphadenopathy in the supraclavicular and cervical regions of the neck.

LABORATORY EVALUATION

MEASUREMENT OF THYROID HORMONES

The enhanced sensitivity and specificity of *TSH assays* have greatly improved laboratory assessment of thyroid function. Because TSH levels change dynamically in response to alterations of T_4 and T_3, a logical approach to thyroid testing is to first determine whether TSH is suppressed, normal, or elevated. With rare exceptions (see below), a normal TSH level excludes a primary abnormality of thyroid function. This strategy depends on the use of immunoradiometric assays (IRMAs) for TSH that are sensitive enough to discriminate between the lower limit of the reference range and the suppressed values that occur with thyrotoxicosis. Extremely sensitive (fourth generation) assays can detect TSH levels ≤0.004 mU/L, but for practical purposes assays sensitive to ≤0.1 mU/L are sufficient. The widespread availability of the TSH IRMA has rendered the TRH stimulation test obsolete, as the failure of TSH to rise after an intravenous bolus of 200 to 400 μg TRH has the same implications as a suppressed basal TSH measured by IRMA.

The finding of an abnormal TSH level must be followed by measurements of circulating thyroid hormone levels to confirm the diagnosis of hyperthyroidism (suppressed TSH) or hypothyroidism (elevated TSH). Radioimmunoassays are widely available for serum *total T_4* and *total T_3* . T_4 and T_3 are highly protein-bound, and numerous factors (illness, medications, genetic factors) can influence protein binding. It is useful, therefore, to measure the free, or unbound, hormone levels, which correspond to the biologically available hormone pool. Two direct methods are used to measure *unbound thyroid hormones*: (1) unbound thyroid hormone competition with radiolabeled T_4 (or an analogue) for binding to a solid-phase antibody, and (2) physical separation of the unbound hormone fraction by ultracentrifugation or equilibrium dialysis. Though early unbound hormone immunoassays suffered from artifacts, newer assays correlate well with the results of the more technically demanding and expensive physical separation methods. An indirect method to estimate unbound thyroid hormone levels is to calculate the free T_3 or free T_4 index from the total T_4 or T_3 concentration and the *thyroid hormone binding ratio* (THBR). The latter is derived from the *T_3-resin uptake test*, which determines the distribution of radiolabeled T_3 between an absorbent resin and the unoccupied thyroid hormone binding proteins in the sample. The binding of the labeled T_3 to the resin is increased when there is reduced unoccupied protein binding sites (e.g., TBG deficiency) or increased total thyroid hormone in the sample; it is decreased under the opposite circumstances. The product of THBR and total T_3 or T_4 provides the *free T_3 or T_4 index*. In effect, the index corrects for anomalous total hormone values caused by abnormalities in hormone-protein binding.

Total thyroid hormone levels are *elevated* when TBG is increased due to estrogens (pregnancy, oral contraceptives, hormone replacement therapy, tamoxifen), and *decreased* when TBG binding is reduced (androgens, the nephrotic syndrome). Genetic disorders and acute illness can also cause abnormalities in thyroid hormone binding proteins, and various drugs (phenytoin, carbamazepine, salicylates, and nonsteroidal anti-inflammatory drugs) can interfere with thyroid hormone binding. Because unbound thyroid hormone levels are normal and the patient is euthyroid in all of these circumstances, assays that measure unbound hormone are preferable to those for total thyroid hormones.

For most purposes, the unbound T_4 level is sufficient to confirm thyrotoxicosis, but 2 to 5% of patients have only an elevated T_3 level (T_3 toxicosis). Thus, unbound T_3 levels should be measured in patients with a suppressed TSH but normal unbound T_4 levels.

There are several clinical conditions in which the use of TSH as a screening test may be misleading, particularly without simultaneous unbound T_4 determinations. Any severe nonthyroidal illness can cause abnormal TSH levels (see below). Although hypothyroidism is the most common cause of an elevated TSH level, rare causes include a TSH-secreting pituitary tumor (Chap. 318), thyroid hormone resistance, and assay artifact. Conversely, a suppressed TSH level, particularly <0.1 mU/L, usually indicates thyrotoxicosis but may also be seen during the first trimester of pregnancy (due to hCG secretion), after treatment of hyperthyroidism (because TSH remains suppressed for several weeks), and in response to certain medications (e.g., high doses of glucocorticoids or dopamine). Importantly, secondary hypothyroidism, caused by hypothalamic-pituitary disease, is associated with a variable (low to high-normal) TSH level, which is inappropriate for the low T_4 level. Thus, *TSH should not be used to assess thyroid function in patients with suspected or known pituitary disease*.

Tests for the end-organ effects of thyroid hormone excess or depletion, such as estimation of basal metabolic rate, tendon reflex relaxation rates, or serum cholesterol, are not useful as clinical determinants of thyroid function.

TESTS TO DETERMINE THE ETIOLOGY OF THYROID DYSFUNCTION

Autoimmune thyroid disease is detected most easily by measuring circulating antibodies against TPO and Tg. As antibodies to Tg alone are uncommon, it is reasonable to measure only TPO antibodies. About 5 to 15% of euthyroid women and up to 2% of euthyroid men have thyroid antibodies; such individuals are at increased risk of developing thyroid dysfunction. Almost all patients with autoimmune hypothyroidism, and up to 80% of those with Graves' disease, have TPO antibodies, usually at high levels.

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TSI are antibodies that stimulate the TSH-R in Graves' disease. They can be measured in bioassays or indirectly in assays that detect antibody binding to the receptor. The main use of these assays is to predict neonatal thyrotoxicosis caused by high maternal levels of TSI in the last trimester of pregnancy.

Serum Tg levels are increased in all types of thyrotoxicosis except *thyrotoxicosis factitia* caused by self-administration of thyroid hormone. The main role for Tg measurement, however, is in the follow-up of thyroid cancer patients. After total thyroidectomy and radioablation, Tg levels should be undetectable; measurable levels (>1 to 2 ng/mL) suggest incomplete ablation or recurrent cancer.

RADIOIODINE UPTAKE AND THYROID SCANNING

The thyroid gland selectively transports radioisotopes of iodine (^{123}I, ^{125}I, ^{131}I) and ^{99m}Tc pertechnetate, allowing thyroid imaging and quantitation of radioactive tracer fractional uptake.

Nuclear imaging of Graves' disease is characterized by an enlarged gland and increased tracer uptake that is distributed homogeneously. Toxic adenomas appear as focal areas of increased uptake, with suppressed tracer uptake in the remainder of the gland. In toxic

multinodular goiter, the gland is enlarged—often with distorted architecture—and there are multiple areas of relatively increased or decreased tracer uptake. Subacute thyroiditis is associated with very low uptake because of follicular cell damage and TSH suppression. Thyrotoxicosis factitia is also associated with low uptake.

Although the use of fine-needle aspiration (FNA) biopsy has diminished the use of thyroid scans in the evaluation of solitary thyroid nodules, the functional features of thyroid nodules have some prognostic significance. So-called cold nodules, which have diminished tracer uptake, are usually benign. However, these nodules are more likely to be malignant (~5 to 10%) than so-called hot nodules, which are almost never malignant.

Thyroid scanning is also used in the follow-up of thyroid cancer. After thyroidectomy and ablation using ^{131}I, there is diminished radioiodine uptake in the thyroid bed, allowing the detection of metastatic thyroid cancer deposits that retain the ability to transport iodine. Whole-body scans using 111 to 185 MBq (3 to 5 mCi) ^{131}I are typically performed after thyroid hormone withdrawal to raise the TSH level or after the administration of recombinant human TSH.

THYROID ULTRASOUND

Ultrasonography is used increasingly to assist in the diagnosis of nodular thyroid disease, a reflection of the limitations of the physical examination and improvements in ultrasound technology. Using 10-MHz instruments, spatial resolution and image quality are excellent, allowing the detection of nodules and cysts >3 mm. In addition to detecting thyroid nodules, ultrasound is useful for monitoring nodule size, for guiding FNA biopsies, and for the aspiration of cystic lesions. Ultrasound is also used in the evaluation of recurrent thyroid cancer, including possible spread to cervical lymph nodes.

HYPOTHYROIDISM

Iodine deficiency remains the most common cause of hypothyroidism worldwide. In areas of iodine sufficiency, autoimmune disease (Hashimoto's thyroiditis) and iatrogenic causes (treatment of hyperthyroidism) are most common (Table 320-4).

TABLE 320-4 Causes of Hypothyroidism

Primary

  Autoimmune hypothyroidism: Hashimoto's thyroiditis, atrophic thyroiditis

  Iatrogenic: ^{131}I treatment, subtotal or total thyroidectomy, external irradiation of neck for lymphoma or cancer

  Drugs: iodine excess (including iodine-containing contrast media and amiodarone), lithium,

antithyroid drugs, *p*-aminosalicyclic acid, interferon-α and other cytokines, aminoglutethimide

Congenital hypothyroidism: absent or ectopic thyroid gland, dyshormonogenesis, TSH-R mutation

Iodine deficiency

Infiltrative disorders: amyloidosis, sarcoidosis, hemochromatosis, scleroderma, cystinosis, Riedel's thyroiditis

Overexpression of type 3 deoiodinase in infantile hemangioma

Transient

Silent thyroiditis, including postpartum thyroiditis

Subacute thyroiditis

Withdrawal of thyroxine treatment in individuals with an intact thyroid

After ^{131}I treatment or subtotal thyroidectomy for Graves' disease

Secondary

Hypopituitarism: tumors, pituitary surgery or irradiation, infiltrative disorders, Sheehan's syndrome, trauma, genetic forms of combined pituitary hormone deficiencies

Isolated TSH deficiency or inactivity

Bexarotene treatment

Hypothalamic disease: tumors, trauma, infiltrative disorders, idiopathic

Note: TSH, thyroid-stimulating hormone; TSH-R, TSH receptor.

CONGENITAL HYPOTHYROIDISM

Prevalence

Hypothyroidism occurs in about 1 in 4000 newborns. It may be transient, especially if the mother has TSH-R blocking antibodies or has received antithyroid drugs, but permanent hypothyroidism occurs in the majority. Neonatal hypothyroidism is due to thyroid gland dysgenesis in 80 to 85%, inborn errors of thyroid hormone synthesis in 10 to 15%, and is TSH-R antibody-mediated in 5% of affected newborns. The developmental abnormalities are twice as common in girls. Mutations that cause congenital hypothyroidism are being increasingly recognized, but the vast majority remain idiopathic (Table 320-1).

Clinical Manifestations

The majority of infants appear normal at birth, and <10% are diagnosed based on clinical features, which include prolonged jaundice, feeding problems, hypotonia, enlarged tongue, delayed bone maturation, and umbilical hernia. Importantly, permanent neurologic damage results if treatment is delayed. Typical features of adult hypothyroidism may also be present (Table 320-5). Other congenital malformations, especially cardiac, are four times more common in congenital hypothyroidism.

TABLE 320-5 Signs and Symptoms of Hypothyroidism (Descending Order of Frequency)

Symptoms
  Tiredness, weakness
  Dry skin
  Feeling cold
  Hair loss
  Difficulty concentrating and poor memory
  Constipation
  Weight gain with poor appetite
  Dyspnea
  Hoarse voice
  Menorrhagia (later oligomenorrhea or amenorrhea)
  Paresthesia
  Impaired hearing
Signs
  Dry coarse skin; cool peripheral extremities
  Puffy face, hands, and feet (myxedema)
  Diffuse alopecia
  Bradycardia
  Peripheral edema
  Delayed tendon reflex relaxation
  Carpal tunnel syndrome
  Serous cavity effusions

Diagnosis and Treatment

Because of the severe neurologic consequences of untreated congenital hypothyroidism, neonatal screening programs have been established in developed countries. These are generally based on measurement of TSH or T_4 levels in heel-prick blood specimens. When the diagnosis is confirmed, T_4 is instituted at a dose of 10 to 15 µg/kg per day and the dosage is adjusted by close monitoring of TSH levels. T_4 requirements are relatively great during the first year of life, and a high circulating T_4 level is usually needed to normalize TSH. Early treatment with T_4 results in normal IQ levels, but subtle neurodevelopmental abnormalities may occur in those with the most severe hypothyroidism at diagnosis or when

treatment is suboptimal.

AUTOIMMUNE HYPOTHYROIDISM

Classification

Autoimmune hypothyroidism may be associated with a goiter (Hashimoto's, or *goitrous thyroiditis*) or, at the later stages of the disease, minimal residual thyroid tissue (*atrophic thyroiditis*). Because the autoimmune process gradually reduces thyroid function, there is a phase of compensation when normal thyroid hormone levels are maintained by a rise in TSH. Though some patients may have minor symptoms, this state is called *subclinical hypothyroidism* or *mild hypothyroidism*. Later, free T_4 levels fall and TSH levels rise further; symptoms become more readily apparent at this stage (usually TSH > 10 mU/L), which is referred to as *clinical hypothyroidism* or *overt hypothyroidism*.

Prevalence

The mean annual incidence rate of autoimmune hypothyroidism is up to 4 per 1000 women and 1 per 1000 men. It is more common in certain populations, such as the Japanese, probably because of genetic factors and chronic exposure to a high-iodine diet. The mean age at diagnosis is 60 years, and the prevalence of overt hypothyroidism increases with age. Subclinical hypothyroidism is found in 6 to 8% of women (10% over the age of 60) and 3% of men. The annual risk of developing clinical hypothyroidism is about 4% when subclinical hypothyroidism is associated with positive TPO antibodies.

Pathogenesis

In Hashimoto's thyroiditis, there is a marked lymphocytic infiltration of the thyroid with germinal center formation, atrophy of the thyroid follicles accompanied by oxyphil metaplasia, absence of colloid, and mild to moderate fibrosis. In atrophic thyroiditis, the fibrosis is much more extensive, lymphocyte infiltration is less pronounced, and thyroid follicles are almost completely absent. Atrophic thyroiditis likely represents the end stage of Hashimoto's thyroiditis rather than a distinct disorder.

As with most autoimmune disorders, susceptibility to autoimmune hypothyroidism is determined by a combination of genetic and environmental factors, and the risk of either autoimmune hypothyroidism or Graves' disease is increased among siblings. HLA-DR polymorphisms are the best documented genetic risk factors for autoimmune hypothyroidism, especially HLA-DR3, -DR4, and -DR5 in Caucasians. A weak association also exists between polymorphisms in *CTLA-4*, a T cell–regulating gene, and autoimmune hypothyroidism. Both of these genetic associations are shared by other autoimmune diseases, which may explain the relationship between autoimmune hypothyroidism and other autoimmune diseases, especially type 1 diabetes mellitus, Addison disease, pernicious anemia, and vitiligo (Chap. 330). HLA-DR and *CTLA*-4 polymorphisms account for approximately half of the genetic susceptibility to autoimmune hypothyroidism. The other contributory loci remain to be identified. A gene on chromosome 21 may be responsible for the association between autoimmune hypothyroidism and Down syndrome.

The female preponderance of thyroid autoimmunity is most likely due to the effects of sex steroids on the immune response, but an X chromosome–related genetic factor is also possible, which may account for the high frequency of autoimmune hypothyroidism in Turner syndrome. Environmental susceptibility factors are also poorly defined at present. A high iodine intake may increase the risk of autoimmune hypothyroidism by immunologic effects or direct thyroid toxicity. There is no convincing evidence for a role of infection, except for the congenital rubella syndrome, in which there is a high frequency of autoimmune hypothyroidism. Viral thyroiditis does not induce subsequent autoimmune thyroid disease.

The thyroid lymphocytic infiltrate in autoimmune hypothyroidism is composed of activated CD4+ and CD8+ T cells, as well as B cells. Thyroid cell destruction is believed to be primarily mediated by the CD8+ cytotoxic T cells, which destroy their targets by either perforin-induced cell necrosis or granzyme B–induced apoptosis. In addition, local T cell production of cytokines, such as tumor necrosis factor (TNF), IL-1, and interferon (IFN) γ, may render thyroid cells more susceptible to apoptosis mediated by death receptors, such as Fas, which are activated by their respective ligands on T cells. These cytokines also impair thyroid cell function directly, and induce the expression of other proinflammatory molecules by the thyroid cells themselves, such as cytokines, HLA class I and class II molecules, adhesion molecules, CD40, and nitric oxide. Administration of high concentrations of cytokines for therapeutic purposes (especially IFN-α) is associated with increased autoimmune thyroid disease, possibly through mechanisms similar to those in sporadic disease.

Antibodies to Tg and TPO are clinically useful markers of thyroid autoimmunity, but any pathogenic effect is restricted to a secondary role in amplifying an ongoing autoimmune response. TPO antibodies fix complement, and complement membrane attack complexes are present in the thyroid in autoimmune hypothyroidism. However, transplacental passage of Tg or TPO antibodies has no effect on the fetal thyroid, which suggests that T cell–mediated injury is required to initiate autoimmune damage to the thyroid. Up to 20% of patients with autoimmune hypothyroidism have antibodies against the TSH-R, which, in contrast to TSI, do not stimulate the receptor but prevent the binding of TSH. These TSH-R-blocking antibodies therefore cause hypothyroidism and, especially in Asian patients, thyroid atrophy. Their transplacental passage may induce transient neonatal hypothyroidism. Rarely, patients have a mixture of TSI- and TSH-R-blocking antibodies, and thyroid function can oscillate between hyperthyroidism and hypothyroidism as one or the other antibody becomes dominant. Predicting the course of disease in such individuals is difficult, and they require close monitoring of thyroid function. Bioassays can be used to document that TSH-R-blocking antibodies reduce the cyclic AMP–inducing effect of TSH on cultured TSH-R-expressing cells, but these assays are difficult to perform. Assays that measure the binding of antibodies to the receptor by competition with radiolabeled TSH [TSH-binding inhibiting immunoglobulins (TBII)] do not distinguish between TSI- and TSH-R-blocking antibodies, but a positive result in a patient with spontaneous hypothyroidism is strong evidence for the presence of blocking antibodies. The use of these assays does not generally alter clinical management, although they may be useful to confirm the cause of transient neonatal hypothyroidism.

Clinical Manifestations

The main clinical features of hypothyroidism are summarized in Table 320-5. The onset is usually insidious, and the patient may become aware of symptoms only when euthyroidism is restored. Patients with Hashimoto's thyroiditis may present because of goiter rather than symptoms of hypothyroidism. The goiter may not be large but is usually irregular and firm in consistency. It is often possible to palpate a pyramidal lobe, normally a vestigial remnant of the thyroglossal duct. Rarely, uncomplicated Hashimoto's thyroiditis is associated with pain.

Patients with atrophic thyroiditis, or the late stage of Hashimoto's thyroiditis, present with symptoms and signs of hypothyroidism. The skin is dry, and there is decreased sweating, thinning of the epidermis, and hyperkeratosis of the stratum corneum. Increased dermal glycosaminoglycan content traps water, giving rise to skin thickening without pitting (*myxedema*). Typical features include a puffy face with edematous eyelids and nonpitting pretibial edema (Fig. 320-4). There is pallor, often with a yellow tinge to the skin due to carotene accumulation. Nail growth is retarded, and hair is dry, brittle, difficult to manage, and falls out easily. In addition to diffuse alopecia, there is thinning of the outer third of the eyebrows, although this is not a specific sign of hypothyroidism.

Other common features include constipation and weight gain (despite a poor appetite). In contrast to popular perception, the weight gain is usually modest and due mainly to fluid retention in the myxedematous tissues. Libido is decreased in both sexes, and there may be oligomenorrhea or amenorrhea in long-standing disease, but menorrhagia is also common. Fertility is reduced and the incidence of miscarriage is increased. Prolactin levels are often modestly increased (Chap. 318) and may contribute to alterations in libido and fertility and cause galactorrhea.

Myocardial contractility and pulse rate are reduced, leading to a

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reduced stroke volume and bradycardia. Increased peripheral resistance may be accompanied by hypertension, particularly diastolic. Blood flow is diverted from the skin, producing the cool extremities. Pericardial effusions occur in up to 30% of patients but rarely compromise cardiac function. Though alterations in myosin heavy chain isoform expression have been documented, cardiomyopathy is unusual. Fluid may also accumulate in other serous cavities and in the middle ear, giving rise to conductive deafness. Pulmonary function is generally normal, but dyspnea may be caused by pleural effusion, impaired respiratory muscle function, diminished ventilatory drive, or sleep apnea.

FIGURE 320-4 Facial appearance in hypothyroidism. Note puffy eyes and thickened, pale skin.

Carpal tunnel and other entrapment syndromes are common, as is impairment of muscle function with stiffness, cramps, and pain. On examination, there may be slow relaxation of tendon reflexes and pseudomyotonia. Memory and concentration are impaired. Rare neurologic problems include reversible cerebellar ataxia, dementia, psychosis, and

myxedema coma. *Hashimoto's encephalopathy* is a rare and distinctive syndrome associated with myoclonus and slow-wave activity on electroencephalography, which can progress to confusion, coma, and death. It is steroid-responsive and may occur in the presence of autoimmune thyroiditis, without hypothyroidism. The hoarse voice and occasionally clumsy speech of hypothyroidism reflect fluid accumulation in the vocal cords and tongue.

The features described above are the consequence of thyroid hormone deficiency. However, autoimmune hypothyroidism may be associated with signs or symptoms of other autoimmune diseases, particularly vitiligo, pernicious anemia, Addison disease, alopecia areata, and type 1 diabetes mellitus. Less common associations include celiac disease, dermatitis herpetiformis, chronic active hepatitis, rheumatoid arthritis, systemic lupus erythematosus (SLE), and Sjögren's syndrome. Thyroid-associated ophthalmopathy, which usually occurs in Graves' disease (see below), occurs in about 5% of patients with autoimmune hypothyroidism.

Autoimmune hypothyroidism is uncommon in children and usually presents with slow growth and delayed facial maturation. The appearance of permanent teeth is also delayed. Myopathy, with muscle swelling, is more common in children than in adults. In most cases, puberty is delayed, but precocious puberty sometimes occurs. There may be intellectual impairment if the onset is before 3 years and the hormone deficiency is severe.

Laboratory Evaluation

A summary of the investigations used to determine the existence and cause of hypothyroidism is provided in Fig. 320-5. A normal TSH level excludes primary (but not secondary) hypothyroidism. If the TSH is elevated, an unbound T_4 level is needed to confirm the presence of clinical hypothyroidism, but T_4 is inferior to TSH when used as a screening test, as it will not detect subclinical or mild hypothyroidism. Circulating unbound T_3 levels are normal in about 25% of patients, reflecting adaptive responses to hypothyroidism. T_3 measurements are therefore not indicated.

FIGURE 320-5 Evaluation of hypothyroidism. TPOAb[+], thyroid peroxidase antibodies present; TPOAb[-], thyroid peroxidase antibodies not present. TSH, thyroid-stimulating hormone.

Once clinical or subclinical hypothyroidism is confirmed, the etiology is usually easily established by demonstrating the presence of TPO antibodies, which are present in 90 to 95% of patients with autoimmune hypothyroidism. TBII can be found in 10 to 20% of patients, but these determinations are not needed routinely. If there is any doubt about the cause of a goiter associated with hypothyroidism, FNA biopsy can be used to confirm the presence of autoimmune thyroiditis. Other abnormal laboratory findings in hypothyroidism may include increased creatine phosphokinase, elevated cholesterol and triglycerides, and anemia (usually normocytic or macrocytic). Except when accompanied by iron deficiency, the anemia and other abnormalities gradually resolve with thyroxine replacement.

Differential Diagnosis

An asymmetric goiter in Hashimoto's thyroiditis may be confused with a multinodular goiter or thyroid carcinoma, in which thyroid antibodies may also be present. Ultrasound can be used to show the presence of a solitary lesion or a multinodular goiter, rather than the heterogeneous thyroid enlargement typical of Hashimoto's thyroiditis. FNA biopsy is useful in the investigation of focal nodules. Other causes of hypothyroidism are discussed below but rarely cause diagnostic confusion (Table 320-4).

OTHER CAUSES OF HYPOTHYROIDISM

Iatrogenic hypothyroidism is a common cause of hypothyroidism and can often be detected by screening before symptoms develop. In the first 3 to 4 months after radioiodine treatment, transient hypothyroidism may occur due to reversible radiation damage rather than to cellular destruction. Low-dose thyroxine treatment can be withdrawn if recovery occurs. Because TSH levels are suppressed by hyperthyroidism, unbound T_4 levels are a better measure of thyroid function than TSH in the months following radioiodine

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treatment. Mild hypothyroidism after subtotal thyroidectomy may also resolve after several months, as the gland remnant is stimulated by increased TSH levels.

Iodine deficiency is responsible for endemic goiter and cretinism but is an uncommon cause of adult hypothyroidism unless the iodine intake is very low or there are complicating factors, such as the consumption of thiocyanates in cassava or selenium deficiency. Though hypothyroidism due to iodine deficiency can be treated with thyroxine, public health measures to improve iodine intake should be advocated to eliminate this problem. Iodized salt or bread or a single bolus of oral or intramuscular iodized oil have all been used successfully.

Paradoxically, chronic iodine excess can also induce goiter and hypothyroidism. The intracellular events that account for this effect are unclear, but individuals with autoimmune thyroiditis are especially susceptible. Iodine excess is responsible for the hypothyroidism that occurs in up to 13% of patients treated with amiodarone (see below). Other drugs, particularly lithium, may also cause hypothyroidism. Transient hypothyroidism caused by thyroiditis is discussed below.

Secondary hypothyroidism is usually diagnosed in the context of other anterior pituitary hormone deficiencies; isolated TSH deficiency is very rare (Chap. 318). TSH levels may be low, normal, or even slightly increased in secondary hypothyroidism; the latter is due to secretion of immunoactive but bioinactive forms of TSH. The diagnosis is confirmed by detecting a low unbound T_4 level. The goal of treatment is to maintain unbound T_4 levels in the upper half of the reference range, as TSH levels cannot be used to monitor therapy.

TREATMENT

Clinical Hypothyroidism

If there is no residual thyroid function, the daily replacement dose of levothyroxine is usually 1.6 μg/kg body weight (typically 100 to 150 μg). In many patients, however,

lower doses suffice until residual thyroid tissue is destroyed. In patients who develop hypothyroidism after the treatment of Graves' disease, there is often underlying autonomous function, necessitating lower replacement doses (typically 75 to 125 µg/d).

Adult patients under 60 without evidence of heart disease may be started on 50 to 100 µg levothyroxine (T_4) daily. The dose is adjusted on the basis of TSH levels, with the goal of treatment being a normal TSH, ideally in the lower half of the reference range. TSH responses are gradual and should be measured about 2 months after instituting treatment or after any subsequent change in levothyroxine dosage. The clinical effects of levothyroxine replacement are often slow to appear. Patients may not experience full relief from symptoms until 3 to 6 months after normal TSH levels are restored. Adjustment of levothyroxine dosage is made in 12.5- or 25-µg increments if the TSH is high; decrements of the same magnitude should be made if the TSH is suppressed. Patients with a suppressed TSH of any cause, including T_4 overtreatment, have an increased risk of atrial fibrillation and reduced bone density.

Although dessicated animal thyroid preparations (thyroid extract USP) are available, they are not recommended as potency and composition vary between batches. Interest in using levothyroxine combined with liothyronine (triiodothyronine, T_3) has been revived, based on studies suggesting that patients feel better when taking the T_4/T_3 combination compared to T_4 alone. However, a long-term benefit from this combination is not established. There is no place for liothyronine alone as long-term replacement, because the short half-life necessitates three or four daily doses and is associated with fluctuating T_3 levels.

Once full replacement is achieved and TSH levels are stable, follow-up measurement of TSH is recommended at annual intervals and may be extended to every 2 to 3 years, if a normal TSH is maintained over several years. It is important to ensure ongoing compliance, however, as patients do not feel any difference after missing a few doses of levothyroxine, this sometimes leads to self-discontinuation.

In patients of normal body weight who are taking ≥200 µg of levothyroxine per day, an elevated TSH level is often a sign of poor compliance. This is also the likely explanation for fluctuating TSH levels, despite a constant levothyroxine dosage. Such patients often have normal or high unbound T_4 levels, despite an elevated TSH, because they remember to take medication for a few days before testing; this is sufficient to normalize T_4, but not TSH, levels. It is important to consider variable compliance, as this pattern of thyroid function tests is otherwise suggestive of disorders associated with inappropriate TSH secretion (Table 320-3). Because T_4 has a long half-life (7 days), patients who miss doses can be advised to take up to three doses of the skipped tablets at once. Other causes of increased levothyroxine requirements must be excluded, particularly malabsorption (e.g., celiac disease, small-bowel surgery), estrogen therapy, and drugs that interfere with T_4 absorption or clearance such as cholestyramine, ferrous sulfate, calcium supplements, lovastatin, aluminum hydroxide, rifampicin, amiodarone, carbamazepine, and phenytoin.

Mild Hypothyroidism

By definition, subclinical or mild hypothyroidism refers to biochemical evidence of thyroid hormone deficiency in patients who have few or no apparent clinical features of

hypothyroidism. There are no universally accepted guidelines for the treatment of mild hypothyroidism. As long as excessive treatment is avoided, there is little risk in correcting a slightly increased TSH, and some patients likely derive modest clinical benefit from treatment. Moreover, there is some risk that patients will progress to overt hypothyroidism, particularly when the TSH level is >6 mU/L and TPO antibodies are present. Treatment is administered by starting with a low dose of levothyroxine (25 to 50 µg/d) with the goal of normalizing TSH. If thyroxine is not given, thyroid function should be evaluated annually.

Special Treatment Considerations

Rarely, levothyroxine replacement is associated with pseudotumor cerebri in *children*. Presentation appears to be idiosyncratic and occurs months after treatment has begun. Women with a history or high risk of hypothyroidism should ensure that they are euthyroid prior to conception and during early pregnancy as maternal hypothyroidism may adversely affect fetal neural development. Thyroid function should be evaluated once pregnancy is confirmed and at the beginning of the second and third trimesters. The dose of levothyroxine may need to be increased by ≥50% during pregnancy and returned to previous levels after delivery. *Elderly* patients may require up to 20% less thyroxine than younger patients. In the elderly, especially patients with known coronary artery disease, the starting dose of levothyroxine is 12.5 to 25 µg/d with similar increments every 2 to 3 months until TSH is normalized. In some patients it may be impossible to achieve full replacement, despite optimal antianginal treatment. *Emergency surgery* is generally safe in patients with untreated hypothyroidism, although routine surgery in a hypothyroid patient should be deferred until euthyroidism is achieved.

Myxedema coma still has a high mortality rate, despite intensive treatment. Clinical manifestations include reduced level of consciousness, sometimes associated with seizures, as well as the other features of hypothyroidism (Table 320-5). Hypothermia can reach 23°C (74°F). There may be a history of treated hypothyroidism with poor compliance, or the patient may be previously undiagnosed. Myxedema coma almost always occurs in the elderly and is usually precipitated by factors that impair respiration, such as drugs (especially sedatives, anesthetics, antidepressants), pneumonia, congestive heart failure, myocardial infarction, gastrointestinal bleeding, or cerebrovascular accidents. Sepsis should also be suspected. Exposure to cold may also be a risk factor. Hypoventilation, leading to hypoxia and hypercapnia, plays a major role in pathogenesis; hypoglycemia and dilutional hyponatremia also contribute to the development of myxedema coma.

Levothyroxine can initially be administered as a single intravenous bolus of 500 µg, which serves as a loading dose. Although further levothyroxine is not strictly necessary for several days, it is usually continued at a dose of 50 to 100 µg/d. If suitable intravenous preparation is not available, the same initial dose of levothyroxine can be given by nasogastric tube (though absorption may be impaired in myxedema). An alternative is to give liothyronine (T_3) intravenously or

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via nasogastric tube, in doses ranging from 10 to 25 µg every 8 to 12 h. This treatment has been advocated because $T_4 \rightarrow T_3$ conversion is impaired in myxedema coma.

However, excess liothyroxine has the potential to provoke arrhythmias. Another option is to combine levothyroxine (200 µg) and liothyronine (25 µg) as a single, initial intravenous bolus followed by daily treatment with levothyroxine (50 to 100 µg/d) and liothyronine (10 µg every 8 h).

Supportive therapy should be provided to correct any associated metabolic disturbances. External warming is indicated only if the temperature is <30°C, as it can result in cardiovascular collapse (Chap. 16). Space blankets should be used to prevent further heat loss. Parenteral hydrocortisone (50 mg every 6 h) should be administered, as there is impaired adrenal reserve in profound hypothyroidism. Any precipitating factors should be treated, including the early use of broad-spectrum antibiotics, pending the exclusion of infection. Ventilatory support with regular blood gas analysis is usually needed during the first 48 h. Hypertonic saline or intravenous glucose may be needed if there is hyponatremia or hypoglycemia; hypotonic intravenous fluids should be avoided because they may exacerbate water retention secondary to reduced renal perfusion and inappropriate vasopressin secretion. The metabolism of most medications is impaired, and sedatives should be avoided if possible or used in reduced doses. Medication blood levels should be monitored, when available, to guide dosage.

THYROTOXICOSIS

Thyrotoxicosis is defined as the state of thyroid hormone excess and is not synonymous with *hyperthyroidism*, which is the result of excessive thyroid function. However, the major etiologies of thyrotoxicosis are hyperthyroidism caused by Graves' disease, toxic multinodular goiter, and toxic adenomas. Other causes are listed in Table 320-6.

TABLE 320-6 Causes of Thyrotoxicosis

Primary hyperthyroidism
  Graves' disease
  Toxic multinodular goiter
  Toxic adenoma
  Functioning thyroid carcinoma metastases
  Activating mutation of the TSH receptor
  Activating mutation of $G_{s\alpha}$ (McCune-Albright syndrome)
  Struma ovarii
  Drugs: iodine excess (Jod-Basedow phenomenon)
Thyrotoxicosis without hyperthyroidism
  Subacute thyroiditis
  Silent thyroiditis
  Other causes of thyroid destruction: amiodarone, radiation, infarction of adenoma
  Ingestion of excess thyroid hormone (thyrotoxicosis factitia) or thyroid tissue
Secondary hyperthyroidism
  TSH-secreting pituitary adenoma
  Thyroid hormone resistance syndrome: occasional patients may have features of thyrotoxicosis

Chorionic gonadotropin-secreting tumors [a]
Gestational thyrotoxicosis[a]

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[a] Circulating TSH levels are low in these forms of secondary hyperthyroidism.

Note: TSH, thyroid-stimulating hormone.

GRAVES' DISEASE

Epidemiology

Graves' disease accounts for 60 to 80% of thyrotoxicosis, but the prevalence varies among populations, depending mainly on iodine intake (high iodine intake is associated with an increased prevalence of Graves' disease). Graves' disease occurs in up to 2% of women but is one-tenth as frequent in men. The disorder rarely begins before adolescence and typically occurs between 20 and 50 years of age, but it also occurs in the elderly.

PATHOGENESIS

AS in autoimmune hypothyroidism, a combination of genetic factors, including HLA-DR and *CTLA-4* polymorphisms, and environmental factors contribute to Graves' disease susceptibility. The concordance for Graves' disease in monozygotic twins is 20 to 30%, compared to <5% in dizygotic twins. Indirect evidence suggests that stress is an important environmental factor, presumably operating through neuroendocrine effects on the immune system. Smoking is a minor risk factor for Graves' disease and a major risk factor for the development of ophthalmopathy. Sudden increases in iodine intake may precipitate Graves' disease, and there is a threefold increase in the occurrence of Graves' disease in the postpartum period.

The hyperthyroidism of Graves' disease is caused by TSI that are synthesized in the thyroid gland as well as in bone marrow and lymph nodes. Such antibodies can be detected by bioassays or using the more widely available TBII assays. The presence of TBII in a patient with thyrotoxicosis is strong indirect evidence for the existence of TSI, and these assays are useful in monitoring pregnant Graves' patients in whom high levels of TSI can cross the placenta and cause neonatal thyrotoxicosis. Other thyroid autoimmune responses, similar to those in autoimmune hypothyroidism (see above), occur concurrently in patients with Graves' disease. In particular, TPO antibodies occur in up to 80% of cases and serve as a readily measurable marker of autoimmunity. Because T cell–mediated cytotoxicity can also affect thyroid function, there is no direct correlation between the level of TSI and thyroid hormone levels. In the long term, spontaneous autoimmune hypothyroidism may develop in up to 15% of Graves' patients.

Cytokines appear to play a major role in thyroid-associated ophthalmopathy. There is

infiltration of the extraocular muscles by activated T cells; the release of cytokines such as IFN-γ, TNF, and IL-1 results in fibroblast activation and increased synthesis of glycosaminoglycans that trap water, thereby leading to characteristic muscle swelling. Late in the disease, there is fibrosis and only then do the muscle cells show evidence of injury. Orbital fibroblasts may be uniquely sensitive to cytokines, perhaps explaining the anatomic localization of the immune response. Though the pathogenesis of thyroid-associated ophthalmopathy remains unclear, there is mounting evidence that expression of the TSH-R may provide an important orbital autoantigen. In support of this idea, injection of TSH-R into certain strains of mice induces autoimmune hyperthyroidism, as well as features of ophthalmopathy. A variety of autoantibodies against orbital muscle and fibroblast antigens have been detected in patients with ophthalmopathy, but these antibodies most likely arise as a secondary phenomenon, dependent on T cell–mediated autoimmune responses. Similar mechanisms are involved in dermopathy.

Clinical Manifestations

Signs and symptoms include features that are common to any cause of thyrotoxicosis (Table 320-7) as well as those specific for Graves' disease. The clinical presentation depends on the severity of thyrotoxicosis, the duration of disease, individual susceptibility to excess thyroid hormone, and the patient's age. In the elderly, features of thyrotoxicosis may be subtle or masked, and patients may present mainly with fatigue and weight loss, leading to *apathetic hyperthyroidism*.

TABLE 320-7 Signs and Symptoms of Thyrotoxicosis (Descending Order of Frequency)

Symptoms
  Hyperactivity, irritability, dysphoria
  Heat intolerance and sweating
  Palpitations
  Fatigue and weakness
  Weight loss with increased appetite
  Diarrhea
  Polyuria
  Oligomenorrhea, loss of libido
Signs a
  Tachycardia; atrial fibrillation in the elderly
  Tremor
  Goiter
  Warm, moist skin
  Muscle weakness, proximal myopathy
  Lid retraction or lag
  Gynecomastia

a Excludes the signs of ophthalmopathy and dermopathy specific for Graves' disease.

Thyrotoxicosis may cause unexplained weight loss, despite an enhanced appetite, due to the increased metabolic rate. Weight gain occurs in 5% of patients, however, because of increased food intake.

Other prominent features include hyperactivity, nervousness, and irritability, ultimately leading to a sense of easy fatiguability in some patients. Insomnia and impaired concentration are common; apathetic thyrotoxicosis may be mistaken for depression in the elderly. Fine tremor is a frequent finding, best elicited by having patients stretch out their fingers and feeling the fingertips with the palm. Common neurologic manifestations include hyperreflexia, muscle wasting, and proximal myopathy without fasciculation. Chorea is a rare feature. Thyrotoxicosis is sometimes associated with a form of hypokalemic periodic paralysis; this disorder is particularly common in Asian males with thyrotoxicosis.

The most common cardiovascular manifestation is sinus tachycardia, often associated with palpitations, occasionally caused by supraventricular tachycardia. The high cardiac output produces a bounding pulse, widened pulse pressure, and an aortic systolic murmur and can lead to worsening of angina or heart failure in the elderly or those with preexisting heart disease. Atrial fibrillation is more common in patients >50 years. Treatment of the thyrotoxic state alone reverts atrial fibrillation to normal sinus rhythm in fewer than half of patients, suggesting the existence of an underlying cardiac problem in the remainder.

The skin is usually warm and moist, and the patient may complain of sweating and heat intolerance, particularly during warm weather. Palmar erythema; onycholysis; and, less commonly, pruritus, urticaria, and diffuse hyperpigmentation may be evident. Hair texture may become fine, and a diffuse alopecia occurs in up to 40% of patients, persisting for months after restoration of euthyroidism. Gastrointestinal transit time is decreased, leading to increased stool frequency, often with diarrhea and occasionally mild steatorrhea. Women frequently experience oligomenorrhea or amenorrhea; in men there may be impaired sexual function and, rarely, gynecomastia. The direct effect of thyroid hormones on bone resorption leads to osteopenia in long-standing thyrotoxicosis; mild hypercalcemia occurs in up to 20% of patients, but hypercalciuria is more common. There is a small increase in fracture rate in patients with a previous history of thyrotoxicosis.

In Graves' disease the thyroid is usually diffusely enlarged to two to three times its normal size. The consistency is firm, but less so than in multinodular goiter. There may be a thrill or bruit due to the increased vascularity of the gland and the hyperdynamic circulation.

Lid retraction, causing a staring appearance, can occur in any form of thyrotoxicosis and is the result of sympathetic overactivity. However, Graves' disease is associated with specific eye signs that comprise *Graves' ophthalmopathy* (Fig. 320-6A). This condition is also called *thyroid-associated ophthalmopathy*, as it occurs in the absence of Graves' disease in 10% of patients. Most of these individuals have autoimmune hypothyroidism or thyroid antibodies. The onset of Graves' ophthalmopathy occurs within the year before or after the diagnosis of thyrotoxicosis in 75% of patients but can sometimes precede or follow thyrotoxicosis by several years, accounting for some cases of euthyroid ophthalmopathy.

Many patients with Graves' disease have little clinical evidence of ophthalmopathy. However, the enlarged extraocular muscles typical of the disease, and other subtle

features, can be detected in almost all patients when investigated by ultrasound or computed tomography (CT) imaging of the orbits. Unilateral signs are found in up to 10% of patients. The earliest manifestations of ophthalmopathy are usually a sensation of grittiness, eye discomfort, and excess tearing. About a third of patients have proptosis, best detected by visualization of the sclera between the lower border of the iris and the lower eyelid, with the eyes in the primary position. Proptosis can be measured using an exophthalmometer. In severe cases, proptosis may cause corneal exposure and damage, especially if the lids fail to close during sleep. Periorbital edema, scleral injection, and chemosis are also frequent. In 5 to 10% of patients, the muscle swelling is so severe that diplopia results, typically but not exclusively when the patient looks up and laterally. The most serious manifestation is compression of the optic nerve at the apex of the orbit, leading to papilledema, peripheral field defects, and, if left untreated, permanent loss of vision.

Many scoring systems have been used to gauge the extent and activity of the orbital changes in Graves' disease. The "NO SPECS" scheme is an acronym derived from the following classes of eye change:

    0 = <u>N</u>o signs or symptoms

    1 = <u>O</u>nly signs (lid retraction or lag), no symptoms

    2 = <u>S</u>oft tissue involvement (periorbital edema)

    3 = <u>P</u>roptosis (>22 mm)

    4 = <u>E</u>xtraocular muscle involvement (diplopia)

    5 = <u>C</u>orneal involvement

    6 = <u>S</u>ight loss

Although useful as a mnemonic, the NO SPECS scheme is inadequate to describe the eye disease fully, and patients do not necessarily progress from one class to another. When Graves' eye disease is active and severe, referral to an ophthalmologist is indicated and objective measurements are needed, such as lid fissure width; corneal staining with fluorescein; and evaluation of extraocular muscle function (e.g., Hess chart), intraocular pressure and visual fields, acuity, and color vision.

Thyroid dermopathy occurs in <5% of patients with Graves' disease

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(Fig. 320-6*B*), almost always in the presence of moderate or severe ophthalmopathy. Although most frequent over the anterior and lateral aspects of the lower leg (hence the term *pretibial myxedema*), skin changes can occur at other sites, particularly after trauma. The typical lesion is a noninflamed, indurated plaque with a deep pink or purple color and an "orange-skin" appearance. Nodular involvement can occur, and the condition can rarely extend over the whole lower leg and foot, mimicking elephantiasis. *Thyroid acropachy* refers to a form of clubbing found in <1% of patients with Graves' disease (Fig. 320-6*C*). It is so strongly associated with thyroid dermopathy that an alternative cause of clubbing

should be sought in a Graves' patient without coincident skin and orbital involvement.

FIGURE 320-6 Features of Graves' disease. *A*. Facial appearance in Graves' disease; lid retraction, periorbital edema, and proptosis are marked. *B*. Thyroid dermopathy over the lateral aspects of the shins. *C*. Thyroid acropachy.

Laboratory Evaluation

Investigations used to determine the existence and cause of thyrotoxicosis are summarized in Fig. 320-7. In Graves' disease, the TSH level is suppressed and total and unbound thyroid hormone levels are increased. In 2 to 5% of patients (and more in areas of borderline iodine intake), only T_3 is increased (T_3 toxicosis). The converse state of T_4 toxicosis, with elevated total and unbound T_4 and normal T_3 levels, is occasionally seen when hyperthyroidism is induced by excess iodine, providing surplus substrate for thyroid hormone synthesis. Measurement of TPO antibodies is useful in differential diagnosis. Measurement of TBII or TSI will confirm the diagnosis but is not needed routinely. Associated abnormalities that may cause diagnostic confusion in thyrotoxicosis include elevation of bilirubin, liver enzymes, and ferritin. Microcytic anemia and thrombocytopenia may occur.

FIGURE 320-7 Evaluation of thyrotoxicosis. [a]Diffuse goiter, positive TPO antibodies, ophthalmopathy, dermopathy; [b]can be confirmed by radionuclide scan. TSH, thyroid-stimulating hormone.

Differential Diagnosis

Diagnosis of Graves' disease is straightforward in a patient with biochemically confirmed thyrotoxicosis, diffuse goiter on palpation, ophthalmopathy, positive TPO antibodies, and often a personal or family history of autoimmune disorders. For patients with thyrotoxicosis who lack these features, the most reliable diagnostic method is a radionuclide (^{99m}Tc, ^{123}I, or ^{131}I) scan of the thyroid, which will distinguish the diffuse, high uptake of Graves' disease from nodular thyroid disease, destructive thyroiditis, ectopic thyroid tissue, and factitious thyrotoxicosis. In secondary hyperthyroidism due to a TSH-secreting pituitary tumor, there is also a diffuse goiter. The presence of a nonsuppressed TSH level and the finding of a pituitary tumor on CT or magnetic resonance imaging (MRI) scan readily identify such patients.

Clinical features of thyrotoxicosis can mimic certain aspects of other disorders including panic attacks, mania, pheochromocytoma, and the weight loss associated with malignancy. The diagnosis of thyrotoxicosis can be easily excluded if the TSH and T_3 levels are normal. A normal TSH also excludes Graves' disease as a cause of diffuse goiter.

Clinical Course

Clinical features generally worsen without treatment; mortality was 10 to 30% before the introduction of satisfactory therapy. Some patients with mild Graves' disease experience spontaneous relapses and remissions. Rarely, there may be fluctuation between hypo- and hyperthyroidism due to changes in the functional activity of TSH-R antibodies. About 15% of patients who enter remission after treatment with antithyroid drugs develop hypothyroidism 10 to 15 years later as a result of the destructive autoimmune process. The clinical course of ophthalmopathy does not follow that of the thyroid disease. Ophthalmopathy typically worsens over the initial 3 to 6 months, followed by a plateau phase over the next 12 to 18 months, with spontaneous improvement, particularly in the soft tissue changes. However, the course is more fulminant in up to 5% of patients, requiring intervention in the acute phase if there is optic nerve compression or corneal ulceration. Diplopia may appear late in the disease due to fibrosis of the extraocular muscles. Some studies suggest that radioiodine treatment for hyperthyroidism worsens the eye disease in a small proportion of patients (especially smokers). Antithyroid drugs or surgery have no adverse effects on the clinical course of ophthalmopathy. Thyroid dermopathy, when it occurs, usually appears 1 to 2 years after the development of Graves' hyperthyroidism; it may improve spontaneously.

TREATMENT

The *hyperthyroidism* of Graves' disease is treated by reducing thyroid hormone synthesis, using antithyroid drugs, or by reducing the amount of thyroid tissue with radioiodine (^{131}I) treatment or by subtotal thyroidectomy. Antithyroid drugs are the predominant therapy in many centers in Europe and Japan, whereas radioiodine is more often the first line of treatment in North America. These differences reflect the fact that no single approach is optimal and that patients may require multiple treatments to achieve remission.

The main *antithyroid drugs* are the thionamides, such as propylthiouracil, carbimazole, and the active metabolite of the latter, methimazole. All inhibit the function of TPO, reducing oxidation and organification of iodide. These drugs also reduce thyroid antibody levels by mechanisms that remain unclear, and they appear to enhance rates of remission. Propylthiouracil inhibits deiodination of $T_4 \rightarrow T_3$. However, this effect is of minor benefit, except in the most severe thyrotoxicosis, and is offset by the much shorter half-life of this drug (90 min) compared to methimazole (6 h).

There are many variations of antithyroid drug regimens. The initial

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dose of carbimazole or methimazole is usually 10 to 20 mg every 8 or 12 h, but once-daily dosing is possible after euthyroidism is restored. Propylthiouracil is given at a dose of 100 to 200 mg every 6 to 8 h, and divided doses are usually given throughout the course. Lower doses of each drug may suffice in areas of low iodine intake. The starting dose of antithyroid drugs can be gradually reduced (titration regimen) as thyrotoxicosis improves. Alternatively, high doses may be given combined with levothyroxine supplementation (block-replace regimen) to avoid drug-induced hypothyroidism. Initial reports suggesting superior remission rates with the block-replace regimen have not been reproduced in several other trials. The titration regimen

is often preferred to minimize the dose of antithyroid drug and provide an index of treatment response.

Thyroid function tests and clinical manifestations are reviewed 3 to 4 weeks after starting treatment, and the dose is titrated based on unbound T_4 levels. Most patients do not achieve euthyroidism until 6 to 8 weeks after treatment is initiated. TSH levels often remain suppressed for several months and therefore do not provide a sensitive index of treatment response. The usual daily maintenance doses of antithyroid drugs in the titration regimen are 2.5 to 10 mg of carbimazole or methimazole and 50 to 100 mg of propylthiouracil. In the block-replace regimen, the initial dose of antithyroid drug is held constant and the dose of levothyroxine is adjusted to maintain normal unbound T_4 levels. When TSH suppression is alleviated, TSH levels can also be used to monitor therapy.

Maximum remission rates (up to 30 to 50% in some populations) are achieved by 18 to 24 months. For unclear reasons, remission rates appear to vary in different geographic regions. Patients with severe hyperthyroidism and large goiters are most likely to relapse when treatment stops, but outcome is difficult to predict. All patients should be followed closely for relapse during the first year after treatment and at least annually thereafter.

The common side effects of antithyroid drugs are rash, urticaria, fever, and arthralgia (1 to 5% of patients). These may resolve spontaneously or after substituting an alternative antithyroid drug. Rare but major side effects include hepatitis, an SLE-like syndrome, and, most importantly, agranulocytosis (<1%). It is essential that antithyroid drugs are stopped and not restarted if a patient develops major side effects. Written instructions should be provided regarding the symptoms of possible agranulocytosis (e.g., sore throat, fever, mouth ulcers) and the need to stop treatment pending a complete blood count to confirm that agranulocytosis is not present. Management of agranulocytosis is described in Chap. 94. It is not useful to monitor blood counts prospectively, as the onset of agranulocytosis is idiosyncratic and abrupt.

Propranolol (20 to 40 mg every 6 h) or longer acting beta blockers, such as atenolol, may be helpful to control adrenergic symptoms, especially in the early stages before antithyroid drugs take effect. The need for anticoagulation with warfarin should be considered in all patients with atrial fibrillation. If digoxin is used, increased doses are often needed in the thyrotoxic state.

Radioiodine causes progressive destruction of thyroid cells and can be used as initial treatment or for relapses after a trial of antithyroid drugs. There is a small risk of thyrotoxic crisis (see below) after radioiodine, which can be minimized by pretreatment with antithyroid drugs for at least a month before treatment. Antecedent treatment with antithyroid drugs should be considered for all elderly patients or for those with cardiac problems, to deplete thyroid hormone stores before administration of radioiodine. Antithyroid drugs must be stopped at least 3 days before radioiodine administration to achieve optimum iodine uptake.

Efforts to calculate an optimal dose of radioiodine that achieves euthyroidism, without a high incidence of relapse or progression to hypothyroidism, have not been successful. Some patients inevitably relapse after a single dose because the biologic effects of

radiation vary between individuals, and hypothyroidism cannot be uniformly avoided even using accurate dosimetry. A practical strategy is to give a fixed dose based on clinical features, such as the severity of thyrotoxicosis, the size of the goiter (increases the dose needed), and the level of radioiodine uptake (decreases the dose needed). ^{131}I dosage generally ranges between 185 MBq (5 mCi) to 555 MBq (15 mCi). Incomplete treatment or early relapse is more common in males and in patients <40 years of age. Many authorities favor an approach aimed at thyroid ablation (as opposed to euthyroidism), given that levothyroxine replacement is straightforward and most patients ultimately progress to hypothyroidism over 5 to 10 years, frequently with some delay in the diagnosis of hypothyroidism.

Certain radiation safety precautions are necessary in the first few days after radioiodine treatment, but the exact guidelines vary depending on local protocols. In general, patients need to avoid close, prolonged contact with children and pregnant women for several days because of possible transmission of residual isotope and excessive exposure to radiation emanating from the gland. Rarely there may be mild pain due to radiation thyroiditis 1 to 2 weeks after treatment. Hyperthyroidism can persist for 2 to 3 months before radioiodine takes full effect. For this reason, β-adrenergic blockers or antithyroid drugs can be used to control symptoms during this interval. Persistent hyperthyroidism can be treated with a second dose of radioiodine, usually 6 months after the first dose. The risk of hypothyroidism after radioiodine depends on the dosage but is at least 10 to 20% in the first year and 5% per year thereafter. Patients should be informed of this possibility before treatment and require close follow-up during the first year and annual thyroid function testing.

Pregnancy and breast feeding are absolute contraindications to radioiodine treatment, but patients can conceive safely 6 months after treatment. The presence of severe ophthalmopathy requires caution, and some authorities advocate the use of prednisone, 40 mg/d, at the time of radioiodine treatment, tapered over 2 to 3 months to prevent exacerbation of ophthalmopathy. The overall risk of cancer after radioiodine treatment in adults is not increased, but many physicians avoid radioiodine in children and adolescents because of the theoretical risks of malignancy.

Subtotal thyroidectomy is an option for patients who relapse after antithyroid drugs and prefer this treatment to radioiodine. Some experts recommend surgery in young individuals, particularly when the goiter is very large. Careful control of thyrotoxicosis with antithyroid drugs, followed by potassium iodide (3 drops SSKI orally tid), is needed prior to surgery to avoid thyrotoxic crisis and to reduce the vascularity of the gland. The major complications of surgery—i.e., bleeding, laryngeal edema, hypoparathyroidism, and damage to the recurrent laryngeal nerves—are unusual when the procedure is performed by highly experienced surgeons. Recurrence rates in the best series are <2%, but the rate of hypothyroidism is only slightly less than that following radioiodine treatment.

The titration regimen of antithyroid drugs should be used to manage Graves' disease in *pregnancy*, as blocking doses of these drugs produce fetal hypothyroidism. Propylthiouracil is usually used because of relatively low transplacental transfer and its ability to block $T_4 \rightarrow T_3$ conversion. Also, carbimazole and methimazole have been associated with rare cases of fetal *aplasia cutis* and other defects, such as choanal

atresia. The lowest effective dose of propylthiouracil should be given, and it is often possible to stop treatmentin the last trimester since TSH-R antibodies tend to decline in pregnancy. Nonetheless, the transplacental transfer of these antibodies rarely causes *fetal thyrotoxicosis* or *neonatal thyrotoxicosis*. Poor intrauterine growth, afetal heart rate of >160 beats/min, and high levels of maternal TSH-R antibodies in the last trimester may herald this complication. Antithyroid drugs given to the mother can be used to treat the fetus and may be needed for 1 to 3 months after delivery, until the maternal antibodies disappear from the baby's circulation. The postpartum period is a time of major risk for relapse of Graves' disease. Breast feeding is safe with low doses of antithyroid drugs. Graves' disease in *children* is best managed with antithyroid drugs, often given as a prolonged course of the titration regimen. Surgery may be indicated for severe disease. Radioiodine

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can also be used in children, although most experts defer this treatment until adolescence or later.

Thyrotoxic crisis, or *thyroid storm*, is rare and presents as a life-threatening exacerbation of hyperthyroidism, accompanied by fever, delirium, seizures, coma, vomiting, diarrhea, and jaundice. The mortality rate due to cardiac failure, arrhythmia, or hyperthermia is as high as 30%, even with treatment. Thyrotoxic crisis is usually precipitated by acute illness (e.g., stroke, infection, trauma, diabetic ketoacidosis), surgery (especially on the thyroid), or radioiodine treatment of a patient with partially treated or untreated hyperthyroidism. Management requires intensive monitoring and supportive care, identification and treatment of the precipitating cause, and measures that reduce thyroid hormone synthesis. Large doses of propylthiouracil (600-mg loading dose and 200 to 300 mg every 6 h) should be given orally or by nasogastric tube or per rectum; the drug's inhibitory action on $T_4 \rightarrow T_3$ conversion makes it the antithyroid drug of choice. One hour after the first dose of propylthiouracil, stable iodide is given to block thyroid hormone synthesis via the Wolff-Chaikoff effect (the delay allows the antithyroid drug to prevent the excess iodine from being incorporated into new hormone). A saturated solution of potassium iodide (5 drops SSKI every 6 h), or ipodate or iopanoic acid (0.5 mg every 12 h), may be given orally. (Sodium iodide, 0.25 g intravenously every 6 h is an alternative but is not generally available.) Propranolol should also be given to reduce tachycardia and other adrenergic manifestations (40 to 60 mg orally every 4 h; or 2 mg intravenously every 4 h). Although other β-adrenergic blockers can be used, high doses of propranolol decrease $T_4 \rightarrow T_3$ conversion, and the doses can be easily adjusted. Caution is needed to avoid acute negative inotropic effects, but controlling the heart rate is important, as some patients develop a form of high-output heart failure. Additional therapeutic measures include glucocorticoids (e.g., dexamethasone, 2 mg every 6 h), antibiotics if infection is present, cooling, oxygen, and intravenous fluids.

Ophthalmopathy requires no active treatment when it is mild or moderate, as there is usually spontaneous improvement. General measures include meticulous control of thyroid hormone levels, advice about cessation of smoking, and an explanation of the natural history of ophthalmopathy. Discomfort can be relieved with artificial tears (e.g., 1% methylcellulose) and the use of dark glasses with side frames. Periorbital edema

may respond to a more upright sleeping position or a diuretic. Corneal exposure during sleep can be avoided by taping the eyelids shut. Minor degrees of diplopia improve with prisms fitted to spectacles. Severe ophthalmopathy, with optic nerve involvement or chemosis resulting in corneal damage, is an emergency requiring joint management with an ophthalmologist. Short-term benefit can be gained in about two-thirds of patients by the use of high-dose glucocorticoids (e.g., prednisone, 40 to 80 mg daily), sometimes combined with cyclosporine. Glucocorticoid doses are tapered by 5 mg every 1 to 2 weeks, but the taper often results in reemergence of congestive symptoms. Pulse therapy with intravenous methylprednisolone (1 g of methylprednisolone in 250 mL of saline infused over 2 h daily for 1 week) followed by an oral regimen is also used. Once the eye disease has stabilized, surgery may be indicated for relief of diplopia and correction of the appearance of the eyes. Orbital decompression can be achieved by removing bone from any wall of the orbit, thereby allowing displacement of fat and swollen extraocular muscles. The transantral route is used most often, as it requires no external incision. Proptosis recedes an average of 5 mm, but there may be residual or even worsened diplopia. Alternatively, retrobulbar tissue can be decompressed without the removal of bony tissue. External beam radiotherapy of the orbits has been used for many years, especially for ophthalmopathy of recent onset, but the objective evidence that this therapy is beneficial remains equivocal.

Thyroid dermopathy does not usually require treatment but can cause cosmetic problems or interfere with the fit of shoes. Surgical removal is not indicated. If necessary, treatment consists of topical, high-potency glucocorticoid ointment under an occlusive dressing. Octreotide may be beneficial.

OTHER CAUSES OF THYROTOXICOSIS

Destructive thyroiditis (subacute or silent thyroiditis) typically presents with a short thyrotoxic phase due to the release of preformed thyroid hormones and catabolism of Tg (see "Subacute Thyroiditis," below). True hyperthyroidism is absent, as demonstrated by a low radionuclide uptake. Circulating Tg and IL-6 levels are usually increased. Other causes of thyrotoxicosis with low or absent thyroid radionuclide uptake include *thyrotoxicosis factitia*; iodine excess and, rarely, ectopic thyroid tissue, particularly teratomas of the ovary (*struma ovarii*); and functional metastatic follicular carcinoma. Whole-body radionuclide studies can demonstrate ectopic thyroid tissue, and thyrotoxicosis factitia can be distinguished from destructive thyroiditis by the clinical features and low levels of Tg. Amiodarone treatment is associated with thyrotoxicosis in up to 10% of patients, particularly in areas of low iodine intake.

TSH-secreting pituitary adenoma is a rare causes of thyrotoxicosis. It can be identified by the presence of an inappropriately normal or increased TSH level in a patient with hyperthyroidism, diffuse goiter, and elevated T_4 and T_3 levels (Chap. 318). Elevated levels of the α subunit of TSH, released by the TSH-secreting adenoma, support this diagnosis, which can be confirmed by demonstrating the pituitary tumor on CT or MRI scan. A combination of transsphenoidal surgery, sella irradiation, and octreotide may be required to normalize TSH, as many of these tumors are large and locally invasive at the time of

diagnosis. Radioiodine or antithyroid drugs can be used to control thyrotoxicosis.

Thyrotoxicosis caused by *toxic multinodular goiter* and *hyperfunctioning solitary nodules* is discussed below.

THYROIDITIS

A clinically useful classification of thyroiditis is based on the onset and duration of disease (Table 320-8).

TABLE 320-8 Causes of Thyroiditis

Acute
  Bacterial infection: especially *Staphylcoccus Streptococcus* and *Enterobacter*
  Fungal infection: *Aspergillus Candida Coccidioides Histoplasma* and *Pneumocystis*

  Radiation thyroiditis after ^{131}I treatment

  Amiodarone (may also be subacute or chronic)

Subacute

  Viral (or granulomatous) thyroiditis

  Silent thyroiditis (including postpartum thyroiditis)

  Mycobacterial infection

Chronic

  Autoimmunity: focal thyroiditis, Hashimoto's thyroiditis, atrophic thyroiditis

  Riedel's thyroiditis

  Parasitic thyroiditis: echinococcosis, strongyloidiasis, cysticercosis

  Traumatic: after palpation

ACUTE THYROIDITIS

Acute thyroiditis is rare and due to suppurative infection of the thyroid. In children and young adults, the most common cause is the presence of a piriform sinus, a remnant of the fourth branchial pouch that connects the oropharynx with the thyroid. Such sinuses are predominantly left sided. A long-standing goiter and degeneration in a thyroid malignancy are risk factors in the elderly. The patient presents with thyroid pain, often referred to the

throat or ears, and a small, tender goiter that may be asymmetric. Fever, dysphagia, and erythema over the thyroid are common, as are systemic symptoms of a febrile illness and lymphadenopathy.

The differential diagnosis of *thyroid pain* includes subacute or, rarely, chronic thyroiditis, hemorrhage into a cyst, malignancy including lymphoma, and, rarely, amiodarone-induced thyroiditis or amyloidosis. However, the abrupt presentation and clinical features of acute thyroiditis rarely cause confusion. The erythrocyte sedimentation rate (ESR) and white cell count are usually increased, but thyroid

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function is normal. FNA biopsy shows infiltration by polymorphonuclear leukocytes; culture of the sample can identify the organism. Caution is needed in immunocompromised patients as fungal, mycobacterial, or *Pneumocystis* thyroiditis can occur in this setting. Antibiotic treatment is guided initially by Gram stain and subsequently by cultures of the FNA biopsy. Surgery may be needed to drain an abscess, which can be localized by CT scan or ultrasound. Tracheal obstruction, septicemia, retropharyngeal abscess, mediastinitis, and jugular venous thrombosis may complicate acute thyroiditis but are uncommon with prompt use of antibiotics.

SUBACUTE THYROIDITIS

This is also termed *de Quervain's thyroiditis*, *granulomatous thyroiditis*, or *viral thyroiditis*. Many viruses have been implicated, including mumps, coxsackie, influenza, adenoviruses, and echoviruses, but attempts to identify the virus in an individual patient are often unsuccessful and do not influence management. The diagnosis of subacute thyroiditis is often overlooked because the symptoms can mimic pharyngitis. The peak incidence occurs at 30 to 50 years, and women are affected three times more frequently than men.

Pathophysiology

The thyroid shows a characteristic patchy inflammatory infiltrate with disruption of the thyroid follicles and multinucleated giant cells within some follicles. The follicular changes progress to granulomas accompanied by fibrosis. Finally, the thyroid returns to normal, usually several months after onset. During the initial phase of follicular destruction, there is release of Tg and thyroid hormones, leading to increased circulating T_4 and T_3 and suppression of TSH (Fig. 320-8). During this destructive phase, radioactive iodine uptake is low or undetectable. After several weeks, the thyroid is depleted of stored thyroid hormone and a phase of hypothyroidism typically occurs, with low unbound T_4 (and sometimes T_3) and moderately increased TSH levels. Radioactive iodine uptake returns to normal or is even increased as a result of the rise in TSH. Finally, thyroid hormone and TSH levels return to normal as the disease subsides.

FIGURE 320-8 Clinical course of subacute thyroiditis. The release of thyroid hormones is initially associated with a thyrotoxic phase and suppressed thyroid-stimulating hormone (TSH). A hypothyroid phase then ensues, with low T_4 and TSH levels that are initially low but gradually increase. During the recovery phase, increased TSH levels combined with resolution of thyroid follicular injury leads to normalization of thyroid function, often several months after the beginning of the illness. ESR,

erythrocyte sedimentation rate; UT_4, unbound T_4.

Clinical Manifestations

The patient usually presents with a painful and enlarged thyroid, sometimes accompanied by fever. There may be features of thyrotoxicosis or hypothyroidism, depending on the phase of the illness. Malaise and symptoms of an upper respiratory tract infection may precede the thyroid-related features by several weeks. In other patients, the onset is acute, severe, and without obvious antecedent. The patient typically complains of a sore throat, and examination reveals a small goiter that is exquisitely tender. Pain is often referred to the jaw or ear. Complete resolution is the usual outcome, but permanent hypothyroidism can occur, particularly in those with coincidental thyroid autoimmunity. A prolonged course over many months, with one or more relapses, occurs in a small percentage of patients.

Laboratory Evaluation

As depicted in Fig. 320-8, thyroid function tests characteristically evolve through three distinct phases over about 6 months: (1) thyrotoxic phase, (2) hypothyroid phase, and (3) recovery phase. In the thyrotoxic phase, T_4 and T_3 levels are increased, reflecting their discharge from the damaged thyroid cells, and TSH is suppressed. The T_4/T_3 ratio is greater than in Graves' disease or thyroid autonomy, in which T_3 is often disproportionately increased. The diagnosis is confirmed by a high ESR and low radioiodine uptake. Serum IL-6 levels increase during the thyrotoxic phase. The white blood cell count may be increased, and thyroid antibodies are negative. If the diagnosis is in doubt, FNA biopsy may be useful, particularly to distinguish unilateral involvement from bleeding into a cyst or neoplasm.

TREATMENT

Relatively large doses of aspirin (e.g., 600 mg every 4 to 6 h) or nonsteroidal anti-inflammatory drugs are sufficient to control symptoms in most cases. If this treatment is inadequate, or if the patient has marked local or systemic symptoms, glucocorticoids should be given. The usual starting dose is 40 to 60 mg prednisone, depending on severity. The dose is gradually tapered over 6 to 8 weeks, in response to improvement in symptoms and the ESR. If a relapse occurs during glucocorticoid withdrawal, treatment should be started again and withdrawn more gradually. In these patients, it is useful to wait until the radioactive iodine uptake normalizes before stopping treatment. Thyroid function should be monitored every 2 to 4 weeks using TSH and unbound T_4 levels. Symptoms of thyrotoxicosis improve spontaneously but may be ameliorated by β-adrenergic blockers; antithyroid drugs play no role in treatment of the thyrotoxic phase. Levothyroxine replacement may be needed if the hypothyroid phase is prolonged, but doses should be low enough (50 to 100 μg daily) to allow TSH-mediated recovery.

SILENT THYROIDITIS

Painless thyroiditis, or *"silent" thyroiditis*, occurs in patients with underlying autoimmune thyroid disease. It has a clinical course similar to that of subacute thyroiditis, except that there is little or no thyroid tenderness. The condition occurs in up to 5% of women 3 to 6 months after pregnancy and is then termed *postpartum thyroiditis*. Typically, patients have a brief phase of thyrotoxicosis, lasting 2 to 4 weeks, followed by hypothyroidism for 4 to 12 weeks, and then resolution; often, however, only one phase is apparent. The condition is associated with the presence of TPO antibodies antepartum, and is three times more common in women with type 1 diabetes mellitus. As in subacute thyroiditis, the radioactive iodine uptake is initially suppressed. In addition to the painless goiter, silent thyroiditis can be distinguished from subacute thyroiditis by the normal ESR and the presence of TPO antibodies. Glucocorticoid treatment is not indicated for silent thyroiditis. Severe thyrotoxic symptoms can be managed with a brief course of propranolol, 20 to 40 mg three or four times daily. Thyroxine replacement may be needed for the hypothyroid phase but should be withdrawn after 6 to 9 months, as recovery is the rule. Annual follow-up thereafter is recommended, as a proportion of these individuals develop permanent hypothyroidism.

DRUG-INDUCED THYROIDITIS

Patients receiving IFN-α, IL-2, or amiodarone may develop painless thyroiditis. IFN-α, which is used to treat chronic hepatitis B or C, causes thyroid dysfunction in up to 5% of treated patients. It has been associated with painless thyroiditis, hypothyroidism, and Graves' disease. IL-2, which has been used to treat various malignancies, has also been associated with thyroiditis and hypothyroidism, though fewer patients have been studied. For discussion of amiodarone, see "Amiodarone Effects on Thyroid Function," below.

CHRONIC THYROIDITIS

Focal thyroiditis is present in 20 to 40% of euthyroid autopsy cases and is associated with serologic evidence of

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autoimmunity, particularly the presence of TPO antibodies. These antibodies are 4 to 10 times more common in otherwise healthy women than men. The most common clinically apparent cause of chronic thyroiditis is *Hashimoto's thyroiditis*, an autoimmune disorder that often presents as a firm or hard goiter of variable size (see above). *Riedel's thyroiditis* is a rare disorder that typically occurs in middle-aged women. It presents with an insidious, painless goiter with local symptoms due to compression of the esophagus, trachea, neck veins, or recurrent laryngeal nerves. Dense fibrosis disrupts normal gland architecture and can extend outside the thyroid capsule. Despite these extensive histologic changes, thyroid dysfunction is uncommon. The goiter is hard, nontender, often asymmetric and fixed, leading to suspicion of a malignancy. Diagnosis requires open biopsy as FNA biopsy is usually inadequate. Treatment is directed to surgical relief of compressive symptoms. Tamoxifen may also be beneficial. There is an association between Riedel's thyroiditis and idiopathic fibrosis at other sites (retroperitoneum, mediastinum, biliary tree, lung, and orbit).

SICK EUTHYROID SYNDROME

Any acute, severe illness can cause abnormalities of circulating TSH or thyroid hormone levels in the absence of underlying thyroid disease, making these measurements potentially misleading. The major cause of these hormonal changes is the release of cytokines. Unless a thyroid disorder is strongly suspected, the routine testing of thyroid function should be avoided in acutely ill patients.

The most common hormone pattern in sick euthyroid syndrome (SES) is a decrease in total and unbound T_3 levels (low T_3 syndrome) with normal levels of T_4 and TSH. The magnitude of the fall in T_3 correlates with the severity of the illness. T_4 conversion to T_3 via peripheral deiodination is impaired, leading to increased reverse T_3 (rT_3). Despite this effect, decreased clearance rather than increased production is the major basis for increased rT_3. Also, T_4 is alternately metabolized to the hormonally inactive T_3 sulfate. It is generally assumed that this low T_3 state is adaptive, as it can be induced in normal individuals by fasting. Teleologically, the fall in T_3 may limit catabolism in starved or ill patients.

Very sick patients may exhibit a dramatic fall in total T_4 and T_3 levels (low T_4 syndrome). This state has a poor prognosis. A key factor in the fall in T_4 levels is altered binding to TBG. T_4 assays usually demonstrate a normal unbound T_4 level in such patients, depending on the assay method used. Fluctuation in TSH levels also creates challenges in the interpretation of thyroid function in sick patients. TSH levels may range from <0.1 to >20 mU/L; these alterations reverse after recovery, confirming the absence of underlying thyroid disease. A rise in cortisol or administration of glucocorticoids may provide a partial explanation for decreased TSH levels. However, the exact mechanisms underlying the subnormal TSH seen in 10% of sick patients and the increased TSH seen in 5% remain unclear.

Any severe illness can induce changes in thyroid hormone levels, but certain disorders exhibit a distinctive pattern of abnormalities. Acute liver disease is associated with an initial rise in total (but not unbound) T_3 and T_4 levels, due to TBG release; these levels become subnormal with progression to liver failure. A transient increase in total and unbound T_4 levels, usually with a normal T_3 level, is seen in 5 to 30% of acutely ill psychiatric patients. TSH values may be transiently low, normal, or high in these patients. In the early stage of HIV infection, T_3 and T_4 levels rise, even if there is weight loss. T_3 levels fall with progression to AIDS, but TSH usually remains normal. Renal disease is often accompanied by low T_3 concentrations, but with normal rather than increased rT_3 levels, due to an unknown factor that increases uptake of rT_3 into the liver.

The diagnosis of SES is challenging. Historic information may be limited, and patients often have multiple metabolic derangements. Useful features to consider include previous history of thyroid disease and thyroid function tests, evaluation of the severity and time course of the patient's acute illness, documentation of medications that may affect thyroid function or thyroid hormone levels, and measurements of rT_3 together with unbound thyroid hormones and TSH. The diagnosis of SES is frequently presumptive, given the clinical context and pattern of laboratory values; only resolution of the test results with clinical recovery can clearly establish this disorder. Treatment of SES with thyroid hormone (T_4 and/or T_3) is controversial, but most authorities recommend monitoring the patient's thyroid function

tests during recovery, without administering thyroid hormone, unless there is historic or clinical evidence suggestive of hypothyroidism. Sufficiently large randomized controlled trials using thyroid hormone are unlikely to resolve this therapeutic controversy in the near future, because clinical presentations and outcomes are highly variable.

AMIODARONE EFFECTS ON THYROID FUNCTION

Amiodarone is a commonly used type III antiarrhythmic agent (Chap. 214). It is structurally related to thyroid hormone and contains 39% iodine by weight. Thus, typical doses of amiodarone (200 mg/d) are associated with very high iodine intake, leading to >40-fold increases in plasma and urinary iodine levels. Moreover, because amiodarone is stored in adipose tissue, high iodine levels persist for >6 months after discontinuation of the drug. Amiodarone inhibits deiodinase activity, and its metabolites function as weak antagonists of thyroid hormone action. Amiodarone has the following effects on thyroid function: (1) acute, transient suppression of thyroid function; (2) hypothyroidism in patients susceptible to the inhibitory effects of a high iodine load; and (3) thyrotoxicosis that may be caused by at least three mechanisms—a Jod-Basedow effect from the iodine load in the setting of multinodular goiter, a thyroiditis-like condition, and possibly induction of autoimmune Graves' disease.

The initiation of amiodarone treatment is associated with a transient decrease of T_4 levels, reflecting the inhibitory effect of iodine on T_4 release. Soon thereafter, most individuals escape from iodide-dependent suppression of the thyroid (Wolff-Chaikoff effect), and the inhibitory effects on deiodinase activity and thyroid hormone receptor action become predominant. These events lead to the following pattern of thyroid function tests: increased T_4, decreased T_3, increased rT_3, and a transient increase of TSH (up to 20 mU/L). TSH levels normalize or are slightly suppressed by 1 to 3 months.

The incidence of hypothyroidism from amiodarone varies geographically, apparently correlating with iodine intake. Hypothyroidism occurs in up to 13% of amiodarone-treated patients in iodine-replete countries, such as the United States, but is less common (<6% incidence) in areas of lower iodine intake, such as Italy or Spain. The pathogenesis appears to involve an inability of the thyroid to escape from the high iodine load. Consequently, amiodarone-associated hypothyroidism is more common in women and individuals with positive TPO antibodies. It is usually unnecessary to discontinue amiodarone for this side effect, as levothyroxine can be used to normalize thyroid function. TSH levels should be monitored, because T_4 levels are often increased for the reasons described above.

The management of amiodarone-induced thyrotoxicosis (AIT) is complicated by the fact that there are several causes of thyrotoxicosis and because the increased thyroid hormone levels exacerbate underlying arrhythmias and coronary artery disease. Amiodarone treatment causes thyrotoxicosis in 10% of patients living in areas of low iodine intake and in 2% of patients in regions of high iodine intake. There are two major forms of AIT, although some patients have features of both. Type 1 AIT is associated with an underlying thyroid abnormality (preclinical Graves' disease or nodular goiter). Thyroid hormone synthesis becomes excessive as a result of increased iodine exposure (Jod-Basedow phenomenon). Type 2 AIT occurs in individuals with no intrinsic thyroid abnormalities and

is the result of drug-induced lysosomal activation leading to destructive thyroiditis with histiocyte accumulation in the thyroid. Mild forms of type 2 AIT can resolve spontaneously or can occasionally lead to hypothyroidism. Color-flow doppler thyroid scanning shows increased vascularity in type 1 AIT

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but decreased vascularity in type 2 AIT. Thyroid scans are difficult to interpret in this setting, because the high endogenous iodine levels diminish tracer uptake. However, the presence of normal or increased uptake favors type 1 AIT.

In AIT the drug should be stopped, if possible, although this is often impractical because of the underlying cardiac disorder. Discontinuation of amiodarone will not have an acute effect because of its storage and prolonged half-life. High doses of antithyroid drugs can be used in type 1 AIT but are often ineffective. In type 2 AIT, oral contrast agents, such as sodium ipodate (500 mg/d) or sodium tyropanoate (500 mg, 1 to 2 doses/d), rapidly reduce T_4 and T_3 levels, decrease $T_4 \rightarrow T_3$ conversion, and may block tissue uptake of thyroid hormones. Potassium perchlorate, 200 mg every 6 h, has been used to reduce thyroidal iodide content. Perchlorate treatment has been associated with agranulocytosis, though the risk appears relatively low with short-term use. Glucocorticoids, administered as for subacute thyroiditis, are of variable benefit in type 2 AIT. Lithium blocks thyroid hormone release and can provide modest benefit. Near-total thyroidectomy rapidly decreases thyroid hormone levels and may be the most effective long-term solution, if the patient can undergo the procedure safely.

THYROID FUNCTION IN PREGNANCY

Four factors alter thyroid function in pregnancy: (1) the transient increase in hCG during the first trimester, which stimulates the TSH-R; (2) the estrogen-induced rise in TBG during the first trimester, which is sustained during pregnancy; (3) alterations in the immune system, leading to the onset, exacerbation, or amelioration of an underlying autoimmune thyroid disease (see above); and (4) increased urinary iodide excretion, which can cause impaired thyroid hormone production in areas of marginal iodine sufficiency. Women with a precarious iodine intake (<50 µg/d) are most at risk of developing a goiter during pregnancy, and iodine supplementation should be considered to prevent maternal and fetal hypothyroidism and the development of neonatal goiter.

The rise in circulating hCG levels during the first trimester is accompanied by a reciprocal fall in TSH that persists into the middle of pregnancy. This appears to reflect weak binding of hCG, which is present at very high levels, to the TSH-R. Rare individuals have been described with variant TSH-R sequences that enhance hCG binding and TSH-R activation. hCG-induced changes in thyroid function can result in transient gestational hyperthyroidism and/or *hyperemesis gravidarum*, a condition characterized by severe nausea and vomiting and risk of volume depletion. Antithyroid drugs are rarely needed, and parenteral fluid replacement usually suffices until the condition resolves.

Maternal hypothyroidism occurs in 2 to 3% of women of child-bearing age and is associated with increased risk of developmental delay in the offspring. Thyroid hormone requirements are increased by 25 to 50 µg/d during pregnancy.

GOITER AND NODULAR THYROID DISEASE

Goiter refers to an enlarged thyroid gland. Biosynthetic defects, iodine deficiency, autoimmune disease, and nodular diseases can each lead to goiter, though by different mechanisms. Biosynthetic defects and iodine deficiency are associated with reduced efficiency of thyroid hormone synthesis, leading to increased TSH, which stimulates thyroid growth as a compensatory mechanism to overcome the block in hormone synthesis. Graves' disease and Hashimoto's thyroiditis are also associated with goiter. In Graves' disease, the goiter results mainly from the TSH-R-mediated effects of TSI. The goitrous form of Hashimoto's thyroiditis occurs because of acquired defects in hormone synthesis, leading to elevated levels of TSH and its consequent growth effects. Lymphocytic infiltration and immune system–induced growth factors also contribute to thyroid enlargement in Hashimoto's thyroiditis. Nodular disease is characterized by the disordered growth of thyroid cells, often combined with the gradual development of fibrosis. Because the management of goiter depends on the etiology, the detection of thyroid enlargement on physical examination should prompt further evaluation to identify its cause.

Nodular thyroid disease is common, occurring in about 3 to 7% of adults when assessed by physical examination. Using more sensitive techniques, such as ultrasound, it is present in >25% of adults. Thyroid nodules may be solitary or multiple, and they may be functional or nonfunctional.

DIFFUSE NONTOXIC (SIMPLE) GOITER

Etiology and Pathogenesis

When diffuse enlargement of the thyroid occurs in the absence of nodules and hyperthyroidism, it is referred to as a *diffuse nontoxic goiter*. This is sometimes called *simple goiter*, because of the absence of nodules, or *colloid goiter*, because of the presence of uniform follicles that are filled with colloid. Worldwide, diffuse goiter is most commonly caused by iodine deficiency and is termed *endemic goiter* when it affects >5% of the population. In nonendemic regions, *sporadic goiter* occurs, and the cause is usually unknown. Thyroid enlargement in teenagers is sometimes referred to as *juvenile goiter*. In general, goiter is more common in women than men, probably because of the greater prevalence of underlying autoimmune disease and the increased iodine demands associated with pregnancy.

In *iodine-deficient areas*, thyroid enlargement reflects a compensatory effort to trap iodide and produce sufficient hormone under conditions in which hormone synthesis is relatively inefficient. Somewhat surprisingly, TSH levels are usually normal or only slightly increased, suggesting increased sensitivity to TSH or activation of other pathways that lead to thyroid growth. Iodide appears to have direct actions on thyroid vasculature and may indirectly affect growth through vasoactive substances such as endothelins and nitric oxide. Endemic goiter is also caused by exposure to environmental *goitrogens* such as cassava root, which contains a thiocyanate, vegetables of the Cruciferae family (e.g., brussels sprouts, cabbage, and cauliflower), and milk from regions where goitrogens are present in grass. Though relatively rare, inherited defects in thyroid hormone synthesis lead to a diffuse

nontoxic goiter. Abnormalities at each step in hormone synthesis, including iodide transport (NIS), Tg synthesis, organification and coupling (TPO), and the regeneration of iodide (dehalogenase), have been described.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

If thyroid function is preserved, most goiters are asymptomatic. Spontaneous hemorrhage into a cyst or nodule may cause the sudden onset of localized pain and swelling. Examination of a diffuse goiter reveals a symmetrically enlarged, nontender, generally soft gland without palpable nodules. Goiter is defined, somewhat arbitrarily, as a lateral lobe with a volume greater than the thumb of the individual being examined. If the thyroid is markedly enlarged, it can cause tracheal or esophageal compression. These features are unusual, however, in the absence of nodular disease and fibrosis. *Substernal goiter* may obstruct the thoracic inlet. *Pemberton's sign* refers to symptoms of faintness with evidence of facial congestion and external jugular venous obstruction when the arms are raised above the head, a maneuver that draws the thyroid into the thoracic inlet. Respiratory flow measurements and CT or MRI should be used to evaluate substernal goiter in patients with obstructive signs or symptoms.

Thyroid function tests should be performed in all patients with goiter to exclude thyrotoxicosis or hypothyroidism. It is not unusual, particularly in iodine deficiency, to find a low total T_4, with normal T_3 and TSH, reflecting enhanced $T_4 \rightarrow T_3$ conversion. A low TSH, particularly in older patients, suggests the possibility of thyroid autonomy or undiagnosed Graves' disease, causing subclinical thyrotoxicosis. TPO antibodies may be useful to identify patients at increased risk of autoimmune thyroid disease. Low urinary iodine levels (<10 μg/dL) support a diagnosis of iodine deficiency. Thyroid scanning is not generally necessary but will reveal increased uptake in iodine deficiency and most cases of dyshormonogenesis. Ultrasound is not generally

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indicated in the evaluation of diffuse goiter, unless a nodule is palpable on physical examination.

TREATMENT

Iodine or thyroid hormone replacement induces variable regression of goiter in iodine deficiency, depending on how long it has been present and the degree of fibrosis that has developed. Because of the possibility of underlying thyroid autonomy, caution should be exercised when instituting suppressive thyroxine therapy in other causes of diffuse nontoxic goiter, particularly if the baseline TSH is in the low-normal range. In younger patients, the dose of levothyroxine can be started at 100 μg/d and adjusted to suppress the TSH into the low-normal but detectable range. Treatment of elderly patients should be initiated at 50 μg/d. The efficacy of suppressive treatment is greater in younger patients and for those with soft goiters. Significant regression is usually seen within 3 to 6 months of treatment; after this time it is unlikely to occur. In older patients, and in those with some degree of nodular disease or fibrosis, fewer than one-third demonstrate significant shrinkage of the goiter. Surgery is rarely indicated for diffuse goiter. Exceptions include documented evidence of tracheal compression or

obstruction of the thoracic inlet, which are more likely to be associated with substernal multinodular goiters (see below). Subtotal or near-total thyroidectomy for these or cosmetic reasons should be performed by an experienced surgeon to minimize complication rates, which occur in up to 10% of cases. Surgery should be followed by mild suppressive treatment with levothyroxine to prevent regrowth of the goiter. Radioiodine reduces goiter size by about 50% in the majority of patients. It is rarely associated with transient acute swelling of the thyroid, which is usually inconsequential unless there is severe tracheal narrowing. If not treated with levothyroxine, patients should be followed after radioiodine treatment for the possible development of hypothyroidism.

NONTOXIC MULTINODULAR GOITER

Etiology and Pathogenesis

Depending on the population studied, multinodular goiter (MNG) occurs in up to 12% of adults. MNG is more common in women than men and increases in prevalence with age. It is more common in iodine-deficient regions but also occurs in regions of iodine sufficiency, reflecting multiple genetic, autoimmune, and environmental influences on the pathogenesis.

There is typically wide variation in nodule size. Histology reveals a spectrum of morphologies ranging from hypercellular regions to cystic areas filled with colloid. Fibrosis is often extensive, and areas of hemorrhage or lymphocytic infiltration may be seen. Using molecular techniques, most nodules within a MNG are polyclonal in origin, suggesting a hyperplastic response to locally produced growth factors and cytokines. TSH, which is usually not elevated, may play a permissive or contributory role. Monoclonal lesions also occur within a MNG, reflecting mutations in genes that confer a selective growth advantage to the progenitor cell.

Clinical Manifestations

Most patients with nontoxic MNG are asymptomic and, by definition, euthyroid. MNG typically develops over many years and is detected on routine physical examination or when an individual notices an enlargement in the neck. If the goiter is large enough, it can ultimately lead to compressive symptoms including difficulty swallowing, respiratory distress (tracheal compression), or plethora (venous congestion), but these symptoms are uncommon. Symptomatic MNGs are usually extraordinarily large and/or develop fibrotic areas that cause compression. Sudden pain in a MNG is usually caused by hemorrhage into a nodule but should raise the possibility of invasive malignancy. Hoarseness, reflecting laryngeal nerve involvement, also suggests malignancy.

Diagnosis

On examination, thyroid architecture is distorted and multiple nodules of varying size can be appreciated. Because many nodules are deeply embedded in thyroid tissue or reside in posterior or substernal locations, it is not possible to palpate all nodules. A TSH level should be measured to exclude subclinical hyper- or hypothyroidism, but thyroid function is

usually normal. Tracheal deviation is common, but compression must usually exceed 70% of the tracheal diameter before there is significant airway compromise. Pulmonary function testing can be used to assess the functional effects of compression and to detect tracheomalacia, which characteristically causes inspiratory stridor. CT or MRI can be used to evaluate the anatomy of the goiter and the extent of substernal extension, which is often much greater than is apparent on physical examination. A barium swallow may reveal the extent of esophageal compression. MNG does not appear to predispose to thyroid carcinoma or to more aggressive carcinoma. For this reason, and because it is not possible to biopsy all nodular lesions, thyroid biopsies should be performed only if malignancy is suspected because of a dominant or enlarging nodule.

TREATMENT

Most nontoxic MNGs can be managed conservatively. T_4 suppression is rarely effective for reducing goiter size and introduces the risk of thyrotoxicosis, particularly if there is underlying autonomy or if it develops during treatment. If levothyroxine is used, it should be started at low doses (50 μg) and advanced gradually while monitoring the TSH level to avoid excessive suppression. Contrast agents and other iodine-containing substances should be avoided because of the risk of inducing the *Jod-Basedow effect*, characterized by enhanced thyroid hormone production by autonomous nodules. Radioiodine is being used with increasing frequency because it often decreases goiter size and may selectively ablate regions of autonomy. Dosage of ^{131}I depends on the size of the goiter and radioiodine uptake but is usually about 3.7 MBq (0.1 mCi) per gram of tissue, corrected for uptake [typical dose, 370 to 1070 Mbq (10 to 29 mCi)]. Repeat treatment may be needed. It is possible to achieve a 40 to 50% reduction in goiter size in most patients. Earlier concerns about radiation-induced thyroid swelling and tracheal compression have diminished as recent studies have shown this complication to be rare. When acute compression occurs, glucocorticoid treatment or surgery may be needed. Radiation-induced hypothyroidism is less common than after treatment for Graves' disease. However, posttreatment autoimmune thyrotoxicosis may occur in up to 5% of patients treated for nontoxic MNG. Surgery remains highly effective but is not without risk, particularly in older patients with underlying cardiopulmonary disease.

TOXIC MULTINODULAR GOITER

The pathogenesis of toxic MNG appears to be similar to that of nontoxic MNG; the major difference is the presence of functional autonomy in toxic MNG. The molecular basis for autonomy in toxic MNG remains unknown. As in nontoxic goiters, many nodules are polyclonal, while others are monoclonal and vary in their clonal origins. Genetic abnormalities known to confer functional autonomy, such as activating TSH-R or $G_{s\alpha}$ mutations (see below), are not usually found in the autonomous regions of toxic MNG goiter.

In addition to features of goiter, the clinical presentation of toxic MNG includes subclinical hyperthyroidism or mild thyrotoxicosis. The patient is usually elderly and may present with

atrial fibrillation or palpitations, tachycardia, nervousness, tremor, or weight loss. Recent exposure to iodine, from contrast dyes or other sources, may precipitate or exacerbate thyrotoxicosis. The TSH level is low. The T_4 level may be normal or minimally increased; T_3 is often elevated to a greater degree than T_4. Thyroid scan shows heterogeneous uptake with multiple regions of increased and decreased uptake; 24-h uptake of radioiodine may not be increased.

TREATMENT

The management of toxic MNG is challenging. Antithyroid drugs, often in combination with beta blockers, can normalize thyroid function and address clinical features of thyrotoxicosis. This treatment, however, often stimulates the growth of the goiter, and, unlike in

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Graves' disease, spontaneous remission does not occur. Radioiodine can be used to treat areas of autonomy, as well as to decrease the mass of the goiter. Usually, however, some degree of autonomy remains, presumably because multiple autonomous regions emerge as soon as others are treated. Nonetheless, a trial of radioiodine should be considered before subjecting patients, many of whom are elderly, to surgery. Surgery provides definitive treatment of underlying thyrotoxicosis as well as goiter. Patients should be rendered euthyroid using antithyroid drugs before operation.

HYPERFUNCTIONING SOLITARY NODULE

A solitary, autonomously functioning thyroid nodule is referred to as *toxic adenoma*. The pathogenesis of this disorder has been unraveled by demonstrating the functional effects of mutations that stimulate the TSH-R signaling pathway. Most patients with solitary hyperfunctioning nodules have acqui