Chapter 65

The Thyroid Gland

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The thyroid gland secretes thyroxine (T_4) and triiodothyronine (T_3), both of which modulate energy utilization and heat production and facilitate growth. The gland consists of two lateral lobes joined by an isthmus. The weight of the adult gland is 10 to 20 g. Microscopically, the thyroid is composed of several follicles containing colloid surrounded by a single layer of thyroid epithelium. The follicular cells synthesize thyroglobulin, which is then stored as colloid. Biosynthesis of T_4 and T_3 occurs by iodination of tyrosine molecules in thyroglobulin.

Thyroid Hormone Physiology

THYROID HORMONE SYNTHESIS

Dietary iodine is essential for synthesis of thyroid hormones. Iodine, after conversion to iodide in the stomach, is rapidly absorbed from the gastrointestinal tract and distributed in the extracellular fluids. After active transport from the blood stream across the follicular cell basement membrane, iodide is enzymatically oxidized by thyroid peroxidase, which also mediates the iodination of the tyrosine residues in thyroglobulin to form monoiodotyrosine and diiodotyrosine. The iodotyrosine molecules couple to form T_4 (3,5,3′,5′-tetraiodothyronine) or T_3 (3,5,3′-triiodothyronine). Once iodinated, thyroglobulin containing newly formed T_4 and T_3 is stored in the follicles. Secretion of free T_4 and T_3 into the circulation occurs after proteolytic digestion of thyroglobulin, which is stimulated by thyroid-stimulating hormone (TSH). Deiodination of monoiodotyrosine and diiodotyrosine by iodotyrosine deiodinase releases iodine, which then reenters the thyroid iodine pool.

THYROID HORMONE TRANSPORT

T_4 and T_3 are tightly bound to serum carrier proteins: thyroxine-binding globulin (TBG), thyroxine-binding pre-albumin, and albumin. The unbound or free fractions are the biologically active fractions and represent only 0.04% of the total T_4 and 0.4% of the total T_3.

PERIPHERAL METABOLISM OF THYROID HORMONES

The normal thyroid gland secretes T_4, T_3, and reverse T_3, a biologically inactive form of T_3. Most of the circulating T_3 is derived from 5′-deiodination of circulating T_4 in the peripheral tissues. Deiodination of T_4 can occur at the outer ring (5′-deiodination), producing T_3 (3,5,3′-triiodothyronine), or at the inner ring, producing reverse T_3 (3,3,5′-triiodothyronine).

CONTROL OF THYROID FUNCTION

Hypothalamic thyrotropin-releasing hormone (TRH) is transported through the hypothalamic-hypophysial portal system to the thyrotrophs of the anterior pituitary gland, stimulating synthesis and release of TSH (Fig. 65–1). TSH, in turn, increases thyroidal iodide uptake and iodination of thyroglobulin, releases T_3 and T_4 from the thyroid gland by increasing hydrolysis of thyroglobulin, and stimulates thyroid cell growth. Hypersecretion of TSH results in thyroid enlargement (goiter). Circulating T_3 exerts negative feedback inhibition of TRH and TSH release.

PHYSIOLOGIC EFFECTS OF THYROID HORMONES

Thyroid hormones increase basal metabolic rate by increasing oxygen consumption and heat production in several body tissues. Thyroid hormones also have specific effects on several organ systems (Table 65–1). These effects are exaggerated in hyperthyroidism and lacking in hypothyroidism, accounting for the well-recognized signs and symptoms of these two disorders.

Thyroid Evaluation

Thyroid gland function and structure can be evaluated by (1) serum thyroid hormone levels, (2) imaging of thyroid gland size and architecture, (3) measurement of thyroid autoantibodies, and (4) thyroid gland biopsy (by fine-needle aspiration [FNA]).

TESTS OF SERUM THYROID HORMONE LEVELS

Total serum T_4 and T_3 measure the total amount of hormone bound to thyroid-binding proteins by radioimmunoassay. Total T_4 and total T_3 levels are elevated in hyperthyroidism and low in hypothyroidism. Increase in TBG (as with pregnancy or estrogen therapy) increases the total T_4 and T_3 measured in the absence of hyperthyroidism. Similarly, total T_4 and T_3 are low

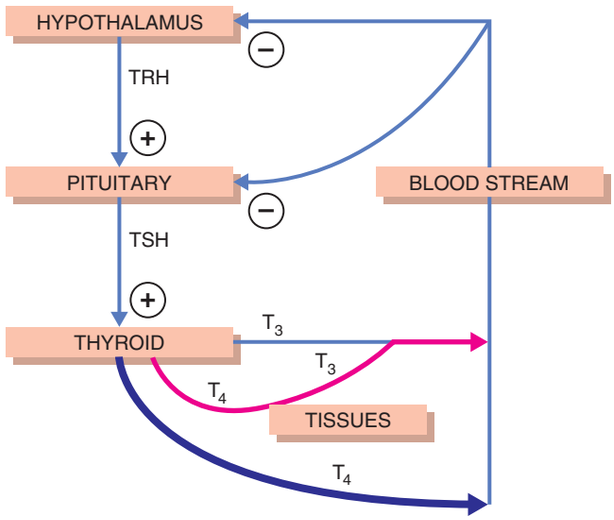

FIGURE 65–1 Hypothalamic-pituitary-thyroid axis. T_3 = triiodothyronine; T_4 = thyroxine; TRH = thyrotropin-releasing hormone; TSH = thyroid-stimulating hormone.

despite euthyroidism in conditions associated with low thyroid-binding proteins (e.g., cirrhosis or nephrotic syndrome). Thus, further tests to assess the free hormone level that reflects biologic activity must be performed. Free T_4 level can be estimated by calculating the free T_4 index or can be measured directly by dialysis.

The free T_4 index is an indirect method of assessing free T_4. It is derived by multiplying the total T_4 by the T_3 resin uptake, which is inversely proportional to the available T_4 binding sites on TBG. Free T_4 can be measured directly by dialysis or ultrafiltration. This is more accurate and is preferred to the free T_4 index.

Serum TSH is measured by a third-generation immunometric assay, which employs at least two different monoclonal antibodies against different regions of the TSH molecule, resulting in accurate discrimination between normal TSH levels and levels below the normal range. Thus, the TSH assay can diagnose clinical hyperthyroidism (elevated free T_4 and suppressed TSH) and subclinical hyperthyroidism (normal free T_4 and suppressed TSH). In primary (thyroidal) hypothyroidism, serum TSH is supranormal because of diminished feedback inhibition. In secondary (pituitary) or tertiary (hypothalamic) hypothyroidism, the TSH is usually low but may be normal.

Serum thyroglobulin measurements are useful in the follow-up of patients with papillary or follicular carcinoma. After thyroidectomy and iodine-131 (^{131}I) ablation therapy, thyroglobulin levels should be less than 2 µg/L while the patient is on suppressive levothyroxine treatment. Levels in excess of this value indicate the presence of persistent or metastatic disease.

Calcitonin is produced by the medullary cells of the thyroid. Calcitonin measurements are invaluable in the diagnosis of medullary carcinoma of the thyroid and for following the effects of therapy for this entity.

TABLE 65–1 Physiologic Effects of Thyroid Hormone

Cardiovascular Effects
Increased heart rate and cardiac output

Gastrointestinal Effects
Increased gut motility

Skeletal Effects
Increased bone turnover and resorption

Pulmonary Effects
Maintenance of normal hypoxic and hypercapnic drive in the respiratory center

Neuromuscular Effects
Increased muscle protein turnover and increased speed of muscle contraction and relaxation

Lipids and Carbohydrate Metabolism Effects
Increased hepatic gluconeogenesis and glycogenolysis as well as intestinal glucose absorption
Increased cholesterol synthesis and degradation
Increased lipolysis

Sympathetic Nervous System Effects
Increased numbers of β-adrenergic receptors in the heart, skeletal muscle, lymphocytes, and adipose cells
Decreased cardiac α-adrenergic receptors
Increased catecholamine sensitivity

Hematopoietic Effects
Increased red blood cell 2,3-diphosphoglycerate, facilitating oxygen dissociation from hemoglobin with increased oxygen available to tissues

THYROID IMAGING

Technetium-99m (^{99m}Tc) pertechnetate is concentrated in the thyroid gland and can be scanned with a gamma camera, yielding information about the size and shape of the gland and the location of the functional activity in the gland (thyroid scan). The thyroid scan is often performed in conjunction with a thyroid uptake assay, usually with iodine-123 (^{123}I), which quantitates thyroid uptake. Functioning thyroid nodules are called "warm" or "hot" nodules; "cold" nodules are nonfunctioning. Malignancy is usually associated with a cold nodule; 16% of surgically removed cold nodules are malignant.

Thyroid ultrasound evaluation is useful in the differentiation of solid from cystic nodules. It can also guide the operator during FNA of a nodule that is difficult to palpate.

THYROID ANTIBODIES

Autoantibodies to several different antigenic components in the thyroid gland, including thyroglobulin (TgAb), thyroid peroxidase (TPO Ab, formerly called antimicrosomal antibodies), and the TSH receptor, can

be measured in the serum. A strongly positive test for TPO Ab indicates autoimmune thyroid disease. Elevated thyroid receptor-stimulating antibody occurs in Graves' disease (see later discussion).

THYROID BIOPSY

FNA of a nodule to obtain thyroid cells for cytology is the best way to differentiate benign from malignant disease. FNA requires adequate tissue samples and interpretation by an experienced cytologist.

Hyperthyroidism

Thyrotoxicosis is the clinical syndrome that results from elevated circulating thyroid hormones. Clinical manifestations of thyrotoxicosis are due to the direct physiologic effects of the thyroid hormones, as well as to the increased sensitivity to catecholamines. Tachycardia, tremor, stare, sweating, and lid lag are due to catecholamine hypersensitivity.

SIGNS AND SYMPTOMS

Table 65–2 lists the signs and symptoms of hyperthyroidism with their frequency of occurrence. Thyrotoxic crisis, or "thyroid storm," is a life-threatening complication of hyperthyroidism that can be precipitated by surgery, radioactive iodine therapy, or severe stress (e.g., uncontrolled diabetes mellitus, myocardial infarction, acute infection). Patients develop fever, flushing, sweating, marked tachycardia, atrial fibrillation, and cardiac failure. Marked agitation, restlessness, delirium, and coma occur frequently. Gastrointestinal manifestations may include nausea, vomiting, and diarrhea. Hyperpyrexia out of proportion to other clinical findings is the hallmark of thyroid storm.

TABLE 65–2 Prevalence of Symptoms and Signs in Patients With Thyrotoxicosis

Symptom	Prevalence (%)
Nervousness	99
Increased sweating	91
Hypersensitivity to heat	89
Palpitation	89
Fatigue	88
Weight loss	85
Tachycardia	82
Dyspnea	75
Weakness	70
Increased appetite	65
Eye complaint (diplopia, pain, swelling)	54
Swelling of legs	35
Diarrhea	23
Anorexia	9
Tachycardia	100
Goiter	100
Skin changes	97
Tremor	97
Eye signs (lid lag, proptosis)	71
Atrial fibrillation	10
Splenomegaly	10
Gynecomastia	10
Liver palms	8

From Williams RH: Thiouracil treatment of thyrotoxicosis. J Clin Endocrinol Metab 1946;6:1–22.

DIFFERENTIAL DIAGNOSIS

Thyrotoxicosis usually reflects hyperactivity of the thyroid gland resulting from Graves' disease, toxic adenoma, multinodular goiter, or thyroiditis (Table 65–3 and Fig. 65–2). However, it may be due to excessive ingestion of thyroid hormone or, rarely, thyroid hormone production from an ectopic site, as seen in struma ovarii.

GRAVES' DISEASE

Graves' disease, the most common cause of thyrotoxicosis, is an autoimmune disease that is more common in women, with a peak age incidence of 20 to 40 years. One or more of the following features are present: (1) goiter; (2) thyrotoxicosis; (3) eye disease ranging from tearing to proptosis, extraocular muscle paralysis, and loss of sight as a result of optic nerve involvement; and (4) thyroid dermopathy, usually presenting as marked skin thickening without pitting in a pretibial distribution (pretibial myxedema).

Pathogenesis

Thyrotoxicosis in Graves' disease is due to overproduction of an antibody that binds to the TSH receptor. These thyroid-stimulating immunoglobulins increase

TABLE 65–3 Causes of Thyrotoxicosis

Common Causes
Graves' disease
Toxic adenoma (solitary)
Toxic multinodular goiter

Less Common Causes
Subacute thyroiditis (de Quervain's or granulomatous)
Hashimoto's thyroiditis with transient hyperthyroid phase
Thyrotoxicosis factitia
Postpartum (probably variant of silent thyroiditis)

Rare Causes
Struma ovarii
Metastatic thyroid carcinoma
Hydatidiform mole
Thyroid-stimulating hormone–secreting pituitary tumor
Pituitary resistance to triiodothyronine and thyroxine

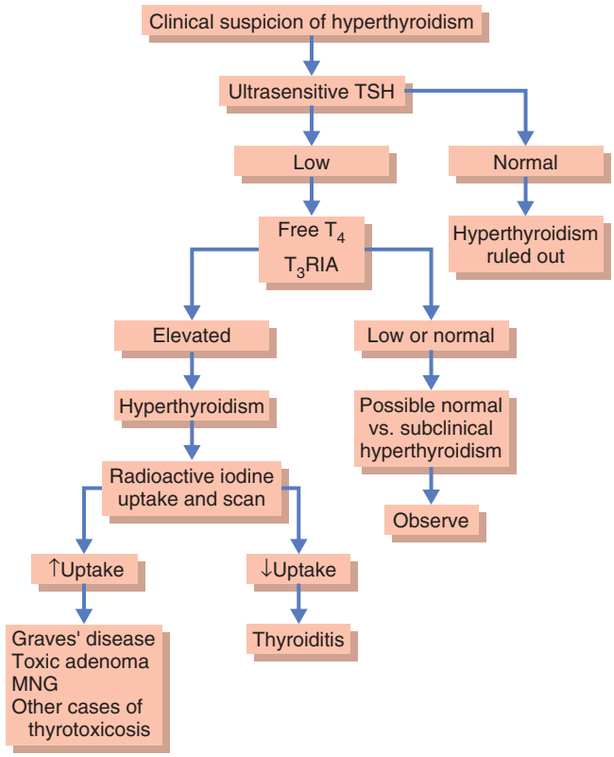

FIGURE 65–2 Algorithm for differential diagnosis of hyperthyroidism. MNG = multinodular goiter; T_3RIA = triiodothyronine radioimmunoassay; T_4 = thyroxine; TSH = thyroid-stimulating hormone.

thyroid cell growth and thyroid hormone secretion. Ophthalmopathy is due to inflammatory infiltration of the extraocular eye muscles by lymphocytes, with mucopolysaccharide deposition. The inflammatory reaction that contributes to the eye signs in Graves' disease may be caused by lymphocytes sensitized to antigens common to the orbital muscles and thyroid.

Clinical Features

The common manifestations of thyrotoxicosis (see Table 65–2) are characteristic features of younger patients with Graves' disease. In addition, patients may present with a diffuse goiter or the eye signs characteristic of Graves' disease. Older patients often do not manifest the florid clinical features of thyrotoxicosis, and the condition termed *apathetic hyperthyroidism* presents as flat affect, emotional lability, weight loss, muscle weakness, or congestive heart failure and atrial fibrillation resistant to standard therapy.

Eye signs of Graves' disease may be either a nonspecific manifestation of hyperthyroidism from any cause (e.g., thyroid stare) or may result from Graves' disease due to a specific inflammatory infiltrate of the orbital tissues leading to periorbital edema, conjunctival congestion and swelling, proptosis, extraocular muscle weakness, and/or optic nerve damage with visual impairment.

Pretibial myxedema (thyroid dermopathy) occurs in 2 to 3% of patients with Graves' disease and presents as thickening of the skin over the lower tibia without pitting. Onycholysis, characterized by separation of the fingernails from their beds, often occurs in Graves' disease. Thyroid acropachy, or clubbing, may also occur in Graves' disease.

Laboratory Findings

Elevated T_4 and/or T_3 and a suppressed TSH confirm the clinical diagnosis of thyrotoxicosis. Thyroid-stimulating immunoglobulin (TSH receptor antibody) is usually elevated and may be useful in patients with eye signs who do not have other characteristic clinical features. Increased uptake of ^{123}I differentiates Graves' disease from early subacute or Hashimoto's thyroiditis, in which uptake is low in the presence of hyperthyroidism. Magnetic resonance imaging or ultrasonography of the orbit usually shows orbital muscle enlargement, whether or not there are clinical signs of ophthalmopathy.

Treatment

Three treatment modalities are employed to control the hyperthyroidism of Graves' disease.

Antithyroid Drugs. The thiocarbamide drugs propylthiouracil, methimazole, and carbimazole block thyroid hormone synthesis by inhibiting thyroid peroxidase. Propylthiouracil also partially inhibits peripheral conversion of T_4 to T_3. Medical therapy must be administered for a prolonged period (12 to 18 months), until the disease undergoes spontaneous remission. On cessation of medication, only a small percentage of patients (20 to 30%) remain in remission, and the patients who experience relapse must then undergo definitive surgery or radioactive iodine treatment. Side effects of the thiocarbamides include pruritus and rash (about 5% of patients), cholestatic jaundice, acute arthralgias, and, rarely, agranulocytosis (0.5% of patients). Patients must be instructed to discontinue the medication and consult a physician if they develop fever or sore throat, because these may indicate agranulocytosis. At the onset of treatment, during the acute phase of thyrotoxicosis, β-adrenergic blocking drugs help alleviate tachycardia, hypertension, and atrial fibrillation. As the thyroid hormone levels return to normal, treatment with β-blockers is tapered.

Radioactive Iodine. In terms of cost, efficacy, ease, and short-term side effects, radioactive iodine has benefits that exceed both surgery and antithyroid drugs. Iodine-131 is the treatment of choice in adults with Graves' disease. Patients with severe thyrotoxicosis, very large glands, or underlying heart disease should be rendered euthyroid with antithyroid medication before receiving radioactive iodine because ^{131}I treatment can cause release into the circulation of preformed thyroid hormone from the thyroid gland; this can precipitate cardiac arrhythmias and exacerbate symptoms of

thyrotoxicosis. After administration of radioactive iodine, the thyroid gland shrinks and patients become euthyroid over a period of 6 weeks to 3 months. Ten to 20% of patients become hypothyroid within the first year of treatment, and thereafter hypothyroidism occurs at a rate of 3 to 5% per year. Ultimately 50 to 80% of patients become hypothyroid after radioactive iodine treatment. Serum TSH levels should be monitored and replacement with levothyroxine instituted if the TSH level rises. Hypothyroidism may also develop after surgery or antithyroid medication, mandating lifelong follow-up in all patients with Graves' disease.

Surgery. Subtotal thyroidectomy is the treatment of choice for patients with very large glands and obstructive symptoms or multinodular glands, or for patients desiring pregnancy within the next year. It is essential that the surgeon be experienced in thyroid surgery. Preoperatively, patients receive 6 weeks of treatment with antithyroid drugs so that they will be euthyroid at the time of surgery. Two weeks before surgery, oral saturated solution of potassium iodide is administered daily to decrease the vascularity of the gland. Permanent hypoparathyroidism and recurrent laryngeal nerve palsy occur in less than 2% of patients postoperatively. Ten percent of patients develop recurrent thyrotoxicosis, which should be treated with radioactive iodine.

TOXIC ADENOMA

Solitary toxic nodules, which usually are benign, occur more frequently in older patients. Clinical manifestations are those of thyrotoxicosis. Physical examination shows a distinct solitary nodule. Laboratory investigation shows suppressed TSH and markedly elevated T_3 levels, often with only moderately elevated T_4. Thyroid scan shows a "hot nodule" of the affected lobe with complete suppression of the unaffected lobe. Solitary toxic nodules are treated with radioactive iodine. However, unilateral lobectomy, after the administration of antithyroid drugs to render the patient euthyroid, may be required for large nodules.

TOXIC MULTINODULAR GOITER

Toxic multinodular goiter occurs in older patients with long-standing multinodular goiter, especially in patients from iodine-deficient regions. The presenting clinical features are frequently tachycardia, heart failure, and arrhythmias.

Physical examination shows a multinodular goiter. The diagnosis is confirmed by laboratory features of suppressed TSH, elevated T_3 and T_4, and a thyroid scan with multiple functioning nodules. The treatment of choice is often ^{131}I ablation. It is especially effective in patients with small glands and a high radioactive uptake.

SUBCLINICAL HYPERTHYROIDISM

In subclinical hyperthyroidism, T_4 and T_3 levels are normal with a suppressed TSH. The causes of this condition include early presentation of all forms of hyperthyroidism, including Graves' disease, toxic adenoma, and toxic multinodular goiter. Because these patients, especially the elderly, are at an increased for developing cardiac dysrhythmias, many patients with a persistently suppressed TSH should be treated with thiocarbamide drugs or radioactive iodine.

Thyroiditis

Thyroiditis may be classified as acute, subacute, or chronic. Although thyroiditis may eventually result in clinical hypothyroidism, the initial presentation is often that of hyperthyroidism as a result of acute release of T_4 and T_3. Hyperthyroidism caused by thyroiditis can be readily differentiated from other causes of hyperthyroidism by suppressed uptake of radioactive iodine, reflecting decreased hormone production by damaged cells.

Acute suppurative thyroiditis, a rare complication of septicemia, presents as high fever, redness of the overlying skin, and thyroid gland tenderness; it may be confused with subacute thyroiditis. If blood cultures are negative, needle aspiration should identify the organism. Intensive antibiotic treatment and, occasionally, incision and drainage are required.

SUBACUTE THYROIDITIS

Subacute thyroiditis (de Quervain's thyroiditis or granulomatous thyroiditis) is an acute inflammatory disorder of the thyroid gland, probably secondary to viral infection, which resolves completely in 90% of cases. Subacute thyroiditis presents as fever and anterior neck pain. The patient may have symptoms and signs of hyperthyroidism. The classic feature on physical examination is an exquisitely tender thyroid gland. Laboratory findings vary with the course of the disease. Initially, the patient may be symptomatically thyrotoxic, with elevated serum T_4, depressed serum TSH, and very low radioactive iodine uptake on scan. Subsequently, the thyroid status will fluctuate through euthyroid and hypothyroid phases and may return to euthyroidism. Increase in radioactive iodine uptake on the scan reflects recovery of the gland. Treatment usually includes nonsteroidal anti-inflammatory drugs, but a short course of prednisone may be required if pain and fever are severe. During the hypothyroid phase, replacement therapy with levothyroxine may be indicated.

Postpartum thyroiditis resembles subacute thyroiditis in its clinical course. It usually presents within the first 6 months after delivery and goes through the triphasic course of hyperthyroidism, hypothyroidism, and then euthyroidism, or it may present with only hypothyroidism. Some patients have an underlying chronic thyroiditis.

CHRONIC THYROIDITIS

Chronic thyroiditis (Hashimoto's thyroiditis or lymphocytic thyroiditis) from destruction of normal thyroidal architecture by lymphocytic infiltration results in hypothyroidism and goiter. Riedel's struma is probably a variant of Hashimoto's thyroiditis, characterized by extensive thyroid fibrosis resulting in a rock-hard thyroid mass. Hashimoto's thyroiditis is more common in women and is the most common cause of goiter and hypothyroidism in the United States. Occasionally, patients with Hashimoto's thyroiditis may have transient hyperthyroidism with low radioactive iodine uptake, owing to release of T_4 and T_3 into the circulation. This can be differentiated from subacute thyroiditis in that the gland is nontender to palpation and antithyroid antibodies are present in high titer. Early in the disease, TgAb is markedly elevated, but it may disappear later. TPO Ab also is present early and generally remains present for years. Radioactive iodine uptake may be high, normal, or low. Serum T_3 and T_4 levels are either normal or low; when low, the TSH is elevated. FNA of the thyroid shows lymphocytes and Hürthle cells (enlarged basophilic follicular cells). Hypothyroidism and marked glandular enlargement (goiter) are indications for levothyroxine therapy. Adequate doses of levothyroxine are administered to normalize TSH levels and shrink the goiter.

Thyrotoxicosis Factitia

Thyrotoxicosis factitia presents as typical features of thyrotoxicosis from ingestion of excessive amounts of thyroxine, often in an attempt to lose weight. Serum T_3 and T_4 levels are elevated, and TSH is suppressed, as is the serum thyroglobulin concentration. Radioactive iodine uptake is absent. Patients may require psychotherapy.

Rare Causes of Thyrotoxicosis

Struma ovarii occurs when an ovarian teratoma contains thyroid tissue, which secretes thyroid hormone. Diagnosis is confirmed by demonstrating uptake of radioiodine in the pelvis on body scan.

Hydatidiform mole is due to proliferation and swelling of the trophoblast during pregnancy, with excess production of chorionic gonadotropin, which has intrinsic TSH-like activity. The hyperthyroidism remits with surgical and medical treatment of the molar pregnancy.

Hypothyroidism

Hypothyroidism is a clinical syndrome caused by deficiency of thyroid hormones. In infants and children, hypothyroidism causes retardation of growth and development and may result in permanent motor and mental retardation. Congenital causes of hypothyroidism include agenesis (complete absence of thyroid tissue), dysgenesis (ectopic or lingual thyroid gland), hypoplastic thyroid, thyroid dyshormogenesis, and congenital pituitary diseases. Adult-onset hypothyroidism results in a slowing of metabolic processes and is reversible with treatment. Hypothyroidism (Table 65–4) is usually primary (thyroid failure), but it may be secondary (hypothalamic or pituitary deficiency) or due to resistance at the thyroid hormone receptor. In adults, autoimmune thyroiditis (Hashimoto's thyroiditis) is the most common cause of hypothyroidism. This may be isolated or part of the polyglandular failure syndrome type II (Schmidt's syndrome), which also includes insulin-dependent diabetes mellitus, pernicious anemia, vitiligo, gonadal failure, hypophysitis, celiac disease, myasthenia gravis, and primary biliary cirrhosis. Iatrogenic causes of hypothyroidism include ^{131}I therapy, thyroidectomy, and treatment with lithium or

TABLE 65–4 Causes of Hypothyroidism

Primary Hypothyroidism

Autoimmune
- Hashimoto's thyroiditis
- Part of polyglandular failure syndrome, type II

Iatrogenic
- ^{131}I therapy
- Thyroidectomy

Drug-induced
- Iodine deficiency
- Iodine excess
- Lithium
- Amiodarone
- Antithyroid drugs

Congenital
- Thyroid agenesis
- Thyroid dysgenesis
- Hypoplastic thyroid
- Biosynthetic defect

Secondary Hypothyroidism

Hypothalamic dysfunction
- Neoplasms
- Tuberculosis
- Sarcoidosis
- Langerhans cell histiocytosis
- Hemochromatosis
- Radiation treatment

Pituitary dysfunction
- Neoplasms
- Pituitary surgery
- Postpartum pituitary necrosis
- Idiopathic hypopituitarism
- Glucocorticoid excess (Cushing's syndrome)
- Radiation treatment

amiodarone. Iodine deficiency or excess can also cause hypothyroidism.

CLINICAL MANIFESTATIONS

The clinical presentation of hypothyroidism (Table 65–5) depends on the age of onset and severity of thyroid deficiency. Infants with congenital hypothyroidism (also called cretinism) may present with feeding problems, hypotonia, inactivity, an open posterior fontanelle, and/or edematous face and hands. Mental retardation, short stature, and delayed puberty occur if treatment is delayed.

Hypothyroidism in adults usually develops insidiously. Patients often have fatigue, lethargy, and gradual weight gain for years before the diagnosis is established. A delayed relaxation phase of deep tendon reflexes ("hung-up" reflexes) is a valuable clinical sign characteristic of severe hypothyroidism. Subcutaneous infiltration by mucopolysaccharides, which bind water, causes the edema (termed *myxedema*) and is responsible for the thickened features and puffy appearance of patients with severe hypothyroidism.

Severe untreated hypothyroidism can result in myxedema coma, characterized by hypothermia, extreme weakness, stupor, hypoventilation, hypoglycemia, and hyponatremia and is often precipitated by cold exposure, infection, or psychoactive drugs.

TABLE 65–5 Clinical Features of Hypothyroidism

Children
Learning disabilities
Mental retardation
Short stature
Delayed bone age
Delayed puberty
Adults
Fatigue
Cold intolerance
Weakness
Lethargy
Weight gain
Constipation
Myalgias
Arthralgias
Menstrual irregularities
Hair loss
Dry, coarse, cold skin
Coarse, thin hair
Hoarse voice
Brittle nails
Periorbital, peripheral edema
Delayed reflexes
Slow reaction time
Orange skin hue
Bradycardia
Pleural, pericardial effusions

LABORATORY TESTS

Laboratory abnormalities in patients with primary hypothyroidism include elevated serum TSH and low total and free T_4. Secondary hypothyroidism is characterized by a low or low-normal morning serum TSH in the setting of hypothalamic or pituitary dysfunction. Often, the serum total and free T_4 levels are at the lower limit of normal.

Hypothyroidism is often associated with hypercholesterolemia and elevated creatine phosphokinase MB fraction (the fraction representative of cardiac muscle). Anemia is usually normocytic, normochromic but may be macrocytic (vitamin B_{12} deficiency resulting from associated pernicious anemia) or microcytic (caused by nutritional deficiencies or menstrual blood loss in women).

DIFFERENTIAL DIAGNOSIS

Because the initial manifestations of hypothyroidism are subtle, the early diagnosis of hypothyroidism demands a high index of suspicion in patients presenting with one or more of the signs or symptoms listed in Table 65–5. Early symptoms that are often overlooked include menstrual irregularities (usually menorrhagia), arthralgias, and myalgias.

Laboratory diagnosis may be complicated by the finding of a low total T_4 in euthyroid states associated with low TBG, such as nephrotic syndrome, cirrhosis, or TBG deficiency; in these situations TSH and free T_4 levels are normal. A low total T_4 may also be found in the "euthyroid sick syndrome," a condition occurring in acutely ill patients. In such patients, total and, occasionally, free T_4 levels are low and the serum TSH level is usually normal but may be mildly elevated. Most of these patients should not be treated with levothyroxine replacement, although select patients may benefit from T_3 treatment. This condition may be differentiated from primary hypothyroidism by absence of a goiter, negative antithyroid antibodies, and elevated serum reverse T_3 levels, as well as by clinical presentation.

TREATMENT

Patients with hypothyroidism initially should be treated with synthetic levothyroxine. Although T_3 is the more bioactive thyroid hormone, peripheral tissues convert T_4 to T_3 to maintain physiologic levels of the latter. Thus administration of levothyroxine results in bioavailable T_3 and T_4. A recent study, however, suggested that brain T_4-to-T_3 conversion may be impaired in some patients and that a select group of patients should be treated with both levothyroxine and T_3 (liothyronine). Because T_3 treatment results in fluctuating blood levels, we recommend that patients be initially treated with levothyroxine, and, if they remain symptomatic despite a normal TSH, then low doses of T_3 given two or three

times a day can be added to levothyroxine cautiously. Levothyroxine has a half-life of 8 days, so it needs to be given only once a day. The average replacement dose for adults is 100 to 150 µg/day. In healthy adults, 100 µg/day is an appropriate starting dose. In elderly patients or those with cardiac disease, levothyroxine should be increased gradually, starting at 25 µg daily and increasing this dose by 25 µg every 2 weeks. The therapeutic response to levothyroxine therapy should be monitored clinically and with serum TSH levels, which should be measured 6 weeks after a dose adjustment. TSH levels between 0.5 and 2.0 mU/L are optimal. Patients with secondary hypothyroidism should be treated with levothyroxine until their free T_4 is in the mid-normal range. Appropriate treatment of these patients will result in suppressed serum TSH levels.

In patients with myxedema coma, 300 to 400 µg of levothyroxine is administered intravenously as a loading dose followed by 50 µg daily as well as hydrocortisone (100 mg intravenously three times a day) and intravenous fluids. The underlying precipitating event should be corrected. Respiratory assistance and treatment of hypothermia with warming blankets may be required. Although myxedema coma carries a high mortality despite appropriate treatment, many patients improve in 1 to 3 days.

Subclinical Hypothyroidism

In subclinical hypothyroidism, T_4 and/or T_3 levels are normal or low normal, with a mildly elevated TSH. It is thought that some, but not all, of these patients will develop overt hypothyroidism. The decision about when to treat patients with a mildly elevated TSH is controversial; we recommend that patients should be treated with levothyroxine if they have a TSH greater than 6 mU/L on two occasions and either positive anti-TPO Ab test results or a goiter. If the patient does not have an appreciable goiter and has negative anti-TPO Ab results, then we would recommend treatment with levothyroxine only if he or she has a TSH greater than 10 mU/L on two occasions.

Goiter

Enlargement of the thyroid gland is called goiter. Patients with goiter may be euthyroid (simple goiter), hyperthyroid (toxic nodular goiter, or Graves' disease), or hypothyroid (nontoxic goiter, or Hashimoto's thyroiditis). Thyroid enlargement (often focal) also may be due to a thyroid adenoma or carcinoma. In nontoxic goiter, inadequate thyroid hormone synthesis leads to TSH stimulation with resultant enlargement of the thyroid gland. Iodine deficiency (endemic goiter) was once the most common cause of nontoxic goiter; with the use of iodized salt, it is now almost nonexistent in North America.

Dietary goitrogens can cause goiter, and iodine is the most common goitrogen. Other goitrogens include lithium and vegetable products such as thioglucosides found in cabbage. Thyroid hormone biosynthetic defects can cause goiter associated with hypothyroidism or, with adequate compensation, euthyroidism.

A careful thyroid examination coupled with thyroid hormone tests can delineate the cause of the goiter. A smooth, symmetrical gland, often with a bruit, and hyperthyroidism are suggestive of Graves' disease. A nodular thyroid gland with hypothyroidism and positive antithyroid antibodies is consistent with Hashimoto's thyroiditis. A diffuse, smooth goiter with hypothyroidism and negative antithyroid antibodies may be indicative of iodine deficiency or a biosynthetic defect. Goiters may become very large, extend substernally, and cause dysphagia, respiratory distress, or hoarseness. An ultrasound evaluation or radioiodine scan delineates the thyroid gland, and a thyroid uptake scan can determine the functional activity of the goiter.

Hypothyroid goiters are treated with thyroid hormone at a dose that normalizes TSH. Euthyroid goiters may be treated with levothyroxine therapy; however, in most cases, especially with long-standing goiters, regression is unlikely. Surgery is indicated for nontoxic goiter only if obstructive symptoms develop or substantial substernal extension is present.

Solitary Thyroid Nodules

Thyroid nodules are common. They can be detected clinically in about 4% of the population and are found in about 50% of the population at autopsy. Benign thyroid nodules are usually follicular adenomas, colloid nodules, benign cysts, or nodular thyroiditis. Patients with Hashimoto's thyroiditis may have one prominent nodule on clinical examination, but thyroid ultrasound evaluation may reveal multiple nodules. Although the majority of nodules are benign, a small percentage is malignant. In addition, most thyroid cancers are of low-grade malignancy. History, physical examination, and laboratory tests can be helpful in differentiating benign from malignant lesions (Table 65–6). For example, lymph node involvement or hoarseness is strongly suggestive of a malignant tumor.

The major etiologic factor for thyroid cancer is childhood or adolescent exposure to head and neck radiation. Previously, radiation was used to treat an enlarged thymus, tonsillar disease, hemangioma, or acne. Recently, exposure to radiation from nuclear plants (e.g., Chernobyl, Ukraine) has contributed to an increased incidence of thyroid cancer. The incidence of thyroid cancer is linearly related to the radiation dose up to 1500 rads. TSH is possibly a co-carcinogen; thus patients exposed to high-risk radiation may benefit from TSH suppression by thyroid hormone. Patients with a history of irradiation should have their thyroid carefully palpated every 2 years. In the absence of palpable disease, imaging procedures are not warranted.

The thyroid status of a patient with a thyroid nodule may dictate further evaluation. A hyperthyroid patient is most likely to have a toxic nodule or thyroiditis, whereas a hypothyroid patient probably has a prominent nodule in a gland with Hashimoto's thyroiditis.

TABLE 65–6 High-Risk Factors for Malignancy in a Thyroid Nodule

History
Head/neck irradiation
Exposure to nuclear radiation
Rapid growth
Recent onset
Young age
Male sex
Familial incidence (medullary)
Physical Examination
Hard consistency of nodule
Fixation of nodule
Lymphadenopathy
Vocal cord paralysis
Distant metastasis
Laboratory/Imaging
Elevated serum calcitonin
"Cold" nodule on technetium scan
Solid lesion on ultrasonography
Levothyroxine Therapy
No regression

These patients are unlikely to have malignant lesions. Euthyroid patients with a solitary nodule should undergo an FNA biopsy. This is a safe procedure that has reduced the need for surgical excision. An expert cytologist can identify most benign lesions (75% of all biopsies). In addition, malignant lesions (5% of biopsies), such as papillary, anaplastic, and medullary carcinoma, can be specifically identified. Follicular neoplasms, however, cannot be diagnosed as benign or malignant by FNA; a cytology report of follicular neoplasia, along with "suspicious" cytology, requires surgical excision.

In the past, thyroid scans were used to evaluate single thyroid nodules. "Hot" thyroid nodules are almost always benign. Most cancers are "cold," but, because most benign lesions are also "cold," these patients still require FNA. Thus thyroid scans have largely been supplanted by aspiration for evaluation of thyroid nodules.

Benign thyroid nodules may be treated with levothyroxine suppression therapy with a follow-up thyroid examination in 6 months. A significant decrease in the size of the nodule occurs in a few cases and may be monitored by ultrasound. Most benign lesions and some cancers remain unchanged in size. An increase in size of the nodule while the patient is on suppression therapy warrants a reevaluation.

Thyroid Carcinoma

The most common type of thyroid carcinoma is papillary carcinoma (65 to 70%). Follicular carcinoma (20%), anaplastic carcinoma (5 to 10%), medullary carcinoma (5%), and lymphoma (1%) occur less frequently. Papillary carcinoma is associated with local invasion and lymph node spread. Poor prognosis is associated with thyroid capsule invasion, size greater than 2.5 cm, age at onset older than 45 years, tall-cell variant, and lymph node involvement. Follicular carcinoma is slightly more aggressive than papillary carcinoma and can spread by local invasion of lymph nodes or hematogenously to bone, brain, or lung. Patients may present with metastases before diagnosis of the primary thyroid lesion. Anaplastic carcinoma tends to occur in older individuals (>50 years), is very aggressive, and rapidly causes pain, dysphagia, and hoarseness. Death usually occurs in the first year.

Medullary thyroid carcinoma is derived from calcitonin-producing parafollicular cells and is more malignant than papillary or follicular carcinoma. It is multifocal and spreads both locally and distally. It may be either sporadic or familial. When familial, it is inherited in an autosomal dominant pattern and is part of multiple endocrine neoplasia type IIA (medullary carcinoma of the thyroid, pheochromocytoma, and hyperparathyroidism) or multiple endocrine neoplasia type IIB (medullary carcinoma of the thyroid, mucosal neuromas, intestinal ganglioneuromas, marfanoid habitus, and pheochromocytoma). Elevated basal serum calcitonin levels confirm the diagnosis. Evaluation for *RET* proto-oncogene mutations should be performed in patients with medullary carcinoma, and, if present, all first-degree relatives of the patients should be examined.

TREATMENT

Lobectomy can be performed for papillary carcinomas less than 1.5 cm. These patients require lifelong levothyroxine suppressive therapy and yearly thyroid examinations. Larger papillary or follicular tumors require near-total thyroidectomy, with modified neck dissection if there is evidence of lymph node metastases. Postoperatively, T_3 is administered for 2 months. The medication is stopped for 2 weeks, and the patient is scanned with 3 mCi of ^{131}I. If uptake occurs, the patient is treated with ^{131}I until no further uptake is observed. Sufficient levothyroxine is then administered to suppress serum TSH to subnormal levels. Frequent neck examinations for masses should be accompanied by measurement of serum thyroglobulin levels. Recurrence/metastases are also evaluated by ^{131}I total-body scans carried out under conditions of TSH stimulation, which increase ^{131}I uptake by the thyroid tissue. Elevated TSH levels can be achieved by withdrawal of thyroxine supplementation for 6 weeks. As an alternative, in order to avoid the resultant symptomatic hypothyroidism, recombinant human TSH can be administered while the patient remains on thyroid hormone. A rise in serum thyroglobulin levels suggests recurrence of thyroid cancer. Local or metastatic lesions that take up ^{131}I (whole-body scan) can be treated with radioactive iodine after the patient has stopped thyroid hormone replacement, whereas those that do not take up ^{131}I can be treated with local x-ray therapy. Medullary carcinoma of the thyroid requires total thyroidectomy with

removal of the central lymph nodes in the neck. Completeness of the procedure is determined by measurement of serum calcitonin, which is also used in monitoring for recurrence.

Anaplastic carcinoma is treated with isthmusectomy to confirm the diagnosis and to prevent tracheal compression, followed by palliative x-ray treatment. Thyroid lymphomas are also treated with x-ray therapy.

The prognosis for well-differentiated thyroid carcinomas is good. Age at the time of diagnosis and sex are the most important prognostic factors. Men older than 40 and women older than 50 have higher recurrence and death rates than do younger patients. The 5-year survival rate for invasive medullary carcinoma is 50%, whereas the mean survival for anaplastic carcinoma is 6 months.

PROSPECTUS FOR THE FUTURE

- Development of short-acting preparations of triiodothyronine, allowing for the treatment of hypothyroidism with a combination of triiodothyronine and levothyroxine
- Use of recombinant thyroid-stimulating hormone (TSH) in combination with radioactive iodine to treat euthyroid goiters and thyroid cancer recurrences and metastases
- Acceptance of a TSH screening regimen to detect asymptomatic thyroid disease

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