Chapter 135: Disorders of the Thyroid Gland

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Thyroid Hormone Synthesis, Regulation, and Function

An understanding of the functional disorders of the thyroid gland rests firmly upon an appreciation of thyroid physiology. The principles of thyroid hormone synthesis and function have been reviewed elsewhere in this text, but several are so important with regard to diagnosing thyroid gland dysfunction that they will be briefly reiterated in this chapter in the context of identifying and managing clinical thyroid dysfunction (Mazzaferri, 1986a).

Thyroid hormone synthesis

The thyroid gland's primary function is the production of thyroid hormones - thyroxine (T_4) and triiodothyronine (T_3). Pituitary thyrotropin (thyroid-stimulating hormone or TSH) normally controls thyroidal iodide-trapping and regulates each subsequent phase of thyroid hormone formation and release. The gland's iodide-trapping activity does not necessarily parallel thyroid hormone formation, however, because the two can be dissociated by congenital or acquired blocks in hormonogenesis. In other situations thyroid function becomes autonomous of TSH control or is regulated by abnormal simulators, resulting in an elevated thyroidal radioiodine uptake (RAIU) and lavish thyroid hormone synthesis. After its synthesis, thyroid hormone is stored in follicular colloid. This serves as a readily available store of hormone that can cause ongoing thyrotoxicosis long after measures to interrupt its formation have been instituted. This is particularly important following antithyroid drug or radioiodine therapy that may impair hormone synthesis without immediately alleviating the effects of thyrotoxicosis.

Circulating thyroid hormones

In the circulation, thyroid hormones are largely bound to three serum proteins: thyroid-binding globulin (TBG), thyroid-binding prealbumin, and albumin. Congenital or acquired protein-binding abnormalities alter total T_4 and T_3 concentrations measured by clinical assays without changing the patient's thyroid metabolic status (Refetoff, 1989). The relatively small fractions that circulate unbound (0.03% of T_4 and 0.3% of T_3) account for the entire biologic activity of thyroid hormones and adjust to normal when binding proteins are altered. Although free T_4 and T_3 estimates more accurately reflect the unbound fraction of thyroid hormone in the blood, most clinical laboratory methods used to determine free hormone concentrations give misleading results with nonthyroidal illnesses and extreme changes in binding proteins.

Peripheral effects of thyroid hormones

Despite its relatively small contribution to intrathyroidal and circulating thyroid hormone concentrations, triiodothyronine is the main source of thyroid metabolic activity. Thyroxin is the principal source of circulating T_3 but may have little other intrinsic biologic activity, serving

mainly as a substrate for T_3 formation. Most of the T_3 in the circulation and within cells, including the pituitary thyrotrope, is formed by enzymatic (5'-deiodinase) deiodination of T_4. Within the effector cell, T_3 binds to specific nuclear receptors and acts by regulating gene function. Two different c-erbA proto-oncogenes, c-erbAalpha and c-erbAbeta, have been identified as putative thyroid hormone receptor genes (Sap et al, 1986; Weinberger et al, 1986). The c-erbAalpha gene is located on chromosomes 17 (alpha-receptor) (Sheer et al, 1985) and the c-erbAbeta gene is on chromosome 3 (beta-receptor) (Drabkin et al, 1988; Weinberger et al, 1986). The c-erbAbeta gene, which is tightly linked to the syndrome of generalized thyroid hormone resistance, codes for a physiologic thyroid hormone receptor (Usala et al, 1988). Mutations of this gene have been shown to result in several clinical variations of the syndrome of generalized thyroid hormone resistance (Usala and Weintraub, 1991).

Pituitary-thyroid axis in thyroid dysfunction

Pituitary TSH production and secretion are directly regulated by ambient thyroid hormone concentrations and modulated by hypothalamic thyrotropin-releasing hormone (TRH). The interactions of hypothalamic TRH and thyroid hormones on the pituitary are complex, but TRH appears to adjust the setpoint for TSH release by influencing the final synthesis of TSH, thus allowing full expression of its bioactivity (Faglia et al, 1983). This is the most plausible explanation for the paradoxically normal or even elevated serum TSH values sometimes seen in patients with pituitary or hypothalamic hypothyroidism (Faglia et al, 1979). Intracellular pituitary T_3, from local 5' deiodination of T_4, directly regulates TSH synthesis and release by occupying specific T_3-receptor sites in the thyrotrope. In primary hypothyroidism, the loss of T_3 feedback inhibition results in uncontrolled, excessive, and sustained pituitary TSH release. In thyrotoxicosis, high intracellular T_3 concentrations suppress pituitary TSH release, lowering serum TSH concentrations to undetectable levels that will not rise in response to TRH stimulation.

Pituitary TSH secretion is exquisitely sensitive to alterations in serum free T_4 levels. Changes in circulating free T_4 concentrations produce logarithmically proportional and inverse responses in pituitary TSH secretion. Thus, a two-fold reduction in serum free T_4 levels leads to about a hundredfold rise in serum TSH (Spencer and Nicoloff, 1990). The opposite occurs with an elevation in serum free T_4 levels. These large TSH responses are especially important in detecting subclinical (occult) hypothyroidism or toxicosis before changes in serum free thyroid hormone concentrations can be appreciated.

Thyroid Function Tests

The relative biologic importance of T_3 and the effects of nonthyroidal illnesses have made the interpretation of thyroid function tests difficult in many circumstances. This is hampered by the fact that there is no "gold standard" test to gauge tissue responses to circulating thyroid hormones. Clinicians are faced with a difficult diagnostic dilemma when thyroid tests are at variation with the clinical situation or when different tests of thyroid function yield varying results. Recent advances in methods to measure TSH have greatly facilitated the assessment of thyroid function, providing a much-improved means for judging the effects of thyroid hormone

on peripheral tissues. However, some difficulties remain in evaluating thyroid function in critically ill patients.

Thyroid function can be assessed from three perspectives by measuring circulating thyroid hormone levels, serum TSH concentrations, and thyroidal ^{123}I uptake.

Measurements of circulating thyroid hormones

Until recently, a measurement of circulating thyroid hormones, typically a free T_4 estimate, was the initial test ordered in most clinical situations. However, "free T_4" determinations offered by clinical laboratories do not directly measure serum free T_4, but instead are done by "index," "two-step," or "analog" methods that only provide an indirect estimate of free hormone concentration. The free T_4 index methods are mathematically derived from two separate tests - usually a total T_4 and an assessment of TBG such as the T_3 resin uptake test. Two-step methods immunoextract an amount of the serum total T_4 proportional to the free T_4 fraction. Analog methods employ a variety of ^{125}I-labeled T_4 molecules designed to react minimally with TBG, permitting an estimate of serum free T_4. Although all three methods provide comparable free T_4 estimates in patients with normal or near-normal binding proteins, their diagnostic accuracies differ substantially when patients have grossly abnormal binding proteins or severe nonthyroidal illness (Spencer, 1986). This has caused increasingly more diagnostic confusion over the past 20 years as progressively larger numbers of clinical situations have been identified in which one or the other of the free T_4 estimates were found to be misleading (Spencer, 1986; Surks et al, 1990). However, the introduction of new TSH methodology now permits an accurate means of estimating thyroid dysfunction that not only provides a way of validating the accuracy of free hormone estimates, but also furnishes a method that mechanistically can be viewed as an endogenous "free thyroid hormone sensor" (Spencer and Nicoloff, 1990).

Measurement of TSH

Until recently, TSH was not a first-line test of thyroid function. Serum TSH measured by radioimmunoassay (RIA) in the past displayed assay sensitivity limits between 1 and 2 mU/L, levels that were not able to separate euthyroid subjects from thyrotoxic patients. In the mid-1980s immunometric assay (IMA) methodology, or "sandwich" technology using monoclonal antibodies, became commercially available. Sensitivity has been remarkably improved by these assays, which are generally termed "sensitive" TSH assays. However, a TSH IMA should be designated as "sensitive" only if it is able to consistently distinguish between the depressed serum TSH values typical of thyrotoxicosis and euthyroid levels with 99% statistical confidence (Larson et al, 1987; Spencer and Nicoloff, 1990). Most TSH IMAs have an order-of-magnitude greater functional sensitivity compared with RIAs - in the range of 0.1 to 0.2 mU/L - whereas the most recently introduced display a further ten-fold improvement in functional sensitivity with assay limits of 0.01 to 0.02 mU/L (Nicoloff and Spencer, 1990). Nonetheless, it is not the assay's precise lower limit of TSH detection that is most important, but its functional capacity. In other words, regardless of the lower detection limit, the most important characteristics of an IMA is its ability to differentiate thyrotoxic patients from euthyroid ones. The normal range of serum TSH IMA

is about 0.5 to 4.5 mU/L, with a mean value around 1.5 mU/L (Spencer and Nicoloff, 1990). The serum TSH response to TRH stimulation is proportional to the basal TSH IMA, which has largely alleviated the need to perform TRH testing to identify thyrotoxic patients (Rohmer et al, 1990). TSH IMAs have identified large numbers of patients with a new problem, subclinical thyrotoxicosis, in which serum TSH is suppressed while free thyroid hormone estimates are normal (Ross, 1991). This is a particularly important problem among postmenopausal women taking thyroid hormone. TSH suppression in patients with thyroid cancer can also be more accurately gauged by TSH IMA. Although currently somewhat more expensive, TSH IMA has replaced free T_4 estimates as the first line test of thyroid function in patients suspected of having thyrotoxicosis or hypothyroidism (Surks et al, 1990). However, its cost is still high enough that some recommend using free T_4 estimates when screening large numbers of asymptomatic patients for thyrotoxicosis (de los Santos et al, 1989; Klein, 1990). Another problem is the effect of nonthyroidal illness on TSH IMAs. In a recent study (Spencer et al, 1987) of hospitalized adults with severe nonthyroidal illnesses, more than 3% displayed serum TSH IMA values below 0.1 mU/L, while 3.6% had values exceeding 6.8 mU/L. At the extremes, a few had TSH values typical of thyrotoxicosis (< 0.005 mU/L) or primary hypothyroidism (> 20 mU/L). The majority had no apparent reason for these transient changes in serum TSH levels, which returned to normal after the acute illness had abated. Thus, serum TSH IMA is particularly reliable in studying ambulatory, otherwise healthy patients, but its use is substantially more complex in acutely ill patients with serious medical or psychiatric illnesses in whom a diagnostic strategy requires measurement of both TSH IMA and free T_4 estimate.

Measurement of thyroidal radioiodine uptake

The third approach to evaluating thyroid function is to assess the thyroid gland's ability to concentrate iodide. This is done by radioiodine uptake (RAIU) determination, which is a useful guide to thyroid gland activity, provided its limitations are borne in mind. The RAIU does not provide information about a patient's thyroid metabolic status. Thyroidal radioiodine uptake, usually employing ^{123}I and expressed as a percentage of the total administered dose, represents the fraction of iodide taken up from the extrathyroid pool and retained with the gland during a given time interval. Uptake within the first 30 minutes, which requires intravenous tracer dose administration, reflects the gland's iodide-trapping function. Uptake 2 to 6 hours following the dose reflects both iodide-trapping activity and organic binding. Peak uptakes in euthyroid subjects are reached 24 to 48 hours after the radioiodine dose and are influenced by the rate of iodine loss from the gland. The normal range for radioiodine uptake after its oral ingestion is about 4% to 12% at 2 hours, 6% to 15% at 6 hours, and 8% to 30% at 24 hours, but varies among laboratories and in different parts of the country depending upon dietary iodine intake. In hyperthyroid patients, thyroidal RAIU is high but may peak early (12 hours), especially when the thyroid iodine pool is small and turning over rapidly. In hypothyroid patients, thyroidal RAIU is usually low unless an intrathyroidal block in thyroid hormone formation is present, which may result in a high uptake. The RAIU will not identify whether a patient is thyrotoxic because radionuclide uptake may be high or low in this situation depending upon the thyroid gland's functional activity if the iodide pool has not been expanded by iodine-containing drugs or radiocontrast materials. A thyroid scintiscan may be performed with ^{123}I, ^{131}I, or ^{99m}technetium.

However, ^{99m}Tc is only trapped by the gland; it is not incorporated into thyroid hormone and the percentage of its uptake may differ from that of radioiodine.

Hypothyroidism

Prevalence

Hypothyrodism occurs with increasing frequency throughout life, affecting women four to six times more often than men. It occurs at all ages but peaks at 40 to 60 years. In one large series of 400 hypothyroid patients, almost 80% were between 30 and 80 years of age at the time of diagnosis (Watanakunakorn et al, 1965). Only about one in 3500 to 4000 infants born in North America or Europe has hypothyroidism, although its frequency at birth differs around the world (Dussault, 1986a). The prevalence of hypothyroidism gradually increases with age. Depending upon the exact criteria for diagnosis, as many as 3% to 5% of subjects over the age of 65 have clinically overt disease while another 10% to 15% have subclinical hypothyroidism marked only by serum TSH elevations (Bahemuka and Hodkinson, 1975; Lloyd and Goldberg, 1961; Sawain et al, 1985; Tunbridge et al, 1977). Although all patients who develop symptomatic hypothyroidism pass through a subclinical phase, the rate and frequency of progression depend upon the underlying cause (Cooper, 1991). Not all subjects with subclinical hypothyroidism progress to symptomatic thyroid failure and some patients appear to be in a stable compensated state of subclinical failure for years (Rosenthal et al, 1987). The disorder is often not readily apparent, especially in the elderly, and should be especially suspected in patients who are at high risk of developing thyroid failure (see box).

Box. Hypothyroidism: indicators of high-risk

Increased age (women)
Graves' disease
Hashimoto's disease
Other autoimmune diseases
Drugs - lithium, amiodarone, iodine-containing compounds
Post-thyroidectomy (any cause)
Euthyroid goiter (any cause)
Prior head-and-neck therapeutic external radiation
Laryngectomy alone or with external radiation.

Etiology

Hypothyroidism may be caused by, in order of decreasing frequency, thyroid (primary), pituitary (secondary), or hypothalamic (tertiary) failure, and can be caused by thyroid hormone receptor defects (thyroid hormone resistance). The most common causes of subclinical and clinical hypothyroidism are autoimmune thyroiditis, other forms of thyroiditis, iodine deficiency, and previous irradiation to the gland or thyroidectomy for treatment of hyperthyroidism (see box). From a clinical standpoint, it is useful to consider primary thyroid failure as goitrous or

nongoitrous.

Box. Causes of primary (thyroidal) hypothyroidism

Thyroid agenesis
Destruction of the thyroid gland
- Surgical removal
- Therapeutic irradiation (^{131}I or external radiation)
- Autoimmune disease (Hashimoto's thyroiditis)
- Replacement by cancer or other disease
- Postthyroiditis (acute or subacute)
- Postlaryngectomy alone or with external irradiation

Inhibition of thyroid hormone synthesis
- Iodine deficiency
- Excess iodine in susceptible patients
- Antithyroid drugs
- Inherited enzyme defects

Transient
- After surgery or ^{131}I therapy
- Postpartum
- During the course of thyroiditis.

Goitrous hypothyroidism

The most common cause of goitrous hypothyroidism in adults in the USA is autoimmune thyroiditis (Hashimoto's disease) (McConahey, 1972). Other less common causes are drugs (lithium, amiodarone, sulfisoxazole, large doses of iodides, p-aminosalicylic acid, and antithyroid drugs), infiltration of the gland with tumor or inflammatory processes, and familial defects in thyroid hormonogenesis. Endemic goiter is uncommon in the USA but the TSH levels of over 50% of subjects with this disorder may be elevated; many of these people may have no clinical features of thyroid failure (Biel and Maisel, 1985). Familial hypothyroidism is usually caused by inherited defects in hormonogenesis, but rarely can be caused by peripheral thyroid hormone resistance (Usala and Weintraub, 1991).

Nongoitrous hypothyroidism

This is most often caused by primary thyroid disease, but may also be caused by pituitary and hypothalamic disease. The most common causes of nongoitrous hypothyroidism are autoimmune diffuse thyroid atrophy and thyroid destruction from ^{131}I therapy or thyroidectomy for Graves' disease or multinodular goiter. There is good evidence that diffuse thyroid atrophy, often called *idiopathic hypothyroidism*, is the result of an autoimmune process. The frequency of symptomatic hypothyroidism following partial thyroidectomy has been reported to range from 3% to 50% of patients, and this generally occurs in the first year after surgery (Cusick et al, 1987; Manfredi et al, 1988). Subclinical hypothyroidism may be present in as many as two thirds

of patients some years after thyroidectomy. Hypothyroidism is more frequent when a smaller thyroid remnant is left behind, but also is related to ongoing autoimmune thyroid disease, preexisting defects in hormonogenesis, and the presence of thyroid-blocking antibodies. It is essential, however, to assess thyroid function at least 6 to 12 months after thyroid surgery because transient or subclinical hypothyroidism is frequently seen in the first few months following surgery and may remit following regeneration of the thyroid remnant (Cusick et al, 1987). Radioiodine therapy is widely used and frequently complicated by hypothyroidism. During the first year after ^{131}I therapy for Graves' disease, from 15% to 30% of patients develop hypothyroidism depending upon the dose used, and thereafter another 1% to 6% develop it annually over many years. In the United States Public Health Service Thyrotoxicosis Follow-up Study of 1100 patients, ^{131}I treatment with a wide range of doses resulted in a 35% prevalence of hypothyroidism after a mean follow-up of 7.5 years (Becker, 1979). A similar pattern is seen after ^{131}I therapy of multinodular goiter, although the initial incidence and subsequent annual increment are smaller (Verelst et al, 1990).

Pituitary and hypothalamic hypothyroidism

Much less common causes of hypothyroidism are pituitary and hypothalamic disease. Ordinarily pituitary tumors do not cause hypothyroidism unless they are very large, extending out of the sella and causing visual field defects. However, pituitary apoplexy may result in profound hypopituitarism. A recently recognized entity, lymphocytic hypophysitis, may cause hypothyroidism. A variety of hypothalamic disorders, including tumors, infarctions, trauma, and infiltrative diseases can cause hypopituitarism and end-organ failure. None of these disorders is very common, and most have multiple manifestations. It is imperative, however, that primary thyroidal hypothyroidism be distinguished from pituitary and hypothalamic disease.

Laryngectomy and radiotherapy

Of particular concern to the otolaryngologist is the fact that hypothyroidism occurs in a substantial number of patients following laryngectomy for hypopharyngeal squamous cell carcinoma. Following treatment of nodal metastases from squamous cell head and neck carcinoma, the prevalence of occult hypothyroidism is estimated to be as high as 25% following either surgery or radiation therapy alone, and 70% after combinations of the two (Biel and Maisel, 1985). Thyroid abnormalities usually begin appearing within the first 4 months after surgery, but may not become clinically apparent for a year (deJong et al, 1982; Posner et al, 1984). In view of the extended survival of patients treated with surgery and irradiation for head and neck squamous cell carcinomas, all patients receiving irradiation to the neck - particularly those undergoing neck dissections or total laryngectomies - should undergo routine thyroid function studies every 3 to 6 months for the first year after treatment, and annually thereafter.

Congenital hypothyroidism

Children who develop thyroid failure in utero, a disorder termed *cretinism,* experience severe mental and growth retardation. It may be either endemic, occurring in certain geographic

areas with low iodine, or sporadic, usually in association with thyroid dysgenesis or agenesis. Congenital hypothyroidism may be transient or permanent.

Etiology

The most frequent causes of transient hypothyroidism in North America are iatrogenic, either caused by antithyroid drugs given to pregnant women with Graves' disease, or by fetal goiter and thyroid failure caused by excessive maternal intake of iodine. Permanent congenital hypothyroidism may be caused by autoimmune thyroid disease, immunoglobulins that block thyroid stimulation, and others that block thyroid growth. Thyroid scans have permitted a simple classification of thyroid dysgenesis: athyreotic when no tissue is demonstrable, hypoplastic dysgenesis when a small remnant is detectable in the normal anatomic region, and ectopic thyroid when a small or relatively large amount of tissue is detectable within the region from the foramen cecum to the anterior mediastinum (Dussault, 1986b).

Clinical features

It is extremely important to identify these infants at the time of birth because the neurologic sequelae of hypothyroidism may be reversed within the first 6 months (Committee of the American Thyroid Association, 1976). Intellectual development can be normal in 85% of infants if a euthyroid state is obtained by 3 months of age (Klein et al, 1972), but only about one third of the infants are diagnosed on the basis of clinical features alone by this age (Dussault, 1986a). Affected children may have severe constipation, and display poor feeding and lethargy. The baby typically has a protuberant abdomen and may experience respiratory difficulty. The infant's face often appears puffy, with yellowish skin and a flat nose. The tongue is enlarged and protruding from an open mouth, fontanelles and sutures may be widened, and the child's cry is hoarse. Endemic cretinism is characterized by a goiter whereas the sporadic type that is caused by thyroid agenesis or dysgenesis typically has no palpable thyroid. Delayed growth, mental retardation, and sensorineural hearing loss become evident if the condition is untreated. Because the diagnosis is not often readily apparent at birth, and because delayed treatment results in irreversible mental damage, routine screening for hypothyroidism is now mandatory at the time of birth in the USA and in many other countries around the world (Dussault, 1986a).

Hearing loss

Endemic cretins often have severe bilateral sensorineural hearing loss whereas sporadic cretins may have a conductive, mixed, or sensorineural hearing loss. Pendred's syndrome, an autosomal recessive disorder, is characterized by goiter due to an inborn defect in thyroid hormone synthesis, an abnormal perchlorate discharge test, and congenital sensorineural hearing loss. Patients usually have only modest thyroid enlargement and are clinically euthyroid, but have severe bilateral sensorineural deafness, especially in the high frequencies (Fraser, 1965; Illum et al, 1972). Recruitment is present, indicating a cochlear lesion site.

Juvenile hypothyroidism

Etiology

Thyroid failure occurring after infancy and before puberty is usually referred to as *juvenile hypothyroidism*. Most of these patients have late onset congenital disease, including defects in hormonogenesis, thyroid hormone resistance, or developmental defects of the thyroid that eventually give way to thyroid failure. Others have autoimmune thyroid disease, endemic or drug-induced goiter.

Clinical features

Hypothyroidism developing after 3 years of age is not associated with mental retardation (Fisher, 1986). The disorder's main characteristics are delayed growth and sexual development. Bone age is delayed and diaphyseal bone growth and epiphyseal growth and maturation are reduced. Although delayed puberty is the rule, a few children with juvenile hypothyroidism develop precocious puberty. Galactorrhea and precocious menarche may develop in girls and testicular enlargement in boys. The hypothalamic-pituitary function may be abnormal, and patients may develop pituitary enlargement with increased TSH and prolactin levels because of chronic pituitary stimulation. Children with hypothyroidism may also develop epiphyseal dysgenesis and muscular hypertrophy. Although mental retardation is not present in these children, they typically have difficulty with their studies at school until the diagnosis is made and therapy begun.

Adult hypothyroidism

Clinical features

The patient with fully developed hypothyroidism has mental sluggishness, lethargy, somnolence, hoarseness, bilateral deafness, dry thick skin, constipation, severe cold intolerance, and a stiff ataxic gait (Bhatia et al, 1977). However, the disease is often impossible to appreciate in its early stages. One should attempt to diagnose the disorder before it advances too far; this can be achieved by screening high-risk patients. Nonetheless, some patients have no apparent risk factors for the disease, which may be impossible to recognize, especially in the absence of goiter, until it is well established.

Hypothyroidism affects virtually every organ system. Vague complaints typically originate from multiple organ systems, and accordingly hypothyroidism is frequently mistaken for primary disease of other systems. Because of the advanced age of many patients with the disorder, its manifestations are often attributed to the aging process. The dry, thick skin, thinning hair, fatigue, cold intolerance, and weight gain are typically not seen as being manifestations of hypothyroidism. The box below lists the most prominent symptoms in a series of 400 patients with hypothyroidism (Watanakunakorn et al, 1965). Neck examination may reveal a goiter - a major diagnostic clue - if the patient has Hashimoto's disease or another form of goitrous

hypothyroidism. A nonpalpable thyroid typically results in delayed diagnosis.

Box. Symptoms and signs of hypothyroidism

General symptoms

Dry thick skin and/or hair
Fatigue, weakness, lethargy
Edema - puffy hands, face, eyes
Pallor with malar flush
Cold intolerance
Weight gain
Alopecia
Loss of sweating

ENT symptoms

Enlarged tongue
Deafness, vertigo, tinnitus
Hoarseness
Middle ear effusion
Blurred vision

Musculoskeletal system

Arthritis, stiff joints, backache
Muscle cramps, stiffness, weakness

Genitourinary system

Menstrual disorders
Polyuria and nocturia

Central nervous system

Mental and physical slowness
Sleepiness, insomnia
Headache, dizziness, nervousness
Psychologic symptoms
Paresthesias
Delayed reflexes

Gastrointestinal system

Constipation
Anorexia, nausea, vomiting
Dysphagia, bloating, indigestion
Ascites

Cardiovascular system

Bradycardia
Hypertension
Angina
Pericardial effusion
Peripheral vascular insufficiency

Pulmonary system

Short of breath
Pleural effusion.

Hearing loss

Other features of hypothyroidism of particular concern to the otolaryngologist are hearing loss and vertigo. The hearing loss may be conductive, mixed, or sensorineural. It occurs more frequently and with greater severity in children with congenital hypothyroidism than in older patients with acquired hypothyroidism (Nilsson et al, 1964). A progressive, mixed hearing loss is reported in half to nearly all children with endemic cretinism (Meyerhoff, 1979) but only about 30% to 40% of adults with myxedema have bilateral sensorineural hearing loss. Children with cretinism may have anomalous ossicles involving any of the bones in the middle ear, and may also have atrophy of the organ of Corti (Meyerhoff, 1976). In children with cretinism, the tectorial membrane is the first structure to change, followed by degeneration of hair cells at the basal turn of the cochlea. Patients with acquired hypothyroidism who have hearing loss may display similar abnormalities. A sensorineural hearing loss that may or may not be reversible is found in patients with sporadic, nonendemic cretinism. Some report that patients with bilaterally symmetric flat neurosensory hearing loss improve with replacement therapy, whereas others find no improvement in hearing with thyroid hormone therapy. In one study of 72 Native Americans with varying degrees of hypothyroidism, 43% had hearing loss that was mild to moderate in all patients except for two patients with cretinism (Bhatia et al, 1977). Conductive hearing loss was found in about 20% of 31 patients with hearing loss whereas the others had sensorineural losses typical of cochlear lesions. None of the six patients in this series on whom data were available improved as a result of replacement therapy. Some adults with severe myxedema develop bilaterally symmetric and progressive sensorineural hearing loss that worsens at the severity of hypothyroidism increases. Conductive losses may also occur as a result of edema of the eustachian tube mucosa. Only a few adults and almost no children with cretinism who have well-

established hearing loss improve with thyroid hormone therapy.

Vertigo

As many as two thirds of hypothyroidism patients experience vertigo. A few patients with Ménière's disease are thought to have hypothyroidism. In one study, about 25% of hypothyroid patients had dizziness (Bhatia et al, 1977). In this study, vertigo attacks were usually mild, brief, and were not associated with ENG changes or concurrent hearing loss.

Hoarseness

Hypothyroidism causes a gradual and progressive hoarseness because of mucopolysaccharide infiltration of the vocal cords. Some have suggested that, in addition to infiltration with mucopolysaccharide, the hoarseness and decreased voice clarity may be caused by tissue edema in either the ambiguous nucleus or the cricothyroid muscles. The presence of bilaterally edematous, mobile vocal cords should raise the suspicion of hypothyroidism. Hoarseness almost invariably dissipates with thyroid hormone replacement, and requires no other therapy to the cords.

Surgery on the hypothyroid patient

Certain clinical features of hypothyroidism are particularly important to the surgeon. Although the prevalence of coronary artery disease is quite high in patients with hypothyroidism, the diagnosis is easily overlooked because patients often have only a few symptoms because of their low metabolic levels or their failure to communicate their symptoms clearly (Bhatia et al, 1977). Pericardial effusions are often apparent but only rarely cause tamponade. In sharp contrast, pulmonary dysfunction caused by hypothyroidism may be a major problem, particularly during the postoperative period. Hypothyroid patients often display upper airway obstruction caused by oropharyngeal muscle dysfunction and tissue infiltration with mucopolysaccharide, and may also develop central sleep apnea because of the direct effect of thyroid hormone deprivation on the brain. There is resistance to the respiratory stimulatory effects of hypoxia and hypercarbia, a manifestation that can lead to severe postoperative hypoxia, with difficulty weaning the patients from a ventilator. Severely hypothyroid patients also have a von Willebrand-like bleeding disorder, respond poorly to stress (by developing hypothermia and hypotension), and will not develop tachycardia in response to infection or hypotension. Shock responds poorly to vasoconstrictors.

Surgery done inadvertently on a patient with unrecognized severe hypothyroidism may lead to serious postoperative complications. Nonetheless, in recent years several studies have shown that life-saving surgery should not be postponed simply to replace thyroid hormone (Becker, 1985). A retrospective case-controlled study comparing 59 hypothyroid patients and 59 controls concluded that it is safe to send patients with mild to moderate hypothyroidism to surgery without preoperative thyroid hormone therapy (Weinberg et al, 1983). This study has been criticized for generalizing beyond the limits of a small sample size (Becker, 1985). A

second retrospective case-controlled study of 40 hypothyroid patients concluded that this group had significantly higher frequencies of perioperative hypotension, gastrointestinal hypomotility, and central nervous system disturbances compared with controls (Ladenson et al, 1984). More serious complications were encountered among 17 patients undergoing cardiac surgery, including impaired hemostasis, delayed recovery from anesthesia, marked friability of the aortic root, and a significantly higher prevalence of perioperative heart failure among hypothyroid patients as compared with controls. However, none of these complications had serious or lasting sequelae. The authors concluded that complications in hypothyroid patients can occur and should be anticipated, but that necessary surgery should not be postponed simply to replete thyroid hormone. This is not true for patients with severe myxedema who should be given preoperative thyroid hormone except in the most urgent of surgical emergencies or in cases of uncontrollable ischemic heart disease.

Laboratory diagnosis

Serum TSH in primary hypothyroidism

The laboratory hallmark of primary hypothyroidism is an elevated serum TSH concentration, which is the single most sensitive test to establish the diagnosis. The TSH will usually rise above 10 mU/L and is often much higher. An elevated TSH precedes, often by many years, a fall in free T_4 and clinical signs and symptoms of hypothyroidism (Rosenthal et al, 1987; Toft, 1988). This is the laboratory picture of occult hypothyroidism, a disorder with few or no clinical findings that may or may not progress to overt hypothyroidism (Cooper, 1991). The free T_4 estimate falls below normal limits as the disorder progresses to over hypothyroidism. Triiodothyronine is of little value in establishing the diagnosis because it is commonly lowered by nonthyroidal disease, and may be normal or even high in occult hypothyroidism.

Pituitary and hypothalamic hypothyroidism

Secondary and tertiary hypothyroidism are characterized by low T_4 and depressed TSH levels, although at times the serum TSH may be inappropriately high in hypothalamic hypothyroidism (Faglia et al, 1979). Differentiation of these two conditions is based on a TRH stimulation test, one of the few remaining indications for this test (Table 135-1).

Table 135-1. Thyroid function tests in hypothyroidism and other low T_4 syndromes

Diagnosis	**T_4**	**T_3RU**	**FT4I**	**T_3**	**TSH**	**TRH**

Hypothyroid

Thyroidal (Primary)

Overt hypothyroidism

Low

Low

Low

Low

High

Excessive

Occult hypothyroidism

NL

NL

NL

NL*

High

Excessive

Pituitary (secondary)

Low

Low

Low

Low

Low

Blunted

Hypothalamic (tertiary)

Low

Low

Low

Low

Low+

NL/high/delayed

Euthyroid

Low TBG

Low

High

NL

Low

NL

Normal

Nonthyroidal illness

Low T_3 syndrome (mild NTI)

NL

NL

	NL			
		Low		
			NL	
				Normal
Severe NTI				
	Low			
		Low/NL		
			Low	
				Low
				NL
				Normal/delayed

NL, Normal level.
* May be high in goitrous hypothyroidism.
+ May be inappropriately high (see text).

Nonthyroidal illness

Up to 70% of hospitalized patients and many ambulatory patients with a variety of mild nonthyroidal illnesses have low serum T_3 concentrations but the serum TSH is usually normal (Klein, 1990; Simons et al, 1990). Critically ill patients, however, may have very low serum T_4 concentrations and free T_4 estimates, sometimes with TSH levels above 20 mU/L (Spencer et al, 1987). Tumor necrosis factor has been identified as a putative mediator of the sick euthyroid syndrome in man (van der poll et al, 1990). Serum T_4 concentrations below 1.0 microg/dL in a critically ill patient with nonthyroidal disease is a poor prognostic indicator for survival, and as many as 80% who have this laboratory abnormality die (Silberman et al, 1988). These laboratory features are summarized in Table 135-1 (Mazzaferri, 1986a). An RAIU is not needed and should not be done to diagnose hypothyroidism. It can, however, with a perchlorate discharge test, help to identify uncommon defects in thyroid hormone synthesis. In addition, a radioiodine scan and thyroid ultrasonography will reveal diminished uptake or absent thyroid mass in congenital thyroid dysgenesis and iatrogenic hypothyroidism, although the latter is almost invariably evident from the history.

Screening for hypothyroidism

Because the diagnosis is often missed until over hypothyroidism with serious manifestations develops, particularly in the aged, some have recommended that all elderly patients should be screened for hypothyroidism. Although this has some merit, most studies show that routine screening of all elderly patients, especially those hospitalized with nonthyroidal illness, results in a relatively low number of true-positive tests and a large number of false-positive tests (Eggertsen et al, 1988; Finucane et al, 1989; Small et al, 1990). One large study of critically ill hospitalized patients routinely screened with TSH IMA found that almost 4% had elevated TSH values that could not be attributed to hypothyroidism (Spencer et al, 1987). The US Public Health Service (Guide to Preventive Services, 1989) recently recommended that

routine screening thyroid function tests should not be done. Instead, the report suggested that it might be prudent to screen elderly females, over the age of 65 years, and patients with unexplained cardiovascular, neurologic, mental, gastrointestinal, or rheumatic complaints. Most agree that the best screening test for hypothyroidism in ambulatory patients is a TSH IMA alone, whereas for hospitalized patients a combination of TSH IMA and a test to estimate free T_4 are necessary (de los Santos et al, 1989; Klein, 1990; Spencer and Nicoloff, 1990).

Treatment

Thyroid hormone administration

Levothyroxine, administered orally, is the treatment of choice for hypothyroidism (Mazzaferri, 1986b). The average daily dose for adults is 112 microg with a range of 75 to 150 microg (Fish et al, 1987). Elderly adults require 10% to 20% less hormone, and the initial doses should be quite small. The usual starting dose is 12.5 microg daily, increasing by about 12.5 microg every 2 weeks until the full replacement dose is reached, which will usually avoid cardiac side effects (Tibaldi and Barzel, 1985). Dosage for children varies according to age. The goal is to return the serum TSH IMA to normal in patients with primary hypothyroidism, whereas a normal FTI alone is the target in secondary and tertiary hypothyroidism (Watts, 1989). In about 20% of hypothyroid patients being treated with L-thyroxine, there is a discrepancy in the laboratory tests: serum TSH concentration is normal whereas the free T_4 is slightly high (Spencer and Nicoloff, 1990). In this case, the TSH most accurately reflects the patient's euthyroid metabolic status. It has been postulated that this discrepancy arises because L-thyroxine contains no T_3, which is normally secreted by the thyroid in small amounts (Spencer and Nicoloff, 1990). It requires about 4 to 8 weeks before the TSH response to L-thyroxine therapy is complete, and laboratory testing should not be done before this time.

Complications of levothyroxine therapy

Commonly used replacement doses of levothyroxin have been recognized in recent years to cause occult thyrotoxicosis (Banovac et al, 1989; Ross, 1991). Excessive levothyroxine treatment in children can lead to accelerated bone maturation, premature craniosynostosis, increased intracranial pressure, and delayed neurologic development (Dussault, 1986b). Adults can develop accelerated bone loss and are at risk for pathologic fractures even if they are not clinically thyrotoxic (Stall et al, 1990). In addition, the elderly patient may develop serious cardiac complications, including cardiac arrhythmias, heart failure, angina, and myocardial infarction if the dose of thyroid hormone is too large (Mazzaferri, 1986b).

Treatment for occult hypothyroidism

A dilemma arising with routine screening is whether occult hypothyroidism should be treated. Some reported subtle improvement in fatigue, cold intolerance, and constipation (Cooper et al, 1984). However, this must be balanced against the expectations of disease progression in patients with occult hypothyroidism. Those who have elevated TSH concentrations following

thyroid ablation with ^{131}I or subtotal thyroidectomy are very likely to develop overt hypothyroidism and probably should be treated. However, patients with autoimmune thyroiditis are not likely to develop hypothyroidism unless the serum TSH is greater than 20 mU/L or antithyroid antibodies are positive in high titers (> 1,600) (Rosenthal et al, 1987).

Myxedema coma

Clinical features

This thyroid emergency is a late manifestation of hypothyroidism characterized by coma or pre-coma with severe clinical manifestations of myxedema (Mazzaferri, 1986a). There often is an underlying infection or other precipitating cause of the myxedema coma. Patients characteristically have extreme hypothermia, bradycardia, hyponatremia, hypoventilation with respiratory acidosis and hypoxia, and pleural and pericardial effusions. Focal or generalized seizures typically precede the coma.

Therapy

Treatment is with large doses of intravenous levothyroxine and hydrocortisone. Although treatment is usually instituted without laboratory confirmation, the clinical diagnosis should be certain before large doses of intravenous levothyroxine are given. Supportive care includes intubation and assisted ventilation, cautious rewarming, support of blood pressure, and treatment of infection. Mortality rates are around 50% and depend upon the severity of superimposed illnesses and underlying coronary heart disease.

Thyrotoxicosis

Classification and etiology

Although the terms *thyrotoxicosis* and *hyperthyroidism* are often used interchangeably, such misuse of terms ignores the important differences between the two conditions that have crucial diagnostic implications. Thyrotoxicosis is the clinical syndrome that results from excessive levels of free thyroid hormone in the blood (Mazzaferri, 1983). The term describes the condition induced by excessive levels of thyroid hormone and implies a pathologic state. The classification of thyrotoxicosis used below, proposed by Dr. Sidney Ingbar (1986), distinguishes between those causes of thyrotoxicosis that are associated with true hyperthyroidism in which there is an increase in the secretion of thyroid hormones, and those that are not. Hyperthyroidism simply indicates that the thyroid gland is overactive. In disorders characterized by hyperthyroidism, whether due to hypersecretion of TSH, an abnormal stimulator, or a functionally autonomous lesion of the thyroid gland itself, sustained thyroid hyperfunction is evident in an elevated RAIU value. In those varieties of thyrotoxicosis that are not the result of hyperthyroidism, the RAIU is low, reflecting appropriate inhibition of TSH secretion by thyroid hormone excess. Hence the TSH and RAIU are the two major laboratory measures for differentiating the two categories of thyrotoxicosis from one another.

Prevalence

The prevalence of thyrotoxicosis is difficult to determine with certainty; however, a study from the Whickham Survey suggests that thyrotoxicosis affected about 2% of the women in the population, with an estimated incidence of around 3 cases per 1000 women annually (Tunbridge et al, 1977). These figures are about ten times higher than some estimates (Eggertsen et al, 1988), but at least one other report from the USA disclosed a similarly high incidence of thyrotoxicosis (dos Remedios et al, 1980). The prevalence of thyrotoxicosis is about ten times more common in women than in men, and the mean age at diagnosis is about 45 years (Mazzaferri, 1986b).

Box. Unusual or misleading manifestations of thyrotoxicosis

Neuromuscular
- Periodic paralysis (G)*
- Myasthenia gravis (G)
- Bulbar paralysis
- Severe proximal myopathy

Cutaneous
- Spider angiomas
- Pruritus or urticaria
- Vitiligo (G)
- Acropathy (G)

Biochemical
- Hypokalemia
- Hypercalcemia
- Elevated alkaline phosphatase
- Neutropenia

Cardiac
- Complete heart block
- Heart failure
- Atrial fibrillation
- Thromboemboli

Thrombocytopenia (ITP) (G)
Weight gain
Unilateral exophthalmos (G)
Gynecomastia
Osteoporosis.

* (G), Unique to Graves' disease.

Clinical features

Stages of thyrotoxicosis include occult and over thyrotoxicosis and thyroid crisis or storm. Symptoms and signs in part are dependent upon the disorder causing the thyrotoxicosis. In

addition, manifestations in elderly thyrotoxic patients may be substantially different from those in younger patients (Table 135-2) (Nordyke et al, 1988). The typical young thyrotoxic patient with well-established disease presents with multiple symptoms and signs, including weight loss despite a good appetite, heat intolerance, severe fatigue, and a flushed, hyperkinetic appearance with a goiter, eye signs, rapid pulse, and a hyperdynamic precordium, tremor, and muscle weakness. Thyrotoxicosis in the elderly is more likely to present with fewer symptoms, especially unexplained weight loss, heart failure, and muscle weakness, which are often attributed to primary cardiac disease or malignancy (Tibaldi et al, 1986). A number of unusual or misleading manifestations of thyrotoxicosis are listed in the box.

Diagnosis

A serum TSH IMA suppressed below the detection limits of the assay is the most sensitive test for establishing the diagnosis. Since TSH IMAs have become widely available, TRH testing is almost never necessary. In most cases both the free T_4 and T_3 estimates are high; occasionally only T_3 is elevated, termed *T_3 toxicosis.* Recently, several patients have been described in whom only the free T_3 concentration was elevated, a condition which was termed *free T_3 toxicosis* (Bitton and Wexler, 1990).

Euthyroid Hyperthyroxinemia

Perhaps the confusion surrounding the diagnosis of thyrotoxicosis has arisen mainly from the many nonthyroidal disorders that can cause elevation of the total or free T_4; this condition is termed *euthyroid hyperthyroxinemia* (Borst and Burman, 1983; Gavin, 1988). Many acute medical conditions, including symptomatic hyponatremia (Cogan and Abramov, 1986), hyperemesis gravidarum (Chin and Lao, 1988), drugs (Cavalieri et al, 1981), acute psychiatric illness (Morley and Shafer, 1982), and alterations in thyroid-binding proteins (Refetoff, 1989) can cause hyperthyroxinemia. A familial disorder called *euthyroid dysalbuminemic hyperthyroxinemia* is characterized by an abnormal binding protein that raises both total T_4 and free T_4 estimates, which can be confused with thyrotoxicosis (Ruiz et al, 1982). Until now, these disorders were often very difficult to distinguish from thyrotoxicosis. With some exceptions, most notably hyperemesis gravidarum and acute nonthyroidal illness, this distinction now can be made readily with the TSH IMA.

Etiology

The causes of thyrotoxicosis are listed in Table 135-3 (Ingbar, 1986). Each is a distinct pathologic entity with different natural history and treatment. In general, disorders associated with hyperthyroidism, except for those characterized by TSH excess, require antithyroid therapy. Disorders not associated with hyperthyroidism require measures that block the effects of thyroid hormone (beta-blockers) or therapy directed against the cause of hormone excess (anti-tumor therapy).

Graves' Disease

Prevalence and etiology

The most common cause of thyrotoxicosis associated with hyperthyroidism is Graves' disease, an autoimmune disorder in which antibodies (thyroid-stimulating immunoglobulins or TSI) stimulate thyroidal TSH receptors (DeGroot and Quintans, 1989; Yamaguchi et al, 1990). This disorder, which typically affects women five or ten times more frequently than men, peaks in the third and fourth decades.

Clinical features

Graves' disease is characterized by the triad of diffuse toxic goiter, infiltrative ophthalmopathy, and infiltrative dermopathy. Toxic goiter may appear alone, or may be seen before, during, or after the patient develops ophthalmopathy. Infiltrative ophthalmopathy ranges from mild periorbital puffiness to severe extraocular muscle dysfunction with proptosis, corneal ulceration, and optic neuritis with blindness. Infiltrative dermopathy usually occurs on the lower extremities in patients with ophthalmopathy and can occasionally lead to severe disfigurement, nerve entrapment, or vascular compromise (Mazzaferri, 1986a). Graves' disease undergoes spontaneous remissions and relapses that are related to the underlying immune disorder. In addition to TSI, TSH-binding inhibitor immunoglobulins (TBII) and thyroid-stimulation blocking immunoglobulins (TSBI) also can be synthesized in Graves' disease, leading to a euthyroid state or spontaneous hypothyroidism (Inomata et al, 1988; Tamai et al, 1987). Although the disease undergoes spontaneous remission, prolonged antithyroid medication, ^{131}I, or surgery are usually necessary to control the thyrotoxicosis. The thyroid gland displays the unique histologic features of Graves' disease, but some glands show typical characteristics of Hashimoto's thyroiditis, sometimes called *Hashitoxicosis* (Fonseca et al, 1988), underscoring the close relationship between the two disorders. Hashimoto's disease causing thyrotoxicosis is only recognized when discovered at surgery. Hashimoto's disease may cause thyrotoxicosis with a high RAIU and infiltrative ophthalmopathy, making it indistinguishable on clinical grounds from Graves' disease. In silent thyroiditis, which is probably a variant of Hashimoto's disease, thyrotoxicosis is self-limited and associated with a depressed RAIU (Mizukami et al, 1988).

Thyroid cancer and Graves' disease

Well-differentiated thyroid cancer is about 2.5 times more prevalent in patients with Graves' disease as compared with the general population (Mazzaferri, 1990). Well-differentiated thyroid cancers contain functional TSH receptors that stimulate both the growth and iodine-trapping function of thyroid cancer. TSI of Graves' disease shares many functional similarities with TSH, and has been shown in vitro to stimulate cyclic AMP formation and DNA replication in thyroid cancer cell lines. Thyroid cancers in patients with Graves' disease are larger, more aggressive tumors, with more local invasion and greater numbers of regional lymph node metastases than those occurring in patients without Graves' disease (Belfiore et al, 1990). When a palpable, hypofunctional thyroid nodule is found in a patient with Graves' disease, it has about

a 45% probability of being thyroid cancer (Belfiore et al, 1990). The practical conclusion is that a palpable hypofunctional nodule in a diffuse toxic goiter of Graves' disease should be highly suspected of being a cancer, and when thyroid cancer is found it should be treated aggressively (Mazzaferri, 1990).

Medical therapy

Medical therapy consists of drugs and ^{131}I. Thionamides, propylthiouracil (PTU) and methimazole (Tapazole), are the mainstay of drug therapy in the USA. Methimazole is more potent than propylthiouracil. The usual daily dose is 300 mg for propylthiouracil and 30 mg for methimazole in divided doses. Both block hormone formation by serving as substrates for thyroid peroxidase, thus diverting oxidized iodide away from thyroglobulin (Cooper, 1984). PTU also decreases peripheral T_4 to T_3 conversion, and thus may be more appropriate in emergencies such as thyroid storm. Neither drug has an effect on the release of thyroid hormones already formed and stored in gland; the onset of action of these drugs is thus relatively slow (weeks), depending upon the severity of disease, size of goiter, and drug dosage and timing. These drugs are available only for oral use, and are readily absorbed from the gastrointestinal tract, reaching peak serum and intrathyroidal levels within 1 to 2 hours of their administration. Although they may be given once daily, administration every 8 hours is more effective in severely thyrotoxic patients. Methimazole is more suited for once-daily therapy because it is more potent and has a longer half-life.

PTU may have a slight advantage over methimazole during pregnancy because it is more tightly protein-bound, crosses the placenta more slowly, and is not excreted in mother's milk in substantial amounts. Most thyroidologists in the USA do not choose thionamides as first-line therapy for Graves' disease (Solomon et al, 1990), but instead use them mainly in younger patients, pregnant women, and any severely thyrotoxic patient before surgery or ^{131}I therapy. These drugs probably do not influence the long-term course of the disease, and relapse is common after therapy is disontinued (Cooper, 1984). Long-term remission depends upon the duration of drug therapy and the dietary iodine content. After treatment for 1 year, permanent remission rates are about 40% in the USA and are higher in countries with lower iodine intake (Solomon et al, 1987). After treatment for 18 months, permanent remission rates as high as 60% are reported (Allannic et al, 1990), but 5-year overall cumulative recurrence of thyrotoxicosis is as high as 60% (DeGroot and Quitans, 1989).

Agranulocytosis, the most feared toxic condition, occurs in fewer than 0.5% of patients and is due to antineutrophil antibodies (Cooper, 1984; International Agranulocytosis and Aplastic Anaemia Study, 1988). It has an abrupt onset and is occasionally fatal, but is quick to reverse with cessation of the drug. Graves' disease patients are sometimes mildly neutropenic, which should not be confused with agranulocytosis and is not a reason to stop therapy. Regular blood counts during thionamide therapy have usually not been recommended because the agranulocytosis occurs so abruptly (Cooper, 1984). However, a recent large study from Japan challenges this concept, suggesting that routine blood counts will predict the onset of agranulocytosis before it is clinically apparent (Tajiri et al, 1991). Agranulocytosis generally

occurs early in the first few weeks or months of treatment, and patients over the age of 40 are more susceptible. A dosage of methimazole of over 30 mg per day is more often associated with agranulocytosis, whereas dosage is not as important with PTU, making the agranulocytosis associated with PTU more unpredictable.

Hepatitis occurs with PTU and is a rare, sometimes fatal complication. In contrast, benign cholestatic jaundice usually occurs with methimazole. Other toxicities include skin rash, fever, arthralgia, myalgia, neuropathy, thrombocytopenia, vasculitis, jaundice, alopecia, lymphadenopathy, edema, toxic psychosis, SLE, and hypocalcemia. Generally, if toxicity occurs with one drug, the other should not be used.

Beta-blockers comprise the other major class of drugs used to treat thyrotoxicosis. These drugs relieve the sympathetic overdrive symptoms of thyrotoxicosis (tachycardia, hyperdynamic cardiac activity) but are contraindicated in patients with thyrotoxic cardiomyopathy and heart failure. They also improve thyrotoxic myopathy and the hypercalcemia of thyrotoxicosis. In addition, they often relieve heat intolerance. Propranolol decreases T_4 to T_3 conversion at high doses whereas most other beta-blockers do not. These drugs serve as adjunctive therapy in most situations but are sometimes used alone in preparing thyrotoxic patients for surgery.

Drugs with minor roles include iodide (SSKI, Lugol's solution), which inhibits both organification and thyroid hormone release, thus causing an abrupt drop in serum T_3 and T_4. Iodides are most useful in thyroid storm. They should not be used in the routine treatment of goiter because iodides can cause thyrotoxicosis in patients with euthyroid Graves' disease. Iodides cross the placenta and cause large goiter, airway obstruction, and fetal death if used for prolonged periods during pregnancy. Lithium has been used to treat thyrotoxicosis. It is similar but not superior to iodide or thionamides and may cause hypothyrodism. Dexamethasone in large doses (2 mg/6 hr) inhibits thyroid hormone secretion and peripheral conversion of T_4 to T_3, and is useful in emergencies such as thyroid storm. Radiographic contrast agents (iopdate (Oragrafin), iopanoic acid (Telepaque)) bloc T_4 to T_3 conversion both in pituitary and peripheral tissues. They are useful if thionamides cannot be used.

Radioiodine therapy

Ablative thyroid gland therapy with ^{131}I is usually effective in 2 to 4 months. It causes transient exacerbation of thyrotoxicosis for the first 1 to 2 weeks because of radiation-induced thyroiditis, which is a major problem in seriously thyrotoxic or elderly patients. Radioiodine therapy commonly leads to hypothyroidism. This is not dose dependent and is not avoidable with low-dose ^{131}I therapy. In the United States Public Health Service Thyrotoxicosis Follow-up Study of 11,000 patients, ^{131}I treatment with a wide range of doses resulted in a 59% prevalence of euthyroidism and 6% recurrent hyperthyroidism after a mean follow-up of 7.5 years (Becker, 1979). Most hypothyroidism occurs during the first posttherapy year, but can occur decades after treatment and is discussed in the earlier section on hypothyroidism. Radioiodine is absolutely contraindicated in pregnancy, but does not pose an especially great hazard to the ovaries of women in their childbearing years. The radiation dose to the ovaries is about equal to two barium

enemas. Radioiodine is the treatment of choice in the USA for most adults, and for children on whom thionamide therapy is unsuccessful or on those who cannot or will not take thionamides (Solomon et al, 1990).

Surgery

Subtotal thyroidectomy is effective and rapid therapy for thyrotoxic Graves' disease. It causes less hypothyroidism than ^{131}I therapy, but hypothyroidism is not unavoidable (Manfredi et al, 1988). Postsurgical hypothyroidism is often a function of the underlying disease, and may occur even when a generous amount of thyroid tissue is left behind (see the earlier section on hypothyroidism). Some prefer surgery as first-line therapy for pregnant women and children. The thyrotoxicosis should be controlled preoperatively when possible with thionamides, but beta-blockers alone have been used successfully to prepare patients for surgery. Complications, mainly permanent hypoparathyroidism and recurrent laryngeal nerve damage, are usually negligible and generally depend upon the surgeon's skill and experience (Tovi et al, 1989). In one large study of 364 patients, complications were not statistically different when the type of disease or extent of surgery were used as discriminating factors, but significantly more complications occurred when two surgical procedures were required as compared with one (Manfredi et al, 1989). Transient hypocalcemia is common in the first few days after surgery, but is usually attributable to a variant of the "hungry bone" syndrome seen after parathyroidectomy, which is the result of rapid calcium deposition into bones that have lost calcium. Thyroid storm can occur, particularly when preoperative control of thyrotoxicosis is inadequate.

Toxic Adenoma

Prevalence

Thyrotoxicosis may be caused by an autonomously hyperfunctioning thyroid nodule ("hot" nodule), but not all such nodules necessarily cause thyrotoxicosis (Hamberger, 1987). Toxic adenomas, particularly smaller hot nodules, are about four times more common in women than men. Larger nodules (> 2.5-3.0 cm) are more likely to cause thyrotoxicosis.

Clinical features

The thyrotoxicosis is typically mild, unrelenting, and commonly caused by triiodothyronine alone; it is termed *T_3 toxicosis.* In some patients the only abnormality revealed by laboratory analysis is an undetectable serum TSH IMA. If the patient is thyrotoxic, the thyroid scan shows ^{131}I uptake only in the palpable nodule because the remainder of the gland is suppressed.

Therapy

Euthyroid patients with "hot" nodules to not require therapy. Spontaneous infarction is common and is manifested by pain radiating to the ear, transient thyrotoxicosis, and nodule

tenderness. Infarcted nodules usually become hypofunctional. Because thyrotoxicosis from hot nodules does not spontaneously abate unless the nodule undergoes infarction, definitive therapy with either surgery or ^{131}I is necessary. Both are effective therapy. Surgical extirpation of the nodule results in prompt cure of the thyrotoxicosis without postoperative hypothyroidism, and usually results in a good cosmetic result. Because it is more costly than medical therapy, it is usually reserved for patients with larger nodules. Medical therapy with ^{131}I does not cause hypothyroidism unless there is ^{131}I uptake in the surrounding normal thyroid tissue. In the past, relatively large doses of ^{131}I, in the range of 30 to 60 mCi, were recommended for large nodules, but more recent studies suggest that smaller doses in the range ordinarily used to treat Graves' disease are effective. However, one disadvantage to medical therapy is that the nodule may not shrink and may become hypofunctional following ^{131}I therapy. Thyroid cancer almost never occurs in toxic nodules, and fear of cancer is not a good reason for recommending surgery. Fine-needle biopsy is sometimes misleading in toxic nodules because the specimens are highly cellular and may show changes that suggest malignancy.

Toxic Multinodular Goiter

Prevalence

Toxic multinodular goiter (MNG) is not common in the USA. This disorder also has a female preponderance similar to Graves' disease, but its peak onset is later, occurring in the fifth to seventh decades.

Clinical features

The disease evolves over decades, particularly in areas of endemic iodine deficiency. It begins as a euthyroid goiter that develops nodules independent of TSH stimulation (Berghout et al, 1990). The serum TSH IMA is often suppressed at this stage (Tenerz et al, 1990) and patients may become thyrotoxic if given thyroid hormone therapy to shrink the gland. Eventually, the nodules grow larger and cause thyrotoxicosis. There is usually an easily palpable multinodular goiter on exam, but thyroid scanning is required to demonstrate the "hot" areas and to exclude subacute thyroiditis. Unlike Graves' disease, spontaneous remissions do not occur with multinodular goiter. The thyrotoxicosis is often initially mild and difficult to recognize because most patients are older, in whom thyrotoxicosis can have unusual or misleading manifestations. Heart failure with atrial fibrillation may be the only clue to the diagnosis, or the patient may sustain weight loss and muscle weakness mimicking an occult cancer.

Therapy

Radioiodine is generally preferred over surgery because of the older age of patients, but thionamide therapy is often necessary before ^{131}I therapy can be given. Radioiodine can be used to ablate the gland even when the goiter is large and causes compressive symptoms, although hypothyroidism occurs in up to 30% of patients within the first few years after therapy (Verelst et al, 1990). Surgery is effective and rapidly cures the thyrotoxicosis. Long-term postoperative

prophylactic levothyroxine therapy is controversial in this situation. One large study of 185 patients found that recurrences occurred in 43% (6 of 14) patients not treated with levothyroxine postoperatively, as compared with 13% (9 of 71) when thyroid hormone suppression was used (Anderson et al, 1990). However, several prospective, placebo-controlled studies (Hegedus et al, 1987; Pearson et al, 1982), recently summarized in a comprehensive review (Smith and Charib, 1991) show little difference between levothyroxine and placebo in preventing recurrent goiter or thyroid nodules. Thus there is mounting evidence to support the notion that thyroid hormone should only be used to treat postoperative hypothyroidism and that it will not prevent MNG recurrence.

Extrathyroidal Sources of Thyroid Hormone

There are common causes of thyrotoxicosis with a low RAIU (Table 135-3). There are four cases of this problem - factitial, accidental, iatrogenic, and ectopic thyroid tissue.

Table 135-3. Ingbar classification of the causes of thyrotoxicosis

Thyrotoxicosis associated with hyperthyroidism

	Pathogenesis	**TSH activity**	**RAIU**
States of TSH excess			
Tumorous	TSH-secreting pituitary tumor	Increased	High
Nontumorous	Pituitary thyrotroph resistance	Increased	High
Abnormal thyroid stimulator			
Graves' disease	TSH-receptor antibody	Decreased	High
Trophoblastic tumors	hCG-like thyroid stimulator	Decreased	High
Intrinsic thyroid autonomy			
Toxic adenoma	Benign tumor	Decreased	High
Toxic multinodular goiter	Foci of functional autonomy	Decreased	High
Iodine-induced thyrotoxicosis (jodbasedow)	Iodine-induced hyperthyroidism	Decreased	High*

Thyrotoxicosis not associated with hyperthyroidism

	Pathogenesis	TSH activity	RAIU
Inflammatory disease			
Subacute thyroiditis	Leakage of hormone	Decreased	Low
Chronic thyroiditis with spontaneously resolving thyrotoxicosis (silent thyroiditis)	Leakage of hormone	Decreased	Low
Extrathyroid source of hormone			
Hormone ingestion	In medication or food	Decreased	Low
Ectopic thyroid tissue	Functioning thyroid cancer metastases or struma ovarii.	Decreased	Low

* The RAIU in iodine-induced thyrotoxicosis is initially low, but if sustained thyrotoxicosis occurs, which is often the case, the RAIU eventually rises.

Factitial thyrotoxicosis

Surreptitious thyroid hormone ingestion of either L-thyroxine or triiodothyronine usually is found in someone with easy access to thyroid hormone. The thyrotoxicosis is often severe with typical symptoms and signs, but may vary widely. The diagnosis is suggested by a high serum free T_4 (or free T_3 if triiodothyronine is ingested), an absent goiter (unless the patient had one before ingesting thyroid hormone), and a low serum thyroglobulin level with a low thyroidal RAIU (< 1%). Treatment is difficult because patients often have severe psychiatric disease.

Iatrogenic thyrotoxicosis

This is a common problem occurring during routine treatment with L-thyroxine, especially in elderly patients (Banovac et al, 1989). Of 47 patients at a VA outpatient clinic who were taking thyroid hormone in usual dosages, we found 26% had subclinical thyrotoxicosis (de los Santos et al, 1989), an observation confirmed by others (Stall et al, 1990). This can be avoided with careful follow-up using TSH IMA to gauge the correct dose. Thyrotoxicosis can occasionally occur from the accidental ingestion of thyroid hormone. A recent outbreak of 121 cases of thyrotoxicosis in southwestern Minnesota and adjacent areas that was initially thought to be caused by thyroiditis, was found to be caused by the inadvertent addition of bovine thyroid to ground beef (Hedberg et al, 1987). Other surreptitious sources of thyroid hormone are some diet pills and some drugs bought at health stores.

Ectopic thyroid tissue

Thyroid tissue in abnormal locations may cause thyrotoxicosis. When it occurs in the head or neck area, ectopic tissue is easily identified by thyroid scan. Other locations may be more difficult to identify. Ovarian struma ovarii, a rare neoplasm containing histologically normal appearing and functionally active thyroid tissue, can present with thyrotoxicosis and a low RAIU. Widely disseminated follicular thyroid carcinoma may cause thyrotoxicosis, which is occasionally T_3 toxicosis (Mazzaferri, 1986c).

Thyrotropin-Induced Hyperthyroidism

Thyrotoxicosis with an inappropriately normal or high serum TSH level may be caused by pituitary resistance to thyroid hormone (Smallridge et al, 1989) or pituitary TSH-secreting tumors (Gesundheit et al, 1989). Although both are uncommon causes of thyrotoxicosis, pituitary thyrotroph microadenomas may occur more frequently than was initially thought to be the case. Such small tumors are difficult to distinguish from pituitary thyroid hormone resistance. Patients with thyrotropin-induced hyperthyroidism present with a diffuse toxic goiter indistinguishable from Graves' disease. The diagnosis is suspected when thyrotoxicosis occurs with an elevated serum free T_4 concentration and inappropriately high serum TSH levels. A pituitary tumor is confirmed by MRI scan and an abnormally elevated beta-TSH subunit (Gesundheit et al, 1989). Normally, both alpha- and beta-TSH subunits are high when TSH is elevated. The treatment of choice for a tumor is pituitary surgery but the long-acting somatostatin analog, octreotide (Sandostatin), and glucocorticoids have been used to lower TSH secretion. Pituitary thyroid hormone resistance causing thyrotoxicosis is a very rare condition that can be transmitted as an autosomal dominant inherited trait or may occur sporadically. A pituitary adenoma is not identified, beta-TSH is not inordinately high, and the TSH response to TRH is not elevated. Treatment is difficult, but the dopamine agonist, bromocryptine, or 3,5,3'-triiodoacetic acid (Triac) may be effective (Usala and Weintraub, 1991).

Trophoblastic Tumors Causing Thyrotoxicosis

Hyperthyroidism occurs in patients with trophoblastic tumors, either choriocarcinoma or hydatidiform moles (Hershman, 1986). Hydatiform mole occurs in about 1 in 2000 pregnancies in the USA and is even more prevalent in Asian and South American countries. Choriocarcinoma occurs in about 1 in 60,000 pregnancies; almost half of choriocarcinomas develop after hydatiform moles. Hyperthyroidism caused by choriocarcinoma is rare. Only about 20 cases in women and just a few cases in men with testicular tumors have been reported (Hershman, 1986). Hyperthyroidism is caused by secretion of an abnormal thyroid stimulator, probably hCG. The thyrotoxicosis is usually mild and occurs with an apparent pregnancy (mole) with a uterus larger than normal for gestational age, or disseminated neoplasm. The diagnosis is established from the clinical features of mild to moderate hyperthyroxinemia, small goiter, low serum TSH, but very high serum beta-hCG, always more than 100, and usually more than 300 U/mL (usual mean peak of hCG in pregnancy is 50 U/mL). One must differentiate this from the hyperthyroxinemia that occurs with hyperemesis gravidarum (Chin and Lao, 1988).

Thyroid Storm

Clinical features

This is one of the rare but truly critical thyroid emergencies (Mazzaferri, 1983). It is characterized by an abrupt exaggeration of the symptoms and signs of thyrotoxicosis, usually ushered in by manic behavior, followed by lethargy, obtundation, and coma, often accompanied by heart failure with atrial fibrillation. Patients develop high fever, sometimes reaching hyperthermic levels (uncomplicated thyrotoxicosis has no fever). Jaundice and diarrhea complete the clinical picture. Thyroid storm is almost always precipitated by stress in some form such as infection or surgery (Bennett and Wainwright, 1989; Howton, 1988).

Therapy

This is a true emergency that requires urgent therapy. Propylthiouracil is given in large doses, 800 to 1000 mg/day orally, via an NG tube, or rectally (Walter and Bartle, 1990). This is accompanied by dexamethasone given intravenously in large doses, sodium iodide 1 g intravenously, given several hours after propylthiouracil has been started, fluids, and treatment of hyperthermia. Treatment of infection and good general medical support are necessary. Intravenous or oral propranolol is usually given unless contraindicated by heart failure. The mortality rate ranges between 10% and 20%, depending on the precipitating cause, underlying disease, age, and other factors.

Thyroiditis

Prevalence and causes

Thyroiditis commonly mimics other thyroid diseases, causing both thyrotoxicosis and hypothyroidism, and a clinical picture that often fluctuates between the two. The thyroid may be diffusely enlarged, nodular, or nonpalpable. Thyroiditis may be confused with Graves' disease, multinodular goiter, or an autonomously hyperfunctioning nodule. Certain forms of thyroiditis present as asymptomatic nodules and are difficult to distinguish from thyroid carcinoma. Conversely, one clinical presentation of papillary thyroid carcinoma with diffuse goiter and antithyroid antibodies so closely mimics Hashimoto's thyroiditis that it has been termed *pseudothyroiditis.*

Although the various forms of thyroiditis can usually be distinguished on clinical grounds, the differentiation may be difficult, and there is often overlap among the various syndromes. For instance, Hashimoto's thyroiditis generally presents as an asymptomatic painless goiter, but on occasion the gland is very symptomatic and simulates subacute thyroiditis. There is also enough overlap between Graves' disease and Hashimoto's thyroiditis that they are sometimes clinically indistinguishable. During pregnancy, silent thyroiditis is a particularly common problem that may be difficult to differentiate from Graves' disease. There is a major increase in the incidence of thyroid lymphoma in patients with Hashimoto's thyroiditis, and the two may be initially difficult

to differentiate. Table 135-4 summarizes the major forms of thyroiditis.

Table 135-4. Types, causes, and frequency of thyroiditis

Type	Cause	Frequency
Hashimoto's	Autoimmune	Common: 10% of all thyroid disease
Subacute (painful or de Quervain's)	Viral	Common: 1% to 2% of thyroid disease
Silent (painless lymphocytic with spontaneously resolving thyrotoxicosis)	(Autoimmune vs viral)	Common: varies with geographic area - as many as 25% of all thyrotoxic patients in some areas
Acute suppurative	Bacteria	Uncommon
Riedel's	Unknown	Rare.

Acute suppurative thyroiditis

Prevalence and etiology

This is a rare problem most commonly caused by *Staphylococcus aureus*, *Streptococcus hemolyticus,* or *Streptococcus pneumoniae,* but occasionally is caused by other organisms such as *Fusobacterium hemophilus* (Rich and Mendelman, 1987). Bacterial infection may be due to trauma, hematologic seeding from a distant site, or direct extension from a deep neck infection. The infection is usually localized to one lobe and commonly becomes an abscess that may rupture through the gland's capsule, extending into the mediastinum or other deep neck spaces.

Clinical features

The disorder is especially common in children. There is a prodrome of malaise followed by an acute onset of fever, neck pain and tenderness, severe systemic symptoms, and marked leukocytosis. Pain may be referred to the mandible or ear and the patient typically will hold the head immobile with the neck in a fixed position. There is localized tenderness over the gland and pain on head movement. Lower neck inflammation and tenderness may prevent identification of a fluctuant abscess. The disease may be difficult to distinguish from subacute nonsuppurative thyroiditis, but pain is more severe, thyroid hormone levels are normal, the erythrocyte sedimentation rate is normal, and the leukocyte count is very high. A thyroid scan may show a hypofunctional area. Hemorrhage into a thyroid nodule will cause acute pain, but this is usually transient. Anaplastic thyroid carcinoma occasionally follows such an aggressive course that it may be confused with thyroiditis. The diagnosis is made on clinical grounds. Needle aspiration will confirm the abscess and establish the bacterial organism causing the infection.

Therapy

Initial therapy is with high-dose antibiotics, usually a penicillinase-resistant penicillin and cephalosporin, but consideration should be given to anaerobic antibiotic coverage. The process can resolve if antibiotic therapy is begun in the cellulitis phase of the infection; however, an abscess discovered on needle aspiration requires surgical intervention. Partial thyroidectomy may be necessary to excise the abscess completely. Because of the loss of tissue planes, particular attention must be given to the parathyroid glands and the recurrent laryngeal nerves. Drains are kept in the neck until the purulent drainage stops. Thyroid function is usually preserved.

Painful (pseudogranulomatous or de Quervain's) thyroiditis

Prevalence and etiology

The true frequency of this disease has been difficult to determine, but it is very common in North America and elsewhere in the world. One recent review of 105 cases of thyroiditis found 48% were due to painful thyroiditis (Kitchener and Chapman, 1989). Females outnumber males by 3.6 to 1, with a peak age of onset in the second to fifth decades of life. Indirect evidence suggests that this is a viral disease. Antibodies have been demonstrated against multiple viruses in patients with this disorder, including coxsackie virus, adenovirus, influenza, and mumps. However, no single virus has been consistently implicated as its cause.

Clinical features

A painful form of thyroiditis caused by viral infection, it presents with sudden onset of flu-like symptoms, myalgia, fever (to 104°F), upper respiratory symptoms, leukocytosis, and the abrupt onset of neck pain radiating to the ear. The thyroid is often slightly enlarged and nodular, and is usually exquisitely tender. The disease lasts for about 2 to 5 months, and may go through four phases (Volpé, 1979). During the first phase the patient develops mild thyrotoxicosis lasting less than a month. A second transient euthyroid phase continues for about a week. This is followed by transient hypothyroidism, which persists for several months. Finally, thyroid function returns to normal and the goiter disappears. However, about 20% of patients experience a relapse of their symptoms.

The thyroid gland often adheres slightly to adjacent structures, but not to the same degree as other more chronic forms of thyroiditis. The gland shows extensive cellular destruction and desquamation with enlarged and disrupted follicles. Histiocytes tend to congregate around masses of colloid, producing giant cells that are quite characteristic of subacute thyroiditis. As the inflammatory process recedes, some fibrosis occurs, but ultimate recovery is almost always complete except for some residual fibrosis.

Diagnosis

Thyrotoxicosis is caused by leakage of thyroid hormones from the inflamed thyroid gland, which accounts for the low RAIU. The diagnosis is suspected from the clinical features and is established by an elevated erythrocyte sedimentation rate (> 100 mm/hr), leukocytosis, absent antithyroid antibodies, elevated serum thyroglobulin levels, and mild thyrotoxicosis with a low RAIU during the initial phase of the disease. Thyroid function tests change through the various phases. Thyroid ultrasonography almost invariably shows localized abnormalities that may persist for several years (Benker et al, 1988).

Therapy

Analgesics and beta-blockers to control the symptoms of mild thyrotoxicosis are required for several weeks in most patients. In severe cases, a short course of glucocorticoids gives dramatic relief of symptoms.

Silent thyrotoxic thyroiditis (lymphocytic thyroiditis with spontaneously resolving thyrotoxicosis)

Prevalence and etiology

This disorder accounts for 15% to 20% of all cases of thyrotoxicosis. Although its etiology has been debated (Volpé, 1988), it is probably a variant of autoimmune thyroiditis, which has some clinical features of subacute thyroiditis. Antithyroid antibodies are commonly present. A recent study of 26 thyroid specimens from 23 patients with clinical silent thyroiditis described focal or diffuse chronic lymphocytic thyroiditis with germinal centers in half the patients (Mizukami et al, 1988). Repeat biopsy during the late recovery phase disclosed resolution of the process with no follicular disruption.

Clinical features

Its clinical course has come of the features of subacute thyroiditis. However, there are no prodromal symptoms of fever and myalgia, the thyroid is neither painful nor tender, and the leukocyte count and erythrocyte sedimentation rare are normal. About half the patients have a painless, non-tender diffuse goiter, whereas the others have a nodular thyroid or no apparent thyroid enlargement. The feature that most resembles painful thyroiditis is the changing thyroid function, which most patients experience.

Postpartum thyroiditis

Silent thyroiditis commonly occurs in the postpartum period, with a reported incidence ranging from 2% to 17%. The variation in the reported incidence has been attributed to racial, dietary, and geographic factors, but may be due to selection bias and variable diagnostic criteria. A recent review of the literature (Kologlu et al, 1990) estimates the incidence of postpartum

thyroiditis to be approximately 5%. It presents more commonly as hypothyroidism alone, thyrotoxicosis alone, or thyrotoxicosis followed by hypothyroidism and is recognized several weeks or months after delivery.

Diagnosis

The diagnosis is based upon finding mild thyrotoxicosis with a small goiter and a low RAIU. The rise in serum T_4 may be relatively greater than that of T_3 because the inflamed gland contains mainly T_4, whereas serum T_3 is disproportionately elevated in Graves' disease (Shigemasa et al, 1987). Antithyroid antibodies may be present. The diagnosis may be more difficult when the disorder is first discovered during the hypothyroid phase, but silent thyroiditis should be suspected in the postpartum hypothyroid woman.

Therapy

The thyrotoxic phase is treated like subacute thyroiditis, with beta-blockers but without antithyroid drugs. Treatment during the hypothyroid phase may be more difficult. Initially one should try not to treat the hypothyroidism because it typically is transient, but some may need L-thyroxine replacement. However, some patients have residual goiter and persistent hypothyroidism. In a review of 105 cases (Kitchener and Chapman, 1989), 11% had long-term hypothyroidism. The presence of high-titer antimicrosomal antibodies and the severity of hypothyroidism may be good predictors of long-term hypothyroidism (Othman et al, 1990).

Hashimoto's thyroiditis

Prevalence and etiology

This autoimmune disease is the most common form of thyroiditis (McConahey, 1972). It is about six times more prevalent in women than in men and peaks between the ages of 40 and 60 years. It may be associated with other autoimmune disorders and is a component of multiple endocrine deficiency syndrome involving the adrenals, parathyroids, pancreas, and gonads, sometimes with mucocutaneous candidiasis. Other autoimmune diseases that may occur with it are rheumatoid arthritis, SLE, chronic active hepatitis, and Sjögren's syndrome.

Clinical features

The thyroid gland is large, firm, lobulated, and relatively avascular or may be nonpalpable and completely fibrotic. Histologically the gland shows follicular degeneration (Askanazy) changes, diffuse lymphocytic infiltration with germinal centers, and fibrosis. A painful form of Hashimoto's thyroiditis exists that may be difficult to distinguish from subacute thyroiditis. Most patients present with an asymptomatic goiter, making this the most common form of euthyroid goiter in the USA. The patient may be thyrotoxic, euthyroid, or hypothyroid. The condition may be associated with exophthalmos, which makes it clinically indistinguishable from Graves' disease. HLA-B8 and HLA-DRw3 are found with increased frequency in patients with atrophic

thyroiditis but goitrous Hashimoto's thyroiditis is more likely to be associated with HLA-Dr5/Deus.

Diagnosis

The diagnosis may be difficult to establish on the basis of thyroid function, which is highly variable. When thyrotoxicosis occurs with a high RAIU, Hashimoto's disease is indistinguishable from Graves' disease. Other patients have euthyroid goiter with low or high RAIU, and normal or high serum TSH levels. When hypothyroidism is present, the RAIU is usually low, but can be normal or even slightly high. Thyroid antithyroglobulin and antimicrosomal antibodies are detectable in as many as 90% of adult patients (Gardas et al, 1988). In addition, TSH receptor and other antibodies may be detectable (Nordmeyer et al, 1988). In young patients with the disorder, however, antibodies are more often undetectable. In contrast, 25% of elderly persons in the USA have detectable antimicrosomal or antithyroglobulin antibodies with no other clinical evidence of the disease, or may have only mildly elevated serum TSH IMA levels (Rosenthal et al, 1987). FNB may identify this disorder but the cytologic picture can be easily confused with that of thyroid cancer.

The natural history of the disease is not well defined. It appears that most patients remain euthyroid, whereas others develop persistent hypothyroidism or thyrotoxicosis, or fluctuating thyroid function. A recent study in elderly patients indicates that when serum TSH IMA is over 20 mU/L or antithyroid antibodies are detectable in titers above 1600, about 80% develop overt hypothyroidism within 4 years (Rosenthal et al, 1987). The incidence of thyroid lymphoma in patients with Hashimoto's thyroiditis may be sixty to eighty times greater (Aozasa, 1990). This complication is recognized by the sudden and symptomatic growth of goiter, usually in elderly women who develop symptoms of local compression, with hoarseness and airway obstruction.

Therapy

The treatment of Hashimoto's disease depends upon the patient's thyroid function. Thyrotoxic patients are treated as are those with Graves' disease. Euthyroid patients are given supplemental L-thyroxin if the TSH is high (> 20 mU/L), or simply followed carefully if the TSH is below this level. There is compelling evidence to treat patients with only slightly elevated serum TSH concentrations if the antithyroid antibody titers are above 1600. Overtly hypothyroid patients are treated with L-thyroxine.

Invasive fibrous (Riedel's) thyroiditis

Prevalence and etiology

This is a rare disorder characterized by extensive fibrosis of the thyroid gland, capsule, and surrounding tissue. Its cause is uncertain, but the disorder is associated with fibrotic processes elsewhere and may represent a local manifestation of a generalized process. An association has been reported between Riedel's thyroiditis and fibrosing cholangitis, orbital

pseudotumor, fibrotic lacrimal glands, and retroperitoneal and mediastinal fibrosis (Katsikas et al, 1976).

Clinical features and diagnosis

Riedel's thyroiditis occurs most often in women between 30 and 60 years of age. The thyroid increases rapidly in size, and is associated with compression symptoms of dysphagia and dyspnea. It may involve only one lobe. Thyroid antibodies, thyroid function, the erythrocyte sedimentation rate, and the leukocyte count are normal.

Therapy

Surgery may be required to establish the diagnosis and to relieve compression of the esophagus and trachea. Wedge resection of the isthmus is usually all that is required. More extensive dissection is often not possible because of the undefined tissue planes and local fibrosis. Steroids and cyclophosphamide may be useful, but it is difficult to be certain that these drugs actually alter the natural course of the disease, which tends to remit and recur spontaneously. In some cases the disease is more chronic and is an incidental finding at necropsy.

Chronic nonsuppurative thyroiditis

Granulomatous infections with tuberculosis, histoplasmosis, syphilis, actinomycosis, and echinococcus of the thyroid are unusual problems. Sarcoid tumors can involve the thyroid gland, Rarely, amyloidosis involves the thyroid.

Euthyroid Goiter

Classification and etiology

Goiter, an ancient word for an enlarged thyroid gland, is a common finding. Goiter has been classified from barely palpable to monstrously enlarged (Table 135-5). A broad variety of thyroid diseases present as goiter (Park et al, 1988), encompassing virtually every disease that affects the thyroid. Many cause no functional disturbance, and are classified as euthyroid goiters. However, it is not uncommon for a "euthyroid" goiter to be actually causing occult thyrotoxicosis or hypothyroidism, which becomes apparent with careful laboratory testing. It is dangerous to make a diagnosis of "goiter" without being certain of its etiology. Some benign-appearing diffuse goiters are actually slow-growing thyroid cancers. The majority of diffuse euthyroid goiters, however, are simply diffuse colloid goiters that eventually develop into multinodular glands. The etiology of this group is probably related to the growth of clones of follicular cells that may have variable sensitivity to TSH.

Table 135-5. Classification of goiter

Grade	Description
0a	Thyroid impalpable or not larger than normal
0b	Thyroid distinctly palpable and enlarged but not visible with the head in a normal or raised position
I	Thyroid easily palpable and visible with the neck extended
II	Thyroid easily palpable and visible with the neck in a normal position
III	Goiter visible at a distance
IV	Monstrous goiter.

Endemic goiter

This is an uncommon problem in the USA but occurs with high frequency in many regions around the world where iodine intake is low. It is estimated to affect between 200 and 250 million people worldwide. Studies from a number of areas have shown that TSH levels may be elevated in over 50% of subjects with endemic goiter, many of whom have no clinical features of thyroid failure (Biel and Maisel, 1985). Endemic goiter is caused by iodine deficiency, dietary goitrogens, inherited defects in hormonogenesis, or other environmental goitrogens. The patient may initially have a diffuse goiter, but with time, most develop nodules independent of TSH stimulation, which eventually may cause thyrotoxicosis (Berghout et al, 1990).

Sporadic goiter

Euthyroid sporadic goiter may be caused by autoimmune thyroid disease, compensated inherited or acquired defects in hormonogenesis, drugs, or other goitrogens. The gland may be infiltrated with thyroid cancer, thyroid lymphoma, other malignancies, granulomatous disease, amyloidosis, or can enlarge by as much as 30% in normal pregnancy (Rasmussen et al, 1990). Many are simple colloid goiters.

Clinical features

Longstanding colloid goiters may cause substantial symptoms. Patients may develop mild obstructive symptoms consisting of dysphagia or dyspnea. One should consider obstructive sleep apnea in patients with large goiters who complain of daytime somnolence, snoring, or fitful sleep. Pulmonary function tests or polysomnography may be helpful in such patients. Hoarseness can be caused by large colloid goiters. In addition, patients may complain of intermittent pain that sometimes radiates to the neck, which is caused by hemorrhagic infarction of colloid nodules within the goiter. These rarely respond to medical therapy.

Diagnosis

Diagnostic evaluation should include TSH IMA, a free T_4 estimate, and antithyroid antibodies. Imaging techniques such as computerized tomography or MRI are particularly helpful in evaluating patients with large goiters because areas of hemorrhagic necrosis and tracheal or esophageal impingement are easily visualized by these techniques. Radioisotopic scanning is less helpful, but will separate functional from nonfunctional nodules. A goiter with one or more suspicious hypofunctional nodules should be carefully evaluated in the same fashion as an isolated thyroid nodule, by fine-needle biopsy (Mazzaferri et al, 1988).

Therapy

It is common practice to prescribe long-term levothyroxine suppressive therapy to patients with euthyroid goiter. However, there is little evidence that this prevents goiter growth or nodule formation (Smith and Gharib, 1991). In addition, most patients are women who are susceptible to osteoporosis, which may be aggravated by long-term thyroid hormone suppression therapy (Stall et al, 1990).

Indications for surgery are obstructive symptoms involving the airway or esophagus, recurrent painful hemorrhage, inability to exclude carcinoma by fine-needle biopsy (indeterminate cytology, and large goiters that are a cosmetic problem to the patient.