HISTORICAL BACKGROUND

Goiters (from the Latin guttur, throat) have been known since 2700 B.C., long before the thyroid gland was recognized. The thyroid gland was first documented by the Italians of the Renaissance period. Leonardo da Vinci originally depicted the thyroid in his drawings as two separate glands on either side of the larynx. The term thyroid gland (Greek thyreoeides, shield-shaped) is attributed to Thomas Wharton in his Adenographia (1656), although Bartholomeus Eustachius had used the description previously; his work, however, was not published until the eighteenth century. In 1619, Hieronymus Fabricius ab Aquispendente recognized that goiters arose from the thyroid gland. It was Albrecht von Haller in 1776 who classified the thyroid as a ductless gland. Many functions were imaginatively ascribed to the thyroid gland, including lubrication of the larynx, providing a reservoir of blood to prevent engorgement of the brain, or beautifying women's necks.

Treatment of goiter was varied; marine preparations, such as burnt seaweed, were among the most effective. In 1811 Bernard Courtois discovered iodine in the ash of burnt seaweed. Surgery of goiters was hazardous, with an exceedingly high complication and mortality rate. The first accounts of thyroid surgery were given by Roger Frugardi in 1170. Failing response to medical treatments, two setons were inserted at right angles into the goiter and tightened twice daily until the goiter separated. The open wound was then treated with caustic powder and left to heal.

Thyroid surgery continued to be hazardous (mortality over 40 percent) until the mid-nineteenth century, when advances in general anesthesia (1840s), antisepsis (1860s), and hemostasis (1870s) enabled surgeons to perform thyroid surgery with significantly reduced mortality. The most notable thyroid surgeons were Emil Theodor Kocher (1841–1917) (Fig. 36-1) and C. A. Theodor Billroth (1829–1894), who performed thousands of operations with increasingly successful results. As patients survived longer, however, problems emerged that had not been previously encountered. After total thyroidectomy, patients became myxedematous with cretinous features; the changes were more noticeable in children. Kocher coined the term “cachexia strumipriva” and wrongly attributed it to operative tracheal trauma giving rise to chronic asphyxia. Felix Semon suggested that myxedema was secondary to the loss of thyroid function, a view originally treated with skepticism. This was later proved true by Victor Horsley's studies on monkeys undergoing total thyroidectomy.

The first successful treatment of myxedema was achieved in 1891 by George Murray when he prepared an extract of sheep's thyroid that he injected subcutaneously into a
patient. The following year, Edward Fox demonstrated that oral therapy in the form of “half a sheep's thyroid, lightly fried and taken with currant jelly once a week” was equally effective.

Few of Billroth's patients developed myxedema, but William Halsted suggested that this was because of a difference in operative technique. Kocher was extremely neat and precise, operating slowly in a bloodless field. He removed all the thyroid, and his patients developed myxedema but rarely suffered laryngeal nerve damage or postoperative tetany. Billroth, however, worked rapidly and with less concern for hemorrhage. He often removed the parathyroid glands but left more thyroid tissue and therefore encountered postoperative hypoparathyroidism but rarely myxedema. In 1909 Kocher received the Nobel Prize for medicine in recognition “for his works on the physiology, pathology, and surgery of the thyroid gland.

EMBRYOLOGY
A clear understanding of the developmental embryology and anatomy of the thyroid gland is essential for the clinician performing a thorough physical examination of the gland and aids in evaluating diagnostic images. Knowledge of possible developmental anomalies and the thyroid gland's relationship to the parathyroid glands and other neck structures is vital in performing safe and effective thyroid operations.

The thyroid gland originates from the base of the tongue in the region of the foramen cecum. Embryologically, it is an offshoot of the primitive alimentary tract. The endoderm cells in the midline of the floor of the pharyngeal anlage thicken and form a median thyroid anlage, which migrates caudally into the neck (Fig. 36-2). The anlage descends along a tract that runs anterior to the structures that form the hyoid bone and the larynx; it is composed of epithelial cells that provide the follicular cells of the thyroid. As it descends, it is joined laterally by a pair of components originating from the ultimobranchial bodies of the fourth and fifth branchial pouches. These lateral components supply the C cells of the thyroid, which secrete calcitonin. When the C cells become neoplastic, the result is medullary carcinoma of the thyroid. An understanding of this anatomy explains why medullary carcinoma usually is located in the upper poles of the thyroid and virtually never in the isthmus or pyramidal lobe. The thyroid gland forms follicles by the end of the tenth week of gestation and concentrates iodine and produces colloid by the end of the twelfth week.

ANOMALIES
Rarely, the thyroid gland, whole or in part, descends more caudally. This results in thyroid tissue located in the superior mediastinum behind the sternum, adjacent to the aortic arch or between the aorta and the pulmonary trunk, within the upper portion of the pericardium, or in the interventricular septum. The following types of anomaly can be encountered.

Pyramidal Lobe
The migratory tract of the developing thyroid gland is known as the thyroglossal tract or duct. Normally the duct atrophies, although it may remain as a fibrous band. In about 80 percent of people, the distal end that connects to the thyroid persists as a pyramidal lobe projecting up from the isthmus, lying just to the left of the midline (Fig. 36-3). In the normal individual the pyramidal lobe is not palpable, but in disorders resulting in thyroid hypertrophy (e.g., Graves' disease, diffuse nodular
goiter, or lymphocytic thyroiditis), the pyramidal lobe usually is enlarged and palpable.

**Lingual Thyroid**

The median thyroid anlage sometimes fails to develop, resulting in athyreosis, or it may develop but fail to descend, leading to a lingual thyroid (Fig. 36-4). Lingual thyroid is estimated to occur in 1 in 3000 cases of thyroid disease. It occurs more commonly in females, and some develop hypothyroidism. In these patients, the lingual thyroid is the only functioning thyroid tissue, although a normally situated thyroid also may be present.

Presentation usually is dependent upon the size of the lingual thyroid. An asymptomatic posterior lingual mass may be discovered because of physiologic thyroid hyperactivity. If tumor formation occurs the patient presents with symptoms of a posterior oral swelling. If the thyroid tissue continues to enlarge, symptoms such as a choking sensation, dysphagia, dyspnea, and dysphonia may predominate.

Diagnosis is established by scanning with radioiodine (123I) (Fig. 36-5) or technetium (99mTc). Treatment consists of thyroid suppression with thyroxine; operation for symptoms or an enlarging mass is rarely necessary and may result in hypothyroidism.

Malignancy is rare, occurring in less than 3 percent of patients with symptomatic lingual thyroids. Diagnosis in these cases may be established by fine-needle aspiration cytology (FNAC) or biopsy.

**Thyroglossal Duct Cyst**

Thyroglossal duct cysts are midline structures containing thyroid epithelium; they may occur anywhere along the course of the thyroglossal duct, though typically they are found between the isthmus of the thyroid gland and the hyoid bone (Fig. 36-6). The cysts usually cause few symptoms but may become infected, prompting the patient to seek medical advice.

Diagnosis may be established by asking the patient to protrude his or her tongue; when the tongue is protruded, the thyroglossal duct cyst moves upward. Treatment is by surgical excision and should include the thyroglossal duct remnant. As the duct may pass anteriorly to, posteriorly to, or through the hyoid bone, the central portion of the hyoid bone is removed to minimize the possibility of recurrence (the Sistrunk procedure).

About 1 percent of thyroglossal duct cysts contain thyroid cancer, and approximately 25 percent of patients with thyroglossal duct cysts that contain papillary cancer have papillary cancer elsewhere within the thyroid gland. Occasionally squamous cell carcinomas develop in thyroglossal duct cysts. Medullary thyroid cancers are not found in thyroglossal duct cysts.

**Lateral Aberrant Thyroid**

Lateral aberrant thyroid tissue is rare. It is believed that the so-called “lateral aberrant thyroid” is almost always a well-differentiated papillary carcinoma (exhibiting a follicular pattern) that has metastasized to a cervical chain lymph node, replacing the node with tumor. Diagnosis of lateral aberrant thyroid should direct the clinician to
search for the primary thyroid tumor, which is almost always present in the ipsilateral lobe of the thyroid. In some patients the primary thyroid cancer is microscopic. Normal ectopic thyroid tissue may be present in the neck; it is always in the central neck (the migratory path of the normal thyroid), it is not situated in lymph nodes, and it is benign.

ANATOMY
The normal adult thyroid gland is light brown in color and firm in consistency, weighing 15 to 20 g. It is formed by two lateral lobes connected centrally by an isthmus. The lobes are approximately 4 cm long, 2 cm wide, and 20 to 40 mm thick, with the isthmus 2 to 6 mm thick. The lateral lobes run alongside the trachea, reaching the level of the middle thyroid cartilage superiorly. Laterally, the lobes are adjacent to the carotid sheath and the sternocleidomastoid muscles; anteriorly, they are adjacent to the strap muscles (sternothyroid and sternohyoid). In approximately 80 percent of individuals, a pyramidal lobe is present, usually just to the left of the midline, extending upward from the isthmus along the anterior surface of the thyroid cartilage. It is a remnant of the thyroglossal duct (see Fig. 36-3).

The four parathyroid glands usually are closely related to the thyroid gland, found on the posterolateral surface of the lobes, within 1 cm of the inferior thyroid artery in 80 percent of individuals. The upper parathyroid glands are more dorsal or posterior and usually are situated at the level of the cricoid cartilage. The lower parathyroid glands are more variable in position but usually are anterior to the recurrent laryngeal nerves. The thyroid gland is enveloped by a loosely connecting fascia that is formed from the partition of the deep cervical fascia into anterior and posterior divisions. The thyroid is attached to the trachea and suspended from the larynx. It moves upward with elevation of the larynx on swallowing. The true capsule of the thyroid is a thin, fibrous layer, densely adherent, that sends out septa that invaginate the gland, forming pseudolobules. Thyroid nodules are palpable in about 4 percent of adults; smaller, occult nodules can be detected by ultrasound or at postmortem examination in more than 50 percent of older adults.

The thyroid gland has an abundant blood supply provided by four major arteries. The paired superior thyroid arteries arise as the first branch of the external carotid artery, approximately at the level of the carotid bifurcation, and descend several centimeters in the neck to the superior pole of each thyroid lobe. Here the arteries divide into anterior and posterior branches as they reach the gland. The paired inferior thyroid arteries arise from the thyrocervical trunk of the subclavian arteries and enter the gland from a posterolateral position. Occasionally a fifth artery, the thyroidea ima, is present, originating directly from the aortic arch or the innominate artery and ascending in front of the trachea to enter the gland in the midline inferiorly. A rich venous plexus forms under the capsule and drains to the internal jugular vein on both sides via the superior thyroid veins (which run with the superior thyroid artery) and the middle thyroid veins, which can vary in number, passing from the lateral aspect of the lobes. The inferior thyroid veins leave the inferior poles bilaterally, usually forming a plexus that drains into the brachiocephalic vein. Lymphatic drainage of the thyroid gland is primarily to the internal jugular nodes. The superior pole and medial isthmus drain to the superior groups of nodes, and the inferior groups drain the lower gland and empty into pretracheal and paratracheal nodes.
Innervation of the gland is by sympathetic fibers from the superior and middle cervical sympathetic ganglia. The fibers enter with the blood vessels and are vasomotor in action. Parasympathetic fibers are derived from the vagus nerve and reach the gland via branches of the laryngeal nerves.

Microscopically, the thyroid is divided into lobules that contain 20 to 40 follicles. There are roughly $3 \times 10^6$ follicles in the adult male thyroid gland. The follicles are spherical and average 30 mm in diameter. Each follicle is lined by cuboidal epithelial cells and contains a central store of colloid secreted from the epithelial cells under the influence of the pituitary hormone, thyroid stimulating hormone (TSH). The second group of thyroid secretory cells are the C cells or parafollicular cells, which contain and secrete the hormone calcitonin. They are found as individual cells or clumped in small groups in the interfollicular stroma, abutting between follicular cells. They are located in the upper poles of the thyroid lobes, reflecting their origin as neuroectodermal cells derived from the ultimobranchial bodies, and are part of the amine containing precursor uptake decarboxylase (APUD) series described by Pearse.

**Laryngeal Nerves**

It is important to note the close relationship of the thyroid gland to the recurrent laryngeal nerves and the possible variations in the course of the recurrent nerves. The recurrent laryngeal nerves supply the intrinsic muscles of the larynx, and damage to one of them leads to ipsilateral vocal cord paralysis. Similarly, the external branch of the superior laryngeal nerve, which innervates the cricothyroid muscle, also is at risk during thyroid surgery. Damage of either nerve may result in a disability of phonation.

Identification of the nerves, rather than attempting to avoid them, should be standard practice for the surgeon. The recurrent laryngeal nerves originate from the vagus nerves. On the right side, the recurrent nerve originates where the vagus nerve crosses the first part of the subclavian artery; the nerve loops under the subclavian artery and ascends slightly obliquely to enter the larynx at the level of the cricoid cartilage and posterior to the cricothyroid muscle. The left recurrent nerve branches from the vagus as it crosses the aortic arch and loops posteriorly around the ligamentum arteriosus before it ascends medially in the tracheoesophageal groove to enter the larynx opposite the contralateral nerve. The variable course taken by the recurrent nerves is demonstrated in Fig. 36-7. The right recurrent nerve is in the tracheoesophageal groove in 64 percent of people, compared to 77 percent on the left. The nerve is lateral to the trachea on the right in 28 percent of people and in 17 percent on the left. In a minority of people the nerve is anterolateral to the trachea (right 8 percent, left 6 percent), exposing it to accidental division during subtotal lobectomy. A misconception is that the recurrent laryngeal nerves run behind the inferior thyroid artery, but this is true in only 53 percent of people on the right and 69 percent on the left. In others the nerve's course is anterior to the artery (right 37 percent, left 24 percent), or between branches of the artery (right 7 percent, left 6 percent). Failure to identify the course of the nerves can lead to accidental damage.

The recurrent laryngeal nerves are not always recurrent; in about 1 percent of people one of the nerves is nonrecurrent. This occurs almost exclusively on the right in association with a vascular anomaly of the right subclavian artery; rarely, it occurs on the left with dextrocardia or situs inversus. In these situations, the nerve arises from
the vagus to run directly to the larynx, often in close proximity to the superior thyroid vessels, and may be at risk when these vessels are transected (Fig. 36-8).

The superior laryngeal nerve arises from the vagus near the base of the skull and descends medial to the carotid vessels. At the level of the hyoid bone it divides into two branches, one sensory (internal branch), and the other motor (external branch). The external branch runs on the lateral surface of the inferior constrictor muscle and descends to innervate the cricothyroid muscle (Fig. 36-9). This muscle alters vocal cord tension and affects the pitch of the voice. In most instances the nerve runs in close proximity to the superior pole vessels, and in 21 percent of people it is closely related to the vessels and is at significant risk if it is not identified at operation. To avoid injury, the superior pole vessels should be individually ligated and divided low on the thyroid gland and dissected laterally to the cricothyroid muscle.

PHYSIOLOGY

Through release of its principal hormones, thyroxine (T4) and triiodothyronine (T3), the thyroid gland influences the metabolic rate of all tissues. Increased secretion increases the metabolic rate; conversely, the rate decreases when secretion is decreased. Release of T4 and T3 is stimulated by the anterior pituitary hormone thyrotropin or thyroid-stimulating hormone (TSH). Secretion of TSH is directly suppressed by T4 and T3 (a negative feedback loop). TSH release also is stimulated by the hypothalamic hormone thyrotropin-releasing hormone (TRH). Thyroid hormone production is influenced by numerous physiologic, pathologic, and pharmacologic factors.

Iodine Metabolism

The formation of thyroid hormones is dependent on the availability of exogenous iodine. The average daily iodine requirement is 0.1 mg. Iodine is found principally in fish, milk, and eggs. In the United States, iodine is routinely added to bread and salt in order to reduce the frequency of iodine deficiency. Iodine is rapidly converted to iodide in the stomach and jejunum and is absorbed into the bloodstream within 1 h; and from there it is distributed uniformly throughout the extracellular space (Fig. 36-10). Iodide is actively transported into the thyroid follicular cells by an ATP-dependent process. The thyroid-serum iodine ratio under normal conditions is about 50:1, and most of the body's store of iodine is found in the thyroid gland (90 percent). Thyroid-serum ratios can be as high as 500:1 in certain instances, such as iodine deficiency or Graves' disease.

One-third of the loss of iodine from the plasma is accounted for by thyroid concentration, and the other two-thirds through renal excretion. In studies involving radiolabeled iodine, all the iodine is concentrated within the thyroid or excreted in the urine within 48 h, and the plasma and tissues are mostly cleared of iodide. Evidence of labeled iodine in serum is accounted for by secretion from the thyroid gland in the form of thyroid hormone.

Synthesis of Thyroid Hormone

Steps in the synthesis of thyroid hormone are: (1) active trapping and concentration of iodide in the follicular cell; (2) rapid oxidation of iodide to iodine; (3) linkage of iodine with tyrosine residues in thyroglobulin; (4) coupling of these iodotyrosines (monoiodo- and diiodotyrosine) to form the active thyroid hormones T4 and T3.
Active accumulation of iodide in the thyroid gland is stimulated by TSH, acting via a specific membrane receptor located in the thyrocyte plasma membrane. This mechanism is probably through changes in cyclic adenosine monophosphate (cAMP). Once inside the thyroid cell, the iodide diffuses through the cytoplasm to the apical membrane. It remains in its free state for a short time before being oxidized by peroxidase and hydrogen peroxidase. Iodine rapidly links to tyrosine residues present in abundance in thyroglobulin, a thyroid-specific protein, resulting in the formation of two separate molecules, monoiodotyrosine (MIT) and diiodotyrosine (DIT). Two molecules of DIT combine to form tetraiodothyronine, or thyroxine (T4); a molecule of MIT and DIT combine to form 3,3',5-triiodothyronine (T3) or 3,3'5'-triiodothyronine, reverse T3 (rT3). The coupling steps are catalyzed by peroxidase in the presence of H2O2 and also are rate dependent on TSH.

When iodide transport is defective or when oxidation to iodine is impaired because of disease or pharmacologic agents, goiter or hypothyroidism may result. The antithyroid drugs (propylthiouracil, methimazole, and carbimazole) inhibit the oxidation of iodide to iodine by competitive inhibition of peroxidase and also may interfere with the coupling reaction. In high doses iodide also inhibits iodine trapping. It also has an antithyroid action by inhibiting the proteolysis involved in the release of thyroid hormone. Potassium iodide tablets often are administered to people exposed to radiation leaks involving radioactive forms of iodine, such as nuclear accidents, because it blocks trapping by the thyroid gland.

Storage, Secretion, and Metabolism of Thyroid Hormone
T4 and T3 are bound to thyroglobulin and are stored in the colloid of the thyroid follicles. Release of the active hormones is by a process of endocytosis. The colloid is taken up by the follicular cell as discrete packets (endosomes), which then fuse with lysosomes containing hydroxylases. Hydrolysis results in production of all component parts, T4, T3, rT3, MIT, and DIT. Through a process of deiodination most of the iodide is released from MIT and DIT and reused in the follicle. The iodothyronines are more resistant to this process and are secreted; these steps also are TSH-dependent.

The active thyroid hormones circulate in the plasma attached to plasma proteins, principally the carrier proteins, thyroid hormone-binding globulin (TBG), thyroid hormone-binding prealbumin (TBPA), and albumin. About 99.98 percent of thyroid hormone circulates in the plasma bound to protein, and the remaining 0.02 percent is unbound and is the free, active physiological fraction. In some conditions TBG may be increased, usually as a result of estrogen effects of pregnancy or the contraceptive pill. This results in a higher circulating amount of T4 because of increased serum binding capacity. In this situation, active free T4 levels remain unaltered.

T3 is the more potent of the two thyroid hormones (rT3 is biologically inert), although its circulating plasma level is much lower than that of T4; the ratio is 10:1 to 20:1. T3 is less tightly bound to protein in the plasma than T4, and so it enters tissues more readily. T3 is three to four times more active than T4 per unit weight, with a half-life of about 1 day, compared to about 7 days for T4. Though the thyroid gland produces some T3 and rT3, it is known that 75 percent of T3 is produced by the extrathyroidal conversion of T4 to T3 in the peripheral tissues. Almost 85 percent of T4 is converted
peripherally to metabolically inert rT3 or T3. Some studies suggest that T4 is a prohormone and that T3 is the only hormone acting at the cellular level.

Molecular Basis of Thyroid Hormone Action
Thyroid hormones are transported across the plasma membrane of tissues by an ATP-dependent transport system. Uptake by the tissue is rate-limited by the amount of free hormone available at the tissue level. At the cellular level T3 is the active hormone, and its activity is mediated through T3 receptors located in the cell nucleus. The receptors bind to regulatory genes and modify the expression of these genes.

T3 receptors belong to a group of hormone-responsive nuclear transcription factors. There are two types of T3 receptor genes, α and β, located on chromosomes 17 and 3. Expression of T3 receptors is tissue specific. T3 receptors α1, α2, and β1 mRNA are expressed in almost all tissues, but some T3 receptors are expressed only in certain tissues, e.g., β2 is found only in the brain. The brain contains mostly α receptors, the liver β receptors, and cardiac muscle expresses both.

Deiodination and Excretion
Deiodination of thyroid hormones is effected by three different types of deiodination enzymes, which are tissue specific. The released iodine is returned to the blood, where it reenters the metabolic pool. The residual T3 and T4 are conjugated with glucuronic acid, which renders the hormones water soluble and facilitates excretion in urine and bile, or sulphate. Some of the excreted iodothyronines are reabsorbed from the small intestine, constituting the enterohepatic circulation. About one-third of total body clearance is effected through the bile, but up to 50 percent of the thyroxine may be reabsorbed. Significant amounts of thyroid hormone and iodine may appear in the milk of lactating mothers.

Regulation of Thyroid Activity
The principal homeostatic control of thyroid hormone secretion is the hypothalamic-pituitary-thyroid axis. The basophil cells of the anterior pituitary produce TSH, which directly regulates thyroid function. TSH acts on the thyroid cell to promote thyroid hormone production at all levels, enhancing iodine uptake, increasing synthesis, and raising secretion of T4. TSH also has a secondary action on thyroid gland growth, increasing cellularity and vascularization of the gland. Secretion of TSH is regulated at two levels. Thyrotropin-releasing hormone (TRH), is produced by the hypothalamus and reaches the gland via the hypophyseal portal system to stimulate TSH release (Fig. 36-11). TRH binds to high-affinity TRH receptors on the anterior pituitary cells. Originally it was thought that TRH exerted its action of TSH release via adenylate cyclase and cAMP, but now it is believed that postreceptor activation is via the phospholipase-C–based hydrolysis of inositol phospholipids, leading to Ca2+ and diacylglycerol activation of protein kinase C. Release of TRH from the hypothalamus is suppressed by T3, acting in a feedback loop. TRH has been shown to be equipotent in stimulating release of prolactin from the pituitary and TSH.

More important to thyroid hormone regulation is the direct feedback exerted on the pituitary by the level of thyroid hormone in the blood. Raised levels of thyroid hormone suppress TSH and TRH secretion, and lowered levels promote secretion. Iodine deficiency increases the goitrogenic effects of TSH on the thyroid.
ASSESSMENT OF PATIENTS WITH THYROID DISEASE

Thyroid disease may be divided into two types: problems relating to function (hyperthyroidism/hypothyroidism) and thyroid masses. The two types are not mutually exclusive and patients frequently present with both problems.

History
Obtaining an accurate history is essential in assessing thyroid disease. Symptoms such as dysphagia, dyspnea, and choking are frequently encountered in patients with goiter and may be exaggerated by patients raising their arms above their heads (Pemberton's sign). Pain is uncommon. Localized pain may suggest malignancy, especially medullary thyroid cancer, whereas pain radiating to the ear often is observed in patients with thyroiditis or hemorrhage within the thyroid gland. A change in the character of the voice should also be of concern because it may suggest involvement of the recurrent laryngeal nerves in a malignant process, with vocal cord paralysis. A past history of exposure to radiation, family history of benign or malignant thyroid disease, living in an iodine-deficient area, or ingestion of goitrogenic drugs also are significant.

Physical Examination
Thyroid masses rise on swallowing; most thyroid swellings are accurately discernible by observing the patient swallow. Failure to observe before palpating the thyroid gland may lead to missing a large retrosternal goiter arising from beneath the sternum and clavicles.

Palpation usually is performed from behind while the patient is sitting in a chair with the neck slightly extended and should include palpation of the gland while the patient swallows. A landmark is the cricoid cartilage; the isthmus almost always crosses a fingerbreadth below the cricoid. The normal thyroid gland usually is not palpable unless the patient has a particularly thin neck. The thyroid gland may be diffuse and bilaterally enlarged (goiter), as encountered in conditions such as Graves' disease (hyperthyroidism), Hashimoto's thyroiditis, or multinodular goiter. A unilateral mass may be palpated, as in a colloid nodule, follicular adenoma, or carcinoma.

The cervical chain of lymph nodes should be assessed as well as the nodes in the posterior triangle. The jugular nodes immediately adjacent to a thyroid nodule often are involved in patients with a papillary thyroid cancer. A Delphian node should be palpated for just above the thyroid isthmus and cricoid cartilage.

(Fine-Needle Aspiration Cytology (FNAC)
Fine-needle aspiration cytology is a simple and low-risk technique that is an integral part of thyroid assessment in the outpatient setting for patients with thyroid nodules. A 23-gauge needle is inserted into the thyroid swelling, and several passes are made while aspirating the syringe. Cells are placed on prelabeled dry glass slides; some are then immediately placed in 70% alcohol while others are air dried. These slides are stained by Papanicolaou or Wright's stains and observed under the microscope. Skilled cytopathologists can accurately diagnose the majority of thyroid diseases using this technique, with a high degree of specificity. This test is less accurate in patients with thyroid nodules and a history of familial nonmedullary thyroid cancer and in patients with a previous history of exposure to low-dose therapeutic radiation.
Benign and malignant thyroid tumors are common in such patients, and the tumors usually are multifocal.

Tests of Thyroid Function
(Thyrotropin (TSH, reference range 0.15–4.2 mU/mL)
Thyrotropin secretion from the anterior pituitary is controlled via a negative feedback loop by serum T3 and T4 levels. In cases in which high T3 and T4 levels are encountered (Graves' disease, toxic nodular goiter), TSH levels will be accordingly low and may be undetectable. When T4 levels are low (primary thyroid destruction, e.g., end-stage Hashimoto's thyroiditis), TSH levels will be correspondingly high. Many clinicians believe that the circulating level of TSH is the single most sensitive test of thyroid function.

Older radioimmunoassays have been replaced with more sophisticated immunometric assays, using monoclonal antibodies that target two separate sites (increasing specificity) on the TSH molecule. One monoclonal antibody is labeled with a nonradioactive marker, allowing readings with an accuracy down to 0.005 mU/mL. A reference range of normal TSH levels has been established in euthyroid patients, against which levels from the test subject can be compared.

Total Thyroxine (TT4, reference range 55–150 nmol/L) and Free Thyroxine (FT4, 12–28 pmol/L)
Total thyroxine concentration reflects the fraction of T4 bound to TBG and other carrier proteins in the serum and also the amount of free T4 in circulation. T4 production from the thyroid is dependent on TSH from the pituitary and an adequate intake of iodine in the diet. When T4 production from the thyroid is increased, the bound and free T4 levels rise (FT4 remains in equilibrium with bound T4), resulting in an increase of TT4. When T4 production from the thyroid decreases, bound and FT4 levels drop, which leads to decreased TT4 levels. Conditions leading to a change in the level of TBG (e.g., estrogen intake) can alter the level of TT4 (as binding sites increase), but are not reflected by changes in circulating FT4, and so the individual remains euthyroid.

Free T4 estimates are not performed as a routine screening tool in thyroid disease. Use of this test is confined to cases of early hyperthyroidism in which TT4 levels may be normal but FT4 levels are raised. In patients with end-organ resistance to T4 (Refetoff syndrome) TT4 levels are increased, but TSH levels usually are normal.

Total Triiodothyronine (TT3, reference range 1.5–3.5 nmol/L) and Free Triiodothyronine (FT3, 3–9 pmol/L)
Levels of total T3 or free T3 are not used as a routine investigation of thyroid function. FT3 is most useful in confirming the diagnosis of early hyperthyroidism, in which levels of FT4 and FT3 rise before TT4 and TT3. Most T3 production comes from the peripheral conversion of T4, and this process may be inhibited by conditions such as starvation illness (low T3 syndrome) or by the effect of certain drugs (e.g., propranolol). There is a rare condition of T3 thyrotoxicosis in which levels of TT4 in the hyperthyroid patient are normal and radioiodine uptake is normal but the TT3 level is raised. This condition is more common in patients from endemic goiter areas and in patients with small solitary thyroid nodules.
HYPERTHYROIDISM/THYROTOXICOSIS

Thyrotoxicosis is the clinical syndrome that results when excessive levels of active thyroid hormone are secreted into the circulation. There are many causes of thyrotoxicosis, but two predominate: Graves' disease (diffuse toxic goiter) and toxic solitary or multinodular goiter (Plummer's disease). The rarer conditions causing thyrotoxicosis are listed in Table 36-1. Conditions resulting in increased thyroid hormone production, such as Graves' and Plummer's disease, or secondary hyperthyroidism because of a TSH-secreting pituitary tumor should be distinguished from conditions in which there is a leak of thyroid hormone, i.e., patients with subacute painless or painful thyroiditis. Hyperthyroidism also can result from taking thyroid hormone (factitious hyperthyroidism), from struma ovarii, from increased secretion of human chorionic gonadotropin with a molar pregnancy, and from rare metastatic thyroid cancers that secrete thyroid hormone.

Graves' Disease (Diffuse Toxic Goiter)

Graves' disease is the most common form of thyrotoxicosis. Although originally described by the Welsh physician Caleb Parry in a posthumous article in 1825, the disease is known as Graves' disease after Robert Graves, a physician from Ireland, who described three patients in 1835. Graves' disease is about six times more common in women, and although it may develop at any age, it is most prevalent in young adults (20 to 40 years of age). Associated extrathyroidal manifestations of this autoimmune disease include exophthalmos, pretibial myxedema, dermopathy, acropachy, and vitiligo.

Pathogenesis and Pathology

Graves' disease is an autoimmune disorder in which pathogenic thyroid-stimulating antibodies or immunoglobulins are directed at the TSH receptor on thyroid follicular cells. Binding of the antibodies stimulates the receptors and leads to excess thyroid hormone secretion, which characterizes the condition. Originally the responsible antibody was thought to be long-acting thyroid stimulating antibody (LATS), described by Adams and Purves in 1956. It is apparent now that a whole family of antibodies contribute to the development of the disease. Thyroid-stimulating immunoglobulins (TSI) or antibodies (TSAb) attach to and stimulate the TSH receptor, and TSH-binding inhibiting immunoglobulins (TSII) or antibodies (TBIA) block the TSH receptor. Current practice is to group all these antibodies together under the term thyroid receptor antibodies (TRAb).

What initiates Graves' disease and antibody production is unclear. One theory suggests a defect in the suppressor T lymphocytes allowing helper T cells to stimulate the production of TSI from helper B cell clones. Another theory is that an immune response is launched to altered antigens on the follicular cell surface, an observation supported by the fact that Graves' disease and ophthalmopathy occur more frequently in patients who have been irradiated to the head and neck. Genetic factors also are clearly involved; identical twins have a 50 percent chance of developing the condition if the twin has it, compared to a 30 percent chance in fraternal, nonidentical twins. This is probably through increased frequency of leukocyte antigen expression (HLA-b8 and DR3 in Caucasians and HLA-Bw35 in Japanese).

Macrosopically, the thyroid gland in patients with Graves' disease is diffuse and smoothly enlarged, and the gland's vascularity also is increased. Microscopically, the
gland is hyperplastic, and the epithelium is columnar, with minimal colloid present. The nuclei exhibit mitosis, and papillary projections of hyperplastic epithelium are common. There may be aggregates of lymphoid tissue, and vascularity is markedly increased.

Clinical Features Common to All Forms of Thyrotoxicosis
The clinical symptoms and signs of thyrotoxicosis are the same in patients with Graves' disease and toxic nodular goiter, except that patients with Graves' disease usually have more severe hyperthyroidism and have extrathyroidal manifestations of disease. Attention should be paid to a family history of autoimmune thyroid disease, including Graves' disease, Hashimoto's thyroiditis, and other autoimmune disorders.

Manifestation of the increased caloric turnover may be evident. Patients develop heat intolerance, increased thirst, sweating, and weight loss despite adequate caloric intake. Women may develop amenorrhea and decreased fertility and have an increased incidence of miscarriage. Cardiovascular manifestations are tachycardia or atrial fibrillation. In cases in which high-output cardiac failure ensues, signs and symptoms of congestive cardiac failure such as dyspnea and peripheral edema or even anasarca may become evident. Adrenergic stimuli may be particularly distressing, and fatigue, agitation and excitability, disturbed sleep pattern, emotional lability, hyperkinesis, and tremor may be present. In marked cases, psychosis can develop. Diarrhea or increased bowel frequency are the most common gastrointestinal manifestations and run an intermittent course during the disease.

On physical examination, weight loss and facial flushing may be evident. The skin may be warm and moist, and patients often have inappropriate sweating in a cool environment. African-American patients often note darkening of their skin. Examination of the pulse usually reveals tachycardia or atrial fibrillation (the latter is especially apparent in the elderly). Cutaneous vasodilation leads to a widening of the pulse pressure and a rapid falloff in the transmitted pulse wave (collapsing pulse). A fine tremor, muscle wasting, and proximal muscle group weakness with hyperactive tendon reflexes often are present.

Clinical Features Specific to Graves' Disease
Graves' disease is characterized by the classic triad of goiter, thyrotoxicosis, and exophthalmos. These features may occur singularly or in any combination. Additionally, patients present with a goiter that is characteristically diffuse, enlarged, and smooth. Evidence that the whole gland is enlarged is demonstrated by enlargement of the pyramidal lobe, which can be palpated as it crosses the cricoid cartilage (Fig. 36-12). Patients with Graves' disease also may have onycholysis or thyroid acropathy, hair loss, pretibial myxedema (3 to 5 percent) (Fig. 36-13), and gynecomastia (3 to 5 percent). An audible bruit resulting from markedly increased vascularity of the gland can be heard over the gland in up to 50 percent of patients. Splenomegaly also may be present.

Exophthalmos may be present in association with thyrotoxicosis (Graves' ophthalmopathy) or as an isolated condition with no evidence of thyrotoxicosis ( euthyroid or ophthalmic Graves' disease). The condition is characterized by: (1) spasm of the upper eyelid, with retraction revealing the sclera above the corneoscleral limbus (Dalrymple's sign) and lid lag (von Graefe's sign); (2) external
ophthalmoplegia; (3) exophthalmos with proptosis; (4) supraorbital and infraorbital swelling; and (5) congestion and edema of the conjunctiva (chemosis) (Fig. 36-14). The exophthalmos is a result of increased retro-orbital tissue and can be assessed objectively with an exophthalmometer (Hertel), which measures the distance from the lateral bony orbital margin to the anterior surface of the cornea. Protrusion may lead to ophthalmoplegia, an inability to move the eyeball (upper rotation being most commonly restricted), leading to diplopia. If proptosis is progressive, optic nerve damage and blindness may occur, usually preceded by decreasing visual acuity and increasingly impaired color vision. This condition is commonly referred to as malignant exophthalmos. An urgent ophthalmic opinion should be sought. Marked protrusion can result in chemosis, in which the sclera and conjunctiva become inflamed, with itching, lacrimation, photophobia, and, eventually, ulceration.

The pathogenesis of ophthalmopathy is controversial; the cross-reaction of the thyroid antigen and ocular muscle antibodies is a possible explanation. Continued hyperthyroidism and hypothyroidism aggravate exophthalmos and should be avoided. Histologically, a diffuse lymphocytic infiltration of the retro-orbital tissues occurs, followed by fibroblast activation with glycosaminoglycan (a mucopolysaccharide) production leading to edema and fibrosis.

Diagnostic Findings in Graves' Disease
Thyrotoxicosis is characterized by an autonomous thyroid function and decreased or undetectable level of TSH in association with elevated concentrations of circulating T3 and/or T4. Raised levels of circulating thyroid autoantibodies are usually detected in the serum. A radioactive thyroid scan with 123I is characterized by diffuse uptake throughout the gland. An uptake of 45 to 90 percent is usually observed (Fig. 36-15).

Treatment of Graves' Disease
Three treatment modalities are available for patients with Graves' disease: medical management in the form of antithyroid drugs, thyroid ablation with radioactive 131I, and subtotal or total thyroidectomy. The treatment chosen depends on the age of the patient, the severity of the disease, the size of the gland, any coexistent pathology, including associated ophthalmopathy, and other factors such as patient's preferences and pregnancy.

Antithyroid Drugs
The hyperdynamic peripheral adrenergic effects of thyrotoxicosis can be alleviated by administering beta-blocking agents. These drugs have the added effect of decreasing the peripheral conversion of T4 to T3. Propranolol is the most commonly prescribed medication. It reduces the heart rate, controls tremor, and to some extent relieves the agitation that these patients have. Beta blockers have no apparent effect on the overall remission rate of thyrotoxicosis.

The main antithyroid drugs are propylthiouracil (PTU) and methimazole (Tapazole) in the United States and carbimazole (in the United Kingdom). These drugs act by inhibiting the organic binding of thyroidal iodine and also inhibit the coupling of iodotyrosines. Propylthiouracil also influences the extrathyroidal conversion of T4 to T3. These medications have no effect on the underlying cause of the disease, although there is evidence that propylthiouracil decreases thyroid autoantibody levels.
These drugs also can cross the placenta, inhibiting fetal thyroid function, and they are excreted in breast milk. Side effects of treatment include skin rashes (1 percent), fever, peripheral neuritis, polyarteritis, granulocytopenia (which is reversible on discontinuing treatment), and, rarely, agranulocytosis (1:250). In rare instances, aplastic anemia, which has a poor prognosis, has been documented. Patients should be monitored for these possible complications and warned to stop medication and seek medical advice should they develop a sore throat or fever.

Standard medical treatment is to start the patient on 100 to 300 mg propylthiouracil three times daily, or 10 to 30 mg methimazole, initially three times daily and then once daily, or 40 mg carbimazole daily. Beta blockers are often used initially, before the diagnosis is made, to treat tachycardia and may be added for symptomatic relief. Patients are observed regularly on an outpatient basis, and the dose of antithyroid medication is titrated as needed in accordance with TSH and T4 levels. Most patients have improved symptoms in 2 weeks and become euthyroid in about 6 weeks. The regimen described here is in wide use, though some physicians add thyroxine 0.05 to 0.10 mg to prevent hypothyroidism (the blocking/replacement regime). The length of treatment with antithyroid drugs is controversial. For patients with small, diffusely enlarged glands or larger glands that decrease in size in response to treatment with antithyroid medication, the relapse rate after treatment for 12 to 18 months is about 50 percent. Patients with larger diffuse glands or toxic nodular goiter develop recurrent hyperthyroidism when the antithyroid medication is discontinued, and hence definitive treatment with thyroidectomy or radioiodine therapy is indicated.

(Radioactive Iodine Therapy (131I)

Most patients in the United States undergo treatment with radioiodine. The major advantages of this form of treatment are the avoidance of a surgical procedure and the concomitant risks of recurrent laryngeal nerve damage and hypoparathyroidism, reduced overall treatment costs, and ease of treatment. The major disadvantage is the high incidence of hypothyroidism requiring lifelong thyroxine replacement therapy, the slower correction of the hyperthyroidism, and a higher relapse rate after initial treatment, necessitating further therapy. Radiiodine therapy also has more of an adverse effect on ophthalmopathy than does thyroidectomy.

Patients most suitable for 131I therapy are those with small or moderate-sized goiters, those who have relapsed after medical or surgical therapy, and those in whom antithyroid drugs or surgery are contraindicated. Younger patients (under 35 years of age) usually are treated with thyroidectomy, and older patients are treated with 131I. Radiiodine therapy is contraindicated in women who are pregnant or breast-feeding. Relative contraindications are opthalmopathy (in which progression of eye signs has been documented), patients with isolated thyroid nodules or toxic nodular goiters, and young age (i.e., especially children and adolescents). Although there is no evidence of long-term problems with infertility or increased incidence of cancer in children who have been treated with 131I, most specialists are reluctant to treat children in this manner and suggest thyroidectomy (usually near-total) for this age group. Children treated with radiiodine for Graves' disease have an increased risk of developing hyperparathyroidism.

Patients should be euthyroid before 131I therapy and should stop all antithyroid drugs for 2 to 3 weeks before treatment in order to allow for adequate uptake into the
thyroid. Treatment is provided in the form of a drink of 131I sodium iodide, the
dosage of which usually is calculated with a formula based on gland volume and 131I
uptake; the typical initial dose is about 10 mCi of 131I (approximately 8500 cGy).
Cure rate after initial therapy is dosage dependent; with 5 mCi, cure rate is 70 percent;
with 10 mCi, 87 percent; and with 15 mCi, 96 percent. The higher the initial dose, the
erlier the onset and the higher the incidence of hypothyroidism.

After standard treatment with radioiodine most patients become euthyroid within 2
months. Approximately 15 percent of patients are hypothyroid at 1 year, with a 3
percent increment each year thereafter. Six months after radioiodine treatment, 50
percent of patients are euthyroid, and the remainder are hyperthyroid or already
hypothyroid. Patients need long-term follow-up with TSH levels monitored on a
regular basis. Close monitoring is essential, because hypothyroidism and recurrent
hyperthyroidism aggravate Graves' ophthalmopathy.

The complications of 131I treatment include: (1) exacerbation of thyrotoxicosis with
arrhythmias; this usually becomes apparent within 10 days and may be a particular
problem in the elderly, precipitating cardiac failure or death; (2) overt thyroid storm
(rare but potentially life threatening); (3) hypothyroidism; (4) risk of fetal damage in
patients who are pregnant (women are advised not to become pregnant for 6 months
to 1 year after treatment); (5) worsening of eye signs, noted to be more common after
131I treatment than after surgery (33 percent compared to 16 percent); and (6)
hyperparathyroidism.

Surgical Treatment
Surgery is advised when radioiodine treatment is contraindicated, such as for young
patients, patients with Graves' ophthalmopathy, pregnant patients, patients with
suspicious thyroid nodules in Graves' glands, and patients with large toxic nodular
goiters with relatively low levels of radioiodine uptake. Thyroidectomy is the
treatment of choice in patients with very large goiters and severe thyrotoxicosis at
initial presentation. There is a higher failure rate with 131I treatment in these groups,
necessitating additional therapy. In the United States radioiodine is the usual
treatment for patients over 35 years of age with Graves' disease; in the United
Kingdom and many other countries thyroidectomy is more frequently used because it
is associated with less hypothyroidism and more rapid correction of hyperthyroidism.
The objective of thyroidectomy for Graves' disease should be the complete and
permanent control of the disease with minimal risk of morbidity in terms of nerve and
parathyroid damage.

Patients should be euthyroid before operation with antithyroid drugs that should be
continued up to the day of surgery. Many physicians prefer to treat patients with
Lugol's iodine solution (3 drops twice daily) in the 10 days before operation, and
some use propranolol. Preoperative treatment with iodine reduces the vascularity of
the gland. All these measures decrease the risk of thyroid storm, which can be
precipitated by surgery in unprepared patients.

Whether subtotal, near-total, or total thyroidectomy should be performed is
controversial. The most commonly undertaken procedure, and perhaps the safest in
terms of morbidity, is bilateral subtotal thyroidectomy, in which about 1 to 2 g of
thyroid tissue is left on both sides, or a total lobectomy on one side and a subtotal
thyroidectomy on the other side (Hartley-Dunhill procedure), leaving about 4 to 5 g of thyroid tissue.

Total thyroidectomy can be performed with minimal risk of morbidity and is the operation of choice in patients with coexisting eye disease. Catz and Perzik reported no progression in 66 of 70 patients with total thyroidectomy. Similarly, Winsa and colleagues reported that ophthalmopathy stabilized or improved in 96 percent of patients 6 months or more postoperatively, which may be the result of removal of the antigenic stimulus. In their series of patients undergoing total thyroidectomy for Graves’ disease, 21 of 25 patients not previously treated with 131I had normalization of TSH-receptor antibodies (TRAb) at 2.5 years.

Advantages of thyroidectomy over radioiodine treatment are: immediate cure of disease and decreased long-term incidence of hypothyroidism. Initial series probably overstated the incidence of hypothyroidism because they failed to account for later recovery of thyroid function. Other advantages include a decreased number of outpatient visits and the potential removal of a coexisting thyroid carcinoma. Disadvantages are: possible recurrent laryngeal nerve injury (approximately 1 percent), hypoparathyroidism (usually transient in approximately 13 percent and permanent in 1 percent), hematoma, and hypertrophic scar formation.

Recurrent thyrotoxicosis usually should be managed by radioiodine treatment, because reoperation carries a higher morbidity risk; when tissue has been left on one side, the risk of complications is less. Long-term follow-up should be maintained for all patients, with clinical review and yearly TSH measurement to detect the possible late onset of hypothyroidism or recurrent hyperthyroidism.

Treatment of Exophthalmos
The severity of Graves' ophthalmopathy is independent of thyrotoxicosis; data suggest, however, that recurrent hyperthyroidism and hypothyroidism aggravate the eye problems. Some reports suggest that total thyroidectomy alleviates the eye disease. It is unproved whether total thyroidectomy is preferable to near-total or subtotal thyroidectomy. Total thyroidectomy should be undertaken only in patients with severe exophthalmos when they are well prepared.

Severe or malignant exophthalmos is rare. Treatment is essentially symptomatic; steroid eye drops or systemic steroids (60mg prednisolone daily) should be used initially to alleviate chemosis. When symptoms are more severe upon awakening, patients should tape their eyes closed at night, and the head of the bed should be elevated. Patients whose eyes are worse during the day should wear glasses to protect the eyes from sun and wind and should use artificial tears to protect against drying.

Lateral tarsorrhaphy to oppose eyelids helps to alleviate drying and subsequent chemosis and corneal ulceration. In extreme situations, retro- orbital radiation or orbital decompression may be necessary to save vision.

Toxic Nodular Goiter
Toxic nodular goiter, also known as Plummer's disease, is a consequence of one or more thyroid nodules trapping and organifying more iodine and secreting more thyroid hormone independently of TSH control. Toxic nodular goiter occurs most
often in areas of endemic goiter. It has been documented that most “hot” or “autonomous” thyroid nodules have TSH-receptor (common) or gsp (less common) mutations.

Hyperthyroidism in patients with toxic nodular goiter is milder than in patients with Graves' disease, and the condition is not accompanied by the extrathyroidal manifestations of ophthalmopathy, pretibial myxedema, vitiligo, or thyroid acropathy. Ingestion or administration of iodides, e.g., iodine supplements or intravenously administered contrast agents, may precipitate iodine-induced hyperthyroidism (Jod-Basedow phenomenon).

Patients with toxic multinodular goiter (MNG) are older at presentation than those with Graves' disease. The thyroid-gland goiters characteristically have one or more nodules on palpation. Symptoms such as dysphagia and dyspnea may be present. Some goiters are retrosternal. Symptoms are often mild, and atrial fibrillation in the elderly is frequently the only clinical finding apart from the goiter. The diagnosis is suggested by the history and physical examination and confirmed by documenting a suppressed serum TSH level and raised thyroid hormone level. Antithyroid antibodies usually are not present.

Therapy with antithyroid medication or beta blockers alleviates symptoms but usually is less effective than in patients with Graves' disease. Radioiodine therapy is not as effective as in Graves' disease because of lower uptake, and hence these patients require larger doses of radiation. 131I uptake is localized to one or more autonomous toxic nodules, and the remaining thyroid tissue is suppressed. 131I ablation may be used in patients who are unsuitable for surgery, but because of the high failure rate with this treatment, thyroidectomy is considered the treatment of choice. For solitary nodules, nodulectomy or thyroid lobectomy are the treatments of choice, because cancer is rare. For toxic multinodular goiter, lobectomy on one side and subtotal lobectomy on the other side is recommended for most patients, negating the need for bilateral reoperation in cases of recurrent disease.

Thyroid Storm
Thyroid storm is life-threatening but is rarely encountered during thyroidal—or other—surgery. Most patients with thyroid storm have had known or unknown untreated hyperthyroidism, and thyroid storm is precipitated by an infection (typically pharyngitis or pneumonitis), labor, administration of iodine (such as amiodarone), or after 131I treatment.

Signs and symptoms resemble those of severe thyrotoxicosis, with profound tachycardia, fever, and confusion. Disorientation associated with dehydration from vomiting, diarrhea, and fever may occur and, in extreme cases, adrenergic hyperactivity can lead to overt mania; coma may result as a late event.

The best management is prophylaxis. Patients with hyperthyroidism should be euthyroid before operation. The history and examination of patients admitted for procedures requiring a general anesthetic should identify undiagnosed hyperthyroidism. In cases of thyroid storm, patients can be treated in the acute phase with a combination of fluid replacement, antithyroid drugs, beta blockers, sodium iodate solution or Lugol's iodine solution, hydrocortisone, and a cooling blanket.
Sedation may be necessary in cases of agitation with hyperactivity. Aspirin should be avoided because it increases free thyroid hormone levels. In extreme cases peritoneal dialysis or hemofiltration may be effective in lowering serum T4 and T3 levels.

**HYPOTHYROIDISM**

Hypothyroidism is the clinical syndrome that arises when there is a deficiency in the circulating levels of thyroid hormone. In neonates the disease is termed cretinism and is characterized by neurological impairment and mental retardation. Early treatment lessens the neurological deficits. Hypothyroidism also may be associated with Pendred's syndrome (deafness and hypothyroidism) and Turner's syndrome. In adults, onset of symptoms is insidious and the patient may be unaware of changes. Causes of hypothyroidism are listed in Table 36-2. The two principal causes of hypothyroidism in the United States are autoimmune thyroiditis and iatrogenic mechanisms such as thyroidectomy, radiation treatment, or medications. Iodine deficiency and dyshormonogenesis are other causes of hypothyroidism and goiter.

**Clinical Manifestations**

When the thyroid gland fails to develop or function in utero, children are born with cretinism and characteristic facies similar to those of Down syndrome and dwarfism (Fig. 36-16). Failure to thrive is apparent, and mental retardation often is severe. Immediate treatment with thyroid hormone at birth can lessen the neurological and intellectual deficits. Hypothyroidism at birth also can occur because of blocking antibodies from the mother. Hypothyroidism developing in childhood or adolescence is termed juvenile hypothyroidism; these children appear younger than their chronologic counterparts and may develop abdominal distention, umbilical hernia, and rectal prolapse. Mental performance may be impaired, but severe retardation is uncommon. Hypothyroidism secondary to autoimmune thyroiditis is far more prevalent in females (80 percent of cases). In adults symptoms in general are nonspecific, including tiredness, weight gain, cold intolerance, constipation, and menorrhagia.

Myxedema is the term given to severe hypothyroidism. In these patients facial features change because of the deposition of glycosaminoglycans in the subcutaneous tissues, leading to facial and periorbital puffiness. The skin becomes rough and dry and can develop a yellowish tinge from reduced conversion of carotene to vitamin A. Hair loss may be marked, with characteristic loss of the outer two-thirds of the eyebrows; remaining hair becomes dry and brittle. Enlargement of the tongue may impair speech, which is already slowed, in keeping with the impairment of mental processes. Untreated dementia may develop (myxedema madness). Abdominal symptoms may predominate. Patients may complain of a nonspecific, dull abdominal pain accompanied by distention and constipation. Libido and fertility are impaired in both sexes.

Cardiovascular changes include bradycardia and cardiomegaly, and a pericardial effusion might be present. Hypotension may be evident with a reduced cardiac output, and some patients develop shortness of breath and pulmonary effusions. Cardiac failure is uncommon. When hypothyroidism occurs as a result of pituitary failure and low TSH levels (secondary hypothyroidism), features of hypopituitarism may be present, such as pale, waxy skin, loss of body hair, and atrophic genitalia.
Laboratory Findings
Hypothyroidism is characterized by low circulating levels of T4 and T3. Raised TSH levels are found in primary thyroid failure, whereas in secondary hypothyroidism TSH levels are low. Secondary hyperthyroidism is rare and can be diagnosed by measuring TSH after a TRH challenge. The TSH level is low and does not increase in response to TRH. Autoimmune thyroid disease is characterized by the presence of thyroid autoantibodies (antithyroglobulin, antimitochondrial, or anti–thyroid-peroxidase [anti-TPO]). Other findings in hypothyroidism include anemia, diminished voltage with flattening or inversion of T waves on electrocardiogram, slow alpha waves with loss of amplitude on electroencephalogram, and raised levels of serum cholesterol (>300 mg/dL). In myxedema, comatose patients also have hyponatremia and CO2 retention.

Treatment
Treatment of hypothyroidism is simple, inexpensive, and effective. Thyroxine is the treatment of choice and is administered in dosages varying from 50 mg to 200 mg per day. Patients are instructed to take tablets in the morning, usually without other medications, or at mealtime to assure good absorption and to avoid any sleep interference.

Young and otherwise healthy individuals tolerate initial starting doses of 100 mg of thyroxine per day, but elderly patients, patients with coexisting heart disease, and patients with profound hypothyroidism are less tolerant of thyroxine and should be started on a lower dose, such as 25 mg to 50 mg, slowly increasing the dose over weeks to months to attain a euthyroid state. An electrocardiogram should be obtained before treatment of patients with severe hypothyroidism for comparison if chest pain develops. Thyroxine dosage is titrated against TSH levels, which should return to normal. Thyroxine supplementation also must be determined by the clinical response of the patient. Whether or not patients with subclinical hypothyroidism (normal T4, slightly raised TSH) should be treated is controversial. Evidence suggests that patients with subclinical hypothyroidism and increased antithyroid antibody levels should be treated, because they progress to more severe hypothyroidism. Patients with mild hypothyroidism may benefit from small doses of T4, as the hypercholesterolemia, which accompanies hypothyroidism in this group of patients, is improved by therapy.

Patients who present with myxedema coma, in contrast to the patients with mild to moderate hypothyroidism, require emergency treatment with large doses of intravenous thyroxine (400mg) followed by 100 mg/day. These patients usually are hyponatremic and hypocapnic and need careful monitoring in an intensive care unit.

THYROIDITIS
(Autoimmune Lymphocytic Thyroiditis (Hashimoto's Thyroiditis)
Chronic lymphocytic thyroiditis, more commonly known as Hashimoto's thyroiditis or disease, after the physician who first described the condition in 1912, is an autoimmune thyroid disease and is the most common cause of hypothyroidism. It is ten times more common in women and more prevalent in the 30- to 60-year-old age group, with a prevalence of about 20 cases per 1000 women and an annual incidence of 1 to 2 new cases per 1000 women in the population. Autoimmune thyroiditis may be familial; up to 50 percent of first-degree relatives of patients with chronic autoimmune thyroiditis have thyroid antibodies inherited as a dominant trait. Chronic
autoimmune thyroiditis is encountered in children but is rare in those under 5 years of age. In adolescents 40 percent of goiters are from autoimmune thyroiditis. Other predisposing conditions to autoimmune thyroiditis include Down syndrome, familial Alzheimer's disease, and Turner's syndrome. It is more common in areas of iodine excess. Studies suggest that thyroid cells in Hashimoto's thyroiditis have increased FAS receptors and that interleukin-1 induces abnormal FAS expression and triggers apoptosis or increased programmed thyroid cell death.

Pathology
In Hashimoto's disease the thyroid gland typically is firm and mildly enlarged. The enlargement usually is symmetrical. Frequently the pyramidal lobe also is enlarged. Histologically, there is follicular and Hürthle cell hyperplasia associated with lymphocytic and plasma cell infiltration and formation of lymphoid follicles. The disease is usually focal but gradually extends to involve the whole gland. Epithelial cell degeneration occurs with fragmentation of the basement membrane, and remaining epithelial cells enlarge and demonstrate oxyphilic changes (Hürthle or Askanazy cells). As lymphocytic infiltration progresses, the thyroid tissue degenerates and may be replaced by fibrous tissue.

Clinical Manifestations
Approximately 20 percent of patients with Hashimoto's thyroiditis present with signs and symptoms of hypothyroidism; a few patients present with hyperthyroidism (Hashitoxicosis). Most patients are euthyroid when the diagnosis is made. The most common presenting symptom is a tightness in the throat, often associated with a painless, nontender enlargement of the thyroid gland. Compression of the trachea or a recurrent laryngeal nerve is rare. Rapid enlargement of the thyroid gland should raise suspicion of thyroid lymphoma or carcinoma. Palpation usually demonstrates a diffusely enlarged, firm, often granular thyroid gland; in some cases the gland also is nodular. Usually the pyramidal lobe is enlarged. Evidence of other autoimmune conditions, such as disseminated lupus, rheumatic arthritis, and myasthenia gravis, may be present.

Diagnostic Findings
In early Hashimoto's thyroiditis, patients may present with a transient rise in serum thyroid hormone levels, but as the disease progresses, the serum TSH level rises as serum T4 and T3 levels fall. The diagnosis is confirmed by the presence of circulating antithyroid antibodies. These antibodies are directed against the membrane-bound enzyme involved in thyroid hormone synthesis, thyroid peroxidase (TPO), formerly called antimitochondrial antibodies, in almost 100 percent of patients and against thyroglobulin in about 50 percent of patients. FNAC examination of the thyroid gland occasionally is useful in confirming the diagnosis of Hashimoto's thyroiditis and in patients in whom malignancy is suspected.

Treatment
In the absence of compressive symptoms, patients demonstrating goiter, with or without evidence of hypothyroidism, are best treated with thyroid hormone. Reduction in thyroid goiter size with thyroxine treatment is variable but is more commonly seen in younger patients. Surgical intervention is indicated for patients complaining of obstructive symptoms, for cosmetically unacceptable goiters, or when
thyroid cancer (other than lymphoma) is found. Thyroxine therapy with long-term follow-up monitoring of TSH levels is recommended.

(Subacute Thyroiditis (De Quervain's Thyroiditis
Subacute thyroiditis, also known as de Quervain's, granulomatous, or giant cell thyroiditis, is an uncommon, acute inflammatory disease of the thyroid. It is thought to be precipitated by a viral infection, although the exact cause is unknown. It is commonly encountered in North America but is relatively rare in the United Kingdom and Europe. The disease may be responsible for up to 10 percent of patients with hyperthyroidism in the United States. It affects women five times more often and usually is seen in patients 20 to 40 years of age.

Clinical Manifestations
Patients usually present with fever, malaise, and unilateral or bilateral thyroid pain and a recent history of an upper respiratory tract or viral infection may be given. Some patients complain of the symptoms of thyrotoxicosis, including palpitations, sweating, and heat intolerance, which are caused by the release of thyroid hormones from disrupted follicles in the inflamed thyroid gland. Palpation of the thyroid gland may reveal a tender, firm gland with mild unilateral or bilateral enlargement.

Pathology and Diagnostic Tests
Histologically, the disease is characterized by an acute inflammatory reaction of the thyroid gland. Degenerative thyroid follicles are surrounded by giant cells forming granulomas, which may be demonstrated on FNAC. Laboratory investigations demonstrate an elevated erythrocyte sedimentation rate (ESR) associated with a neutrophilia. Thyroid function tests usually show elevated levels of thyroid hormones (T4 and T3) with suppression of TSH. As the disease resolves, thyroid hormone levels return to normal, although the TSH level can remain low for some time. In contrast to Graves' disease, radioiodine uptake in the acute stage of the disease is low or negligible, because the released thyroid hormone, as result of inflammation, suppresses the serum TSH concentration.

Treatment
Usually treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) for pain relief is all that is necessary. Treatment with NSAIDs should be continued for several weeks after the disease has resolved in an effort to prevent recurrence. Beta blockers (e.g., propranolol) in the initial stages of the disease can be useful for relief of thyrotoxic symptoms. In the more severe cases it might be necessary to prescribe steroids for short periods. Prednisolone 40 mg once daily for 1 to 2 weeks, followed by a gradual reduction of the dose over the ensuing month, is recommended in such cases.

The disease usually lasts 1 to 6 weeks and resolves spontaneously. In some cases the disease lasts from several weeks or months and runs a course alternating between bouts of exacerbation followed by periods of remission. Most patients have complete resolution of the disease, although 10 percent of patients experience permanent hypothyroidism and require thyroxine replacement therapy.

Riedel's Thyroiditis
Riedel's thyroiditis is a rare disease of the thyroid characterized by a marked dense, invasive fibrosis that may extend beyond the thyroid capsule and involve surrounding
structures. Fibrosis may involve the strap muscles, blood vessels, trachea, esophagus, and, on occasion, the parathyroid glands, which leads to hypoparathyroidism. Severe cases can result in the patient's becoming hypothyroid. The cause of the condition is unknown, but it may be part of a more generalized condition known as fibrosclerosis that causes fibrosis in other parts of the body, including the retroperitoneum, mediastinum, lacrimal glands, and bile ducts (sclerosing cholangitis).

Patients usually present with symptoms of compression such as hoarseness, stridor, and dyspnea. In more progressive cases involving the esophagus, dysphagia may be present. There often is rapid enlargement of the thyroid gland, which on palpation is "woody," hard, and nontender. Laboratory investigations usually are normal.

Riedel's thyroiditis resembles anaplastic thyroid cancer, except that the goiter is smaller. Diagnosis usually is established by FNAC, although open biopsy occasionally is needed. Treatment with tamoxifen and steroids often is helpful. Isthmectomy to relieve compressive symptoms or to establish the diagnosis is necessary in some patients. Most operations are difficult because of the loss of tissue planes and should only be embarked on by experienced surgeons. Thyroxine replacement therapy is necessary in patients with hypothyroidism.

Acute Suppurative Thyroiditis
Acute suppurative thyroiditis is rare. It is predominantly a disease of childhood or adolescence and is invariably associated with an acute upper respiratory tract infection. The disease is manifested by acute thyroid pain associated with dysphagia, fever, and, occasionally, rigors. The most common bacterial causative agents are streptococci, staphylococci, and pneumococci, but it also can be caused by Escherichia coli and Coccidioides immitis. Suppuration usually is unilateral but may extend into the deep spaces in the neck, invading the trachea, esophagus, or mediastinum. FNAC with smear and culture is diagnostic. Treatment consists of intravenous antibiotics and drainage of any abscess. Thyroid lobectomy rarely is required. Most patients recover completely and are euthyroid.

GOITER
Simple or nontoxic goiter is an enlargement of the thyroid gland in a euthyroid patient, not associated with any neoplastic or inflammatory process. It may be diffuse and symmetrical or nodular. Several forms of goiter have been described.

Familial Goiter
Familial goiters usually are regarded as goiters caused by an inherited enzymatic defect (dyshormonogenesis) that may cause impairment of iodine accumulation, organification, or coupling of iodotyrosine in the thyroid gland. The inborn error of metabolism generally is inherited as an autosomal recessive trait, but dominant traits have been described. Familial goiters usually are associated with hypothyroidism, although patients may remain euthyroid. Familial goiter also is associated with deafness (Pendred's syndrome).

Endemic Goiter
Endemic goiter is defined as thyroid enlargement affecting a significant number of inhabitants of a particular locale. The most important factor in the development of this
condition is iodine deficiency. It is most commonly encountered in mountainous areas where the iodine content of drinking water is particularly low. Most countries throughout the world have had one or more areas where endemic goiter was encountered; in the United States it was formerly in the Midwestern mountainous regions. Administration of iodine, usually as an additive in table salt, has proved successful as a prophylaxis in reducing the incidence of this condition.

Sporadic Goiter
Sporadic goiter is the term given to a goiter for which no definitive cause can be established. It excludes goiters caused from thyroiditis and neoplasia as well as endemic goiter.

Pathology
The thyroid gland may be diffusely enlarged and smooth, or enlarged and markedly nodular. In the early stages of the disease, the gland may be hyperplastic and diffusely enlarged, a condition that may be reversed by the administration of iodine or thyroid hormone. Nontoxic nodular goiter is a multinodular gland in which the nodules vary considerably in size and number. Nodules are filled with gelatinous, colloid-rich material, and scattered between nodules are areas of normal thyroid tissue. Gross or microscopic cyst formation may be present, with evidence of degeneration, hemorrhage, and calcification.

Clinical Manifestations
Most patients with goiters are asymptomatic. The most common symptom is a sensation of pressure in the neck coupled with a mass. If the goiter enlarges significantly, patients may complain of compressive symptoms such as dysphagia or dyspnea. Paralysis of a recurrent laryngeal nerve is rare and should raise the suspicion of malignancy. On occasion a recurrent laryngeal nerve is stretched over a rapidly enlarging thyroid nodular cyst and ceases to function. Goiters may extend into the thorax and become retrosternal (Fig. 36-17), which may be associated with an impedance of venous return in the jugular veins (Fig. 36-18) and consequent facial flushing. Such flushing is accentuated by the patient's raising his or her arms above the head (positive Pemberton's sign). Sudden pain, frequently associated with rapid enlargement of the thyroid gland, usually is related to hemorrhage into a colloid nodule or cyst.

Examination reveals a diffusely enlarged, soft thyroid goiter in patients with simple goiter or an enlarged gland with nodules of varying size and firmness in multinodular goiter (Fig. 36-19). In patients in whom one nodule predominates, or is painful, or has recently enlarged, FNAC is recommended because it is sensitive and specific in the diagnosis of colloid nodule.

Results of laboratory investigations usually are normal, although in patients over the age of 60 years with long-standing multinodular goiters (>17 years), a significant number develop thyrotoxicosis (Plummer's disease). Most of these hyperthyroid patients have a suppressed TSH and increased T3 level but normal T4 (T3 toxicosis).

Treatment
Most euthyroid patients with small, diffuse, simple goiters need no treatment. If the goiter is of significant size, treatment with thyroxine may depress TSH stimulation of
the thyroid gland and reduce hyperplasia, decreasing goiter size or preventing increases in size. Endemic goiter is managed by the administration of iodine. Surgery should be reserved for patients with cosmetically unacceptable goiters, compressive symptoms, or retrosternal goiters or when malignancy is suspected or demonstrated on FNAC.

SOLITARY OR DOMINANT THYROID NODULE
Solitary thyroid nodules are present in about 4 percent of the population of the United States. Thyroid cancer has an incidence of 40 new cases per 1,000,000 people. The vast majority of thyroid nodules are benign and do not require removal. The physician or surgeon should be able to perform an accurate clinical assessment of any thyroid nodule, appreciate the risk factors of thyroid cancer, and be able to evaluate which patients would benefit from surgery.

Risk Factors for Cancer
Two groups are at risk for having carcinoma of the thyroid: patients exposed to low-dose radiation to the head and neck regions and patients in whose family another member has developed thyroid cancer. Medullary thyroid cancer, which is the greatest risk factor because it may be inherited as an autosomal dominant trait, can be diagnosed by testing for a RET point mutation. Approximately 6 percent of patients with papillary thyroid cancer have familial disease. Papillary thyroid cancer also occurs more commonly in patients with Cowden's syndrome and familial polyposis.

Irradiation of the Head and Neck
A history of low-dose ionizing radiation (<2000 rad) to the thyroid gland places the patient at increased risk for developing thyroid cancer. The risk increases linearly from 6.5 to 2000 cGy; beyond this the incidence declines as the radiation causes destruction of the thyroid tissue, although patients who receive 4000 cGy for treatment of Hodgkin's disease have been shown to have a higher incidence of thyroid cancer. Low-dose therapeutic radiation was used to treat conditions such as “enlarged thymus” in an effort to prevent “sudden crib death” (150 cGy), tonsils and adenoids to prevent the need for tonsillectomy (750 cGy), acne vulgaris (1500 cGy) and other conditions such as hemangioma, ringworm, and scrofula.

There is a 40 percent chance that patients presenting with a thyroid nodule and a history of radiation have thyroid cancer. Of those patients who have thyroid cancer, the cancer is located in the nodule in 60 percent of patients and in the remaining 40 percent of patients the cancer is in another area of the thyroid gland. In children living near the Chernobyl nuclear power plant, where an accident caused radiation leakage in 1986, there has been a 60-fold increase in thyroid cancer, with most cancers occurring in those who were infants at the time of exposure.

Thyroid cancer in patients with a history of radiation exposure tends to be of the papillary type and frequently is multifocal with a higher incidence of lymph node metastases. To prevent higher doses of radiation exposure to the thyroid, scanning with 123I or 99mTc has largely replaced scanning with 131I in most hospitals.

Evaluation
Most thyroid nodules are benign and are colloid nodules or adenomas. To distinguish between suspicious thyroid nodules that may be malignant and benign thyroid nodules, certain issues should be considered.

Because 40 percent of patients with a solitary nodule or multiple thyroid nodules with a history of previous head and neck irradiation will have cancer of the thyroid gland, a history of external radiation to the head or neck is important. The age and gender of the patient are also important. Thyroid nodules in children and elderly patients are more likely to be malignant. Solitary nodules also are more common in men over 40 and women over 50 years of age. Signs that should prompt concern are rapid enlargement of an old or new thyroid nodule, symptoms of local invasion (e.g., unilateral vocal cord paralysis), or compressive symptoms (e.g., dysphagia and dyspnea from invasion into the trachea and esophagus).

Approximately 15 percent of solitary thyroid nodules are malignant, and in hard solitary thyroid nodules the risk of malignancy is two or three times higher. When the apparently solitary nodule is found to be a dominant nodule in a multinodular thyroid gland, the incidence of thyroid cancer in this nodule is less than 5 percent. An exception to this is a history of previous head and neck irradiation or a history of familial thyroid cancer. Lesions that are hard, gritty, or fixed to surrounding structures such as the trachea or strap muscles are probably malignant. The presence of palpable cervical lymphadenopathy adjacent to a thyroid nodule should be suspected as a carcinoma. Cervical lymphadenopathy because of metastatic thyroid cancer may be present when no thyroid nodule is palpable. These patients almost always have a thyroid cancer that usually is present in the ipsilateral thyroid lobe. This cancer may be microscopic and demonstrated only after careful sectioning of the thyroid gland.

Investigations
Fine-Needle Aspiration Cytology
The procedure of choice in evaluating thyroid nodules is fine-needle aspiration cytology (FNAC). The test is fast, is minimally invasive, has few risks, causes little discomfort to the patient, and has been shown to be specific and sensitive. It has replaced radionuclide and ultrasonographic imaging in the preoperative evaluation of thyroid nodules.

Ninety percent of nodules can be categorized into the following groups: benign, 65 percent; suspicious, 15 percent; malignant, 5 percent; and nondiagnostic, 15 percent. The incidence of false-positive results is about 1 percent, and false-negative results, about 5 percent.

FNAC is the investigation of choice in patients with thyroid nodules, but it has limitations. The proportion of patients with suspicious cytology results ranges from 11 to 20 percent. Most have follicular or Hürthle cell neoplasms, and 20 percent of these patients have a thyroid malignancy. There is no accurate method of predicting which of these patients has a thyroid cancer, because the diagnosis depends on demonstrating capsular or vascular invasion, which is not possible on FNAC. The technique also is less reliable in patients who have previous irradiation to the head and neck or have a family history of thyroid cancer, as many of these patients have multifocal lesions.
When a cyst is encountered on FNAC it should be drained completely, which is curative in about 75 percent of simple cysts (Fig. 36-20), although some require a second or third aspiration. If the cyst persists after three attempts at aspiration, unilateral thyroid lobectomy is recommended. In cases in which the cyst is larger than 4 cm in diameter or is complex (i.e., has solid and cystic components), thyroid lobectomy is recommended, because these cysts have a higher incidence of malignancy (15 percent).

Thyroid Imaging
Ultrasonographic Imaging
Ultrasound evaluation of the thyroid gland is helpful for detecting nonpalpable nodules and for differentiating solid from cystic nodules. It provides a noninvasive and inexpensive method of following the size of suspected benign nodules diagnosed by FNAC. This is especially useful in determining whether the nodule or the surrounding normal thyroid tissue decreases in size when the patient is treated with thyroid hormone. Ultrasonographic imaging has no role in screening for thyroid nodules in asymptomatic patients.

CT and MRI
Computed tomography and magnetic resonance imaging usually are unnecessary in the evaluation of thyroid tumors except for large or retrosternal lesions and for assessing suspected invasion into surrounding structures. MRI is more accurate than CT in distinguishing recurrent or persistent thyroid tumor from postoperative fibrosis.

Thyroid Isotope Scanning
Scanning the thyroid with 123I or 99mTc can indicate the functional activity of a nodule and of the thyroid and correlate the location of palpable nodules with the nodules seen with scanning. Scanning with 131I has been largely replaced by 123I or 99mTc scans to lower the dose of radiation delivered to the thyroid gland during the investigation. Nodules that trap less iodine than the surrounding thyroid tissue are termed "cold," nonfunctional, or hypofunctional (Fig. 36-21). Almost 85 percent of nodules on scanning are cold, and these lesions have a 10 to 25 percent chance of malignancy. Of the 5 percent of nodules shown to be “hot” on scanning, approximately 1 percent are malignant. Thyroid scanning is recommended in the assessment of thyroid nodules only in those patients who have follicular thyroid nodules on FNAC.

Laboratory Findings
Thyroid function tests are not useful in the assessment of patients with thyroid nodules, because most patients with thyroid cancer are euthyroid. In those patients presenting with hyperthyroidism and a solitary nodule, the chances of the nodule's being malignant are very low. Serum thyroglobulin levels cannot differentiate benign from malignant thyroid nodules unless the levels are extremely high, in which case metastatic thyroid cancer should be suspected. Thyroglobulin levels are useful in following patients who have undergone total thyroidectomy for thyroid cancer, excluding medullary thyroid cancer, and also for monitoring patients with nodules being followed nonoperatively. Serum calcitonin levels should be obtained in patients with a family history of medullary thyroid cancer or multiple endocrine neoplasia type II (MEN II) and where FNAC demonstrates medullary thyroid cancer to be present. Patients who are RET oncogene positive should always have a 24-h urine collection.
with measurements of levels of vanillylmandelic acid (VMA), metanephrine, and catecholamine to rule out a coexisting pheochromocytoma.

Treatment
The algorithm for the diagnosis of a thyroid nodule is shown in Fig. 36-22. When a diagnosis of colloid nodule is made cytologically, thyroidectomy is not necessary except for cosmetic or symptomatic reasons, and these patients can be safely observed. A second FNAC is recommended 6 to 8 months after the initial FNAC if the nodule enlarges. Patients with benign nodules should undergo ultrasound determination of the size of the lesion and a baseline thyroglobulin level should be obtained. Patients may be prescribed thyroxine in doses sufficient to maintain a serum TSH level between 0.1 and 1.0 mU/mL. Approximately 50 percent of these nodules significantly decrease in size in response to the TSH suppression of this regimen. Thyroidectomy should be performed if a nodule enlarges or develops in a patient whose serum thyroglobulin increases despite TSH suppression therapy with thyroxine. An exception to this general rule is the patient who has had previous irradiation of the thyroid gland. In these patients total or near- total thyroidectomy is recommended with FNAC because of the high incidence of thyroid cancer (40 percent).

Thyroidectomy is recommended in patients in whom a thyroid cyst has recurred after three aspirations and in patients with a cyst that is larger than 4 cm or is found to be a complex cyst on ultrasound examination. Signs and symptoms such as pressure, hoarseness, dysphagia, vocal cord paralysis, dyspnea, adjacent cervical lymphadenopathy, or recent rapid increase in size of a thyroid nodule (unless FNAC demonstrates hemorrhage) all favor thyroid lobectomy. Patients with a thyroid nodule and a family history of papillary or Hurthle cell cancer probably warrant thyroidectomy. Patients with medullary carcinoma or MEN II with an elevated basal or stimulated calcitonin level or positive RET oncogene also should have a total thyroidectomy, even in the absence of a palpable mass.

MALIGNANT TUMORS
In the United States thyroid cancer occurs in about 40 per 1,000,000 people each year and accounts for less than 1 percent of all malignancies. Thyroid cancer is responsible for six deaths per million persons annually. Most patients present with a palpable swelling in the neck, which initiates assessment through a combination of history, palpation, and FNAC examination. Diagnosed correctly and managed properly, most patients with differentiated thyroid carcinoma of follicular cell origin are curable.

Several different types of primary thyroid carcinoma are recognized, although 90 to 95 percent of thyroid carcinomas are differentiated tumors of follicular cell origin (differentiated thyroid cancer) giving rise to papillary, follicular, or Hurthle cell carcinoma. About 6 percent of patients with papillary and Hurthle cell cancer have familial disease; follicular and anaplastic thyroid cancer are more common in patients from iodine-deficient areas. Medullary thyroid cancers account for about 6 percent of thyroid cancers, and approximately 30 percent of these tumors are familial.

Molecular Basis of Thyroid Tumors
Oncogene (onc) is the title given to a gene that contributes directly to tumor genesis. Cellular oncogenes (c-onc) or proto-oncogenes are cellular genes that can give rise to
oncogenes when they are altered or when their expression is modified. The modified genes may encode for a mutated receptor on the cell surface, resulting in an abnormal growth signal being transmitted to the nucleus through overexpression of the receptor or by the receptor's being continually (constitutively) activated. Inappropriate cell division results and may lead to malignant transformation. The fact that these genes have survived in the evolutionary process and play a role in cell transformation suggests that proto-oncogenes are involved in the normal control of cell growth and differentiation.

Several oncogenes are involved in thyroid tumor genesis. Mutations in TSH-receptor and Gs genes are found in hyperfunctioning thyroid nodules, for example, and probably constitutively activate the adenylate cyclase–protein kinase A signal transduction pathway, leading to a well-differentiated tumor. An oncogene that has a significant role in the development of papillary thyroid cancer is the RET oncogene. Rearrangement of this gene occurs in papillary thyroid cancer (PTC) and is more common in childhood thyroid cancers. Point mutations involving RET have been demonstrated in patients with familial medullary thyroid cancer, MEN IIA, and MEN IIB.

The RET proto-oncogene encodes for a tyrosine kinase receptor on the cytoplasmic membrane; the ligand has been identified as glial cell line–derived neurotrophic factor (GDNF). RET is expressed during embryogenesis in the nervous and excretory systems. Disruption of RET results in developmental abnormalities in these systems, including the enteric nervous system (Hirschsprung's disease). Tumors arising from the neural crest cells (medullary thyroid cancer and pheochromocytoma) also contain RET point mutations. The RET gene is located on chromosome 10, and rearrangement of RET by fusion with heterologous genes creates transforming oncogenes, which have been implicated in the pathogenesis of PTC. These oncogenes are RET/PTC1, RET/PTC2, and RET/PTC3.

Not all patients with PTC possess the RET/PTC gene, and expression markedly varies geographically, e.g., being low in Japan (3 percent) and high in Italy (34.6 percent). It also is more common in thyroid cancers in children that develop after radiation exposure. In vitro irradiation induces RET/PTC formation, and 66 percent of the papillary thyroid cancers that were removed from patients living near Chernobyl demonstrated RET/PTC1 and RET/PTC3.

A second oncogene associated with PTC is TRK-A, found on chromosome 1, which encodes for a cell surface receptor for nerve growth factor. Mutated ras oncogenes have been demonstrated in a wide variety of human tumors and occur more frequently in human thyroid tumors of follicular origin. Point mutations in ras occur in thyroid adenomas and multinodular goiters, as well as follicular carcinoma, and are believed to be an early mutation.

A molecular defect associated with the development of follicular adenoma is allelic loss of genes on the short arm of chromosome 11 (11q). Deletion of 3p accompanies transformation from follicular adenoma to a follicular adenocarcinoma.

The p53 gene is a tumor suppressor gene encoding for a protein (p53) that acts as a transcriptional regulator. Its function is to maintain genomic integrity. Point mutations
in the p53 gene result in a protein that lacks this ability, which in turn results in proliferation of malignant cells. A mutated p53 gene is found in most anaplastic thyroid cancers and in thyroid cell lines.

Papillary Carcinoma

Papillary carcinoma is the most common of thyroid malignancies, accounting for 80 percent of all thyroid cancers. It is the predominant thyroid cancer in children (75 percent) and in people who were previously exposed to radiation in the neck (85 to 90 percent). Papillary carcinoma occurs more often in women, with a 2:1 female-to-male ratio, and the mean age at presentation is 30 to 40 years.

Pathology

Papillary thyroid cancers, including mixed papillary follicular carcinoma and the follicular variant of papillary carcinoma, usually are hard and whitish and remain flat on sectioning with a blade, rather than bulging as does normal tissue or benign nodular lesions. Macroscopic calcification, necrosis, or cystic change may be apparent. Smaller tumors occasionally may be present inside thyroid cysts.

Histologically, papillary carcinomas may exhibit papillary projections, a mixed pattern (papillary/follicular structures), or a pure follicular pattern with intranuclear inclusions. The diagnosis is established by characteristic cellular features. Cells are cuboidal with pale, abundant cytoplasm, crowded nuclei, and intranuclear cytoplasmic inclusions, the so-called Orphan Annie cells (Fig. 36-23). A characteristic fibrovascular stroma with calcium deposits (psammoma bodies) may be present. Tumors that exhibit papillary features such as mixed tumor or the follicular variant of papillary carcinoma should be classified as papillary carcinomas because they act biologically as papillary carcinomas. Multifocality in papillary carcinoma is common (30 to 87.5 percent) and is a minor risk factor in prognosis. Papillary cancers exhibit a propensity for lymphatic spread within the thyroid and to local lymph nodes (paratracheal and cervical chain). Papillary tumors may invade local structures such as the trachea, esophagus, and recurrent laryngeal nerves and rarely are encapsulated. Blood-borne metastases usually are a late feature.

Macroscopically, there are three recognized forms of papillary thyroid cancer, each based on the size and extent of the primary disease. Minimal or occult/microcarcinoma tumors originally included papillary cancers up to 1.5 cm in diameter. They now are defined as tumors of 1 cm or less in size with no evidence of local invasiveness through the thyroid capsule and that are not associated with lymph node metastases. They are nonpalpable and usually are incidental findings at operative, histologic, or autopsy examination. Studies have demonstrated occult papillary thyroid cancer to be present in 2 to 36 percent of thyroid glands removed at autopsy. Recurrence rate in patients with tumors 1.5 cm or smaller after removal is about 7 percent and the mortality about 0.5 percent. Intrathyroidal tumors are greater than 1 cm and are confined to the thyroid gland, with no evidence of extrathyroid invasion. Extrathyroidal tumors are locally advanced with invasion through the thyroid capsule into adjacent structures. All types of primary thyroid cancers can be associated with lymph node metastases and invasion into intrathyroidal blood vessels or occasionally distant metastases. Long-term prognosis is better for intrathyroidal lesions.
Other types of papillary carcinoma of the thyroid are: tall cell, columnar, diffuse sclerosing, clear cell, trabecular, Hürthle cell, and poorly differentiated variants. Most of these variants behave more aggressively. Angioinvasion also predicts more recurrences and a worse prognosis, but coexisting lymphocytic thyroiditis suggests fewer recurrences and a better prognosis. There usually is no significant difference in management.

Clinical Manifestations
Most patients are euthyroid and present with a slow-growing painless mass in the neck. Accompanying symptoms, which usually are associated with advanced locally invasive disease, may include dysphagia, dyspnea, and hoarseness. Ipsilateral enlarged cervical lymph glands also may be present and most commonly are encountered in younger patients. Nodal involvement may be more apparent than the primary lesion; the so-called lateral aberrant thyroid usually is a cervical lymph node that has been invaded by metastatic cancer.

Distant metastases are uncommon at initial presentation (1 to 15 percent), depending on whether detected by physical examination and symptoms or by radioiodine scanning and thyroglobulin determination after thyroidectomy. Distant metastases to the lung are more commonly encountered in children, although up to 20 percent of all patients ultimately develop distant disease (Fig. 36-24).

Thyroid cancer often is suspected by history or physical examination. In most cases the diagnosis is easily established in the outpatient setting by FNAC, which is specific and sensitive in papillary, medullary, and anaplastic thyroid cancer. Radioiodine thyroid scans are not necessary in preoperative evaluation. CT and MRI are used selectively in patients with extensive local or substernal disease or lymph node involvement.

Prognostic Indicators
Ideal treatment objectives for thyroid cancer are detailed in Table 36-3. In order to compare the merits of different surgical therapies, a method of accurately assessing various prognostic factors is necessary.

AGES Scale
This is a postoperative prognostic scale of risk of dying from papillary cancer. Factors taken into account are Age, pathologic tumor Grade, Extent of disease and Size of tumor. Two groups are identified with this system: low-risk patients (young, with well-differentiated tumors, no metastases, and small primary lesions) and high-risk patients (older, with poorly differentiated tumors, local invasion, distant metastases, and large primary lesions). Of 860 patients in one study, 85 percent were in the low-risk group, with a cancer risk mortality of 2 percent at 25 years; the cancer risk mortality in the high-risk group was 46 percent.

MACIS Scale
This more sophisticated postoperative scale is a modification of the AGES system. Factors assessed are distant Metastases, Age at presentation (<40 or >40 years), Completeness of original surgical resection, extrathyroidal Invasion, and Size of original lesion (in cm) (Fig. 36-25).
DNA Ploidy

Measurement of DNA ploidy is of some use in prognosis because aneuploidy is noted in 10 percent of all papillary carcinomas but is present in 25 to 50 percent of patients who die from thyroid cancers. Aneuploid DNA measurements are encountered infrequently in papillary thyroid cancers among survivors.

The most significant single prognostic indicator overall is distant metastases, especially to bone. Local invasion of the primary tumor through the thyroid capsule into the adjacent structures increases the mortality tenfold over matched patients with intrathyroidal tumors.

The other frequently used classification systems are AMES (Age, Metastases, Extent, Size) and TNM (Tumor size, Nodal involvement, and Metastases to distant sites). Patients less than 45 years of age without distant metastases usually are considered to be at low risk.

Surgical Treatment

When patients are found to have a minimal papillary thyroid carcinoma in a thyroid specimen removed for other reasons, unilateral thyroid lobectomy and isthmectomy usually is sufficient surgical treatment unless there is angioinvasion or the tumor is at the margins of resection. Similarly, in rare cases of encapsulated papillary thyroid carcinoma, total lobectomy is all that is needed. In all other patients with papillary thyroid cancer, total or near-total thyroidectomy is the procedure of choice.

The Case for Total Thyroidectomy

There are several arguments for the treatment of papillary carcinoma by total thyroidectomy: multifocal disease, decreased incidence of local recurrence, reduced risk of anaplasia in any residual tissue, facilitation of diagnosing unsuspected metastatic disease by radioiodine scanning or treatment with 131I (reducing incidence of distant recurrence), and greater sensitivity of blood thyroglobulin levels to predict recurrent or persistent disease.

Multifocal disease in papillary carcinoma is well documented (up to 85 percent). Unilateral lobectomy therefore may leave residual disease in the contralateral lobe. Recurrence rates in the contralateral lobe after thyroid lobectomy range from 4.2 to 26 percent. In one study, the recurrence rate was 19 percent at 10 years after lobectomy versus 11 percent in similar patients treated with total thyroidectomy.

Whether total thyroidectomy has any survival advantage over near-total thyroidectomy (total lobectomy with subtotal resection of the contralateral lobe) is unclear. Studies from the Mayo Clinic demonstrated that in low- and high-risk AGES categories local recurrence was higher after lobectomy than after total or near-total resection. Total thyroidectomy did not have better survival rates than near total thyroidectomy. It is suggested that subtotal resection on the side opposite the tumor decreases the chances of damage to the parathyroid and the recurrent laryngeal nerve. This argument is valid in the case of patients whose parathyroid glands are anteriorly located on the thyroid, so that some thyroid tissue is left to preserve the blood supply to the parathyroid glands. When the parathyroid glands are situated off the thyroid gland, there is little benefit in leaving thyroid tissue. In experienced hands the incidence of permanent hypoparathyroidism or nerve damage after total
thyroidectomy is about 1 percent. Differentiation of the residual thyroid cancer to anaplastic carcinoma occurs in about 1 percent of patients and is almost always fatal.

Total thyroidectomy, by removing all residual normal thyroid tissue, facilitates the uptake of radioactive 131I extrinsic to the gland and helps identify and ablate metastatic thyroid cancer. Once all thyroid tissue has been removed, thyroglobulin levels should remain below 3 ng/mL; by monitoring thyroglobulin levels, disease progress can be followed. When thyroglobulin levels increase, recurrent disease must be present and appropriate screening with 131I should be done.

The patient with a thyroid nodule that is suspected to be papillary thyroid cancer should have FNAC performed. When papillary thyroid cancer is diagnosed, the definitive operation can be done without confirming the diagnosis on histologic examination. Patients with a nodule that might be papillary cancer should be treated by thyroid lobectomy, isthmectomy, and removal of any pyramidal lobe or adjacent lymph nodes. When intraoperative frozen-section examination of a lymph node or of the primary tumor confirms carcinoma, completion total or near-total thyroidectomy should be performed. If a definitive diagnosis cannot be made, the operation is terminated. When final histology confirms carcinoma, completion total thyroidectomy usually should be performed. For patients who have minimal papillary thyroid cancers confined to the thyroid gland without angioinvasion, no further operative treatment is recommended. Treatment with thyroid hormone to suppress TSH is recommended. For patients at low risk should have serum TSH levels between 0.1 and 1.0 mU/mL, whereas patients at high risk should have serum TSH levels suppressed to less than 0.1 mU/mL.

Local recurrence is a serious complication, with a disease-related mortality rate of 33 to 50 percent. Patients with nodal recurrence usually do better than those with tumor recurrence in the thyroid bed or with distant metastases. Lymph node metastases in the lateral neck in patients with papillary carcinoma usually should be managed with modified radical neck dissection, and en-bloc dissection of all fibrofatty tissue and lymphatic tissue. The jugular lymph node chain is removed, while preserving the sternocleidomastoid muscle, the internal jugular vein, and the spinal accessory nerve (which are all taken in a radical dissection). Dissection of the posterior triangle and suprathyroid dissection usually are not necessary but should be performed when appropriate. Prophylactic neck node dissection is not necessary in patients with papillary thyroid cancer, because micrometastases appear to be ablated with radiiodine therapy. Survival rates for the different treatment modalities are summarized in Fig. 36-26.

Follicular Carcinoma
Follicular carcinoma, which accounts for about 10 percent of thyroid malignancies, is decreasing in incidence in the United States. This cancer occurs more often in women, with a female-to-male ratio of 3:1, and it presents in an older age group, mean age at presentation of 50 years, compared to a mean age of 35 in patients with papillary carcinoma. Follicular carcinoma occurs more frequently in iodine-deficient areas, and a rare form of familial disease is reported in patients with dyshormonogenesis.

Pathology
Follicular carcinoma usually is solitary and approximately 90 percent are surrounded by a tumor capsule. Follicular carcinoma differs from papillary carcinoma in that vascular invasion and hematogenous spread to bone, lung, and liver is seen more commonly than lymphatic spread, which usually is encountered in late stages. Lymph node metastases occur in less than 10 percent of patients. Histologically, follicles are present, but the lumen may be devoid of colloid. Architectural patterns depend on the degree of differentiation demonstrated by the tumor.

Two types of follicular carcinoma are recognized. In minimally invasive tumors there is evidence of invasion into but not through the tumor capsule at one or more spots. Previously, these tumors may have been reported as atypical adenomas, although there are reports of metastases occurring, and they should be regarded as low-grade carcinomas. In the second type, frankly invasive tumors, there is evidence of vascular invasion or tumor invasion through the tumor capsule. Tumor infiltration and invasion may be apparent at surgery, with tumor thrombus in the middle thyroid or jugular veins.

Clinical Manifestations
Follicular cancers usually present as solitary thyroid nodules, occasionally with a history of rapid size increase, and long-standing goiter. When hemorrhage into the nodule has occurred, pain may be a presenting feature, but usually the tumors are painless. At initial presentation cervical lymphadenopathy is uncommon, although distant metastases are more frequently encountered than papillary carcinoma. Rarely, follicular cancers may be hyperfunctioning (1 percent), and patients may present with signs and symptoms of thyrotoxicosis.

Unless distant metastases have been confirmed as follicular thyroid cancer, definitive preoperative diagnosis usually is not possible in follicular thyroid carcinoma. This is because FNAC is unable to distinguish between follicular cells from a benign follicular adenoma and from a carcinoma. Approximately 20 percent of all FNAC aspirates showing follicular cells are carcinomas; the remaining 80 percent are adenomas.

Surgical Treatment and Prognosis
Patients diagnosed by FNAC as having a follicular lesion should undergo thyroid lobectomy, including the isthmus and the pyramidal lobe. Intraoperative frozen-section examination usually is not helpful but should be performed when there is evidence of capsular or vascular invasion or when adjacent lymphadenopathy is present. Total thyroidectomy should be performed when thyroid cancer is diagnosed, except in patients with minimally invasive follicular cancers because the prognosis in these patients is so good. In older patients, when follicular neoplasms diagnosed by FNAC are greater than 4 cm and macroscopically suspicious for cancer, some surgeons proceed with total thyroidectomy, because the risk of cancer is about 50 percent. A diagnosis of invasive carcinoma necessitates completion total thyroidectomy primarily so that 131I can be used to detect and ablate metastatic disease. Prophylactic nodal dissection is unwarranted because nodal involvement is infrequent, but therapeutic neck dissection is recommended.

The cumulative percentage of patient mortality from follicular thyroid cancer is about 15 percent at 10 years and 30 percent at 20 years. Factors that significantly worsen
long-term prognosis are; age over 50 years at presentation, tumor size greater than 4 cm, higher tumor grade, marked vascular invasion, extrathyroidal invasion, and distant metastases at the time of diagnosis

Hürthle Cell Carcinoma
Hürthle cell tumors are considered by the World Health Organization classification to be a variant of follicular cell neoplasms. Tumors contain sheets of eosinophilic cells packed with mitochondria. They are derived from the oxyphilic cells of the thyroid gland, and although the function of the cells is unknown, Hürthle cell tumors possess TSH receptors and produce thyroglobulin. Only about 10 percent of these tumors trap radioiodine.

Hürthle cell carcinomas account for approximately 3 percent of thyroid malignancies. They differ from follicular carcinoma in that they are more often multifocal and bilateral, are more likely to metastasize to local nodes (25 percent), and usually do not take up 131I. Hürthle cell neoplasms usually are diagnosed by FNAC, and about 20 percent of these tumors are found to be malignant. There is controversy as to whether all Hürthle cell neoplasms are malignant. Grant and colleagues reported that the mortality rate was less than 1 percent of 642 patients with Hürthle cell adenoma. Adenomas, as in follicular neoplasms, have no vascular or capsular invasion, whereas cancers do have vascular or capsular invasion.

Management is similar to that of follicular neoplasms, with lobectomy, isthmectomy, and pyramidal lobe resection being sufficient surgical treatment for unilateral Hürthle cell adenomas. When Hürthle cell neoplasms are found to be invasive on intraoperative frozen-section or definitive paraffin-section histology, then total thyroidectomy should be performed. These patients should also undergo routine central neck node removal, similar to patients with medullary thyroid cancer, and modified radical neck dissection when lateral neck nodes are palpable. T4 treatment is recommended postoperatively.

Although radioiodine scanning and ablation usually are ineffective, they probably should be considered to ablate any residual normal thyroid tissue and occasionally ablate tumor, since there is no other good therapy. 99mTc- sestamibi scanning has been reported to be useful for detecting persistent local or metastatic disease. The mortality rate from Hürthle cell cancer is higher than from follicular thyroid cancer.

Medullary Carcinoma
Medullary thyroid cancer (MTC) accounts for about 5 percent of thyroid carcinomas. Although MTC was originally classified as an anaplastic tumor, Hazard and associates recognized that it was a separate entity, because patients survived longer than they did with anaplastic carcinoma. Williams determined that medullary thyroid cancer arose from the parafollicular or C cells of the thyroid. These cells are neuroectodermal and originate from the ultimobranchial bodies of the fourth and fifth branchial pouches. They descend to join the thyroid gland proper and are concentrated mainly in the superior poles laterally. This also is where C-cell hyperplasia is most evident and where medullary thyroid cancers develop. Pearse demonstrated the ability of the C cells or parafollicular cells to secrete calcitonin, a 32- amino-acid polypeptide that has an opposing action to parathyroid hormone (PTH) in that it is an antihypercalcemic hormone and lowers serum calcium levels. In some animals,
especially those that lay eggs with shells, calcitonin is a significant regulator of calcium metabolism, but in human beings it has only minimal physiologic effects.

In 1966 Sipple described a postmortem case in which thyroid cancer, hyperplastic parathyroid glands, and pheochromocytoma coexisted; additional review of 500 cases of pheochromocytoma showed thyroid cancer to be six to fourteen times more frequently associated with this condition than expected. Since these initial observations, families have been identified whose members have only MTC; have MTC, hyperparathyroidism, and pheochromocytoma (MEN IIA or Sipple's syndrome), and patients with MTC, pheochromocytoma, ganglioneuromatosis, and Marfan's syndrome (MEN IIB). Patients with MEN IIA also may have Hirschsprung's disease and lichen cutaneous amyloidosis. Patients with von Hippel–Lindau disease also appear to be prone to developing pheochromocytoma and medullary thyroid cancer.

Pathology
Medullary carcinomas are located in the middle to upper thyroid poles (in keeping with the embryological origin of the C cells). Tumors typically are unilateral (75 percent). With familial cases, C-cell hyperplasia and multicentricity are prevalent, and 90 percent of the patients have bilateral tumors.

Microscopically, tumors are composed of sheets of infiltrating neoplastic cells separated by collagen and amyloid. Marked heterogeneity is present; cells may be polygonal or spindle-shaped. The presence of amyloid is a diagnostic finding, but immunohistochemistry for calcitonin has superseded it as a diagnostic tumor marker. C-cell hyperplasia is a premalignant precursor of MTC. These tumors also stain positively for carcinoembryonic antigen (CEA), histaminase, and calcitonin gene–related peptide (CGRP).

Tumors spread initially to local lymph nodes in the neck and the superior mediastinum. Distant blood-borne metastases to liver, bone (frequently osteoblastic), and lung usually arise later in the disease. Local invasion into the trachea and esophagus also occurs.

Clinical Manifestations
Patients with MTC usually present with a neck mass that may be associated with palpable cervical lymphadenopathy (15 to 20 percent). Local pain is more common in patients with these tumors, and local invasion may produce symptoms of dysphagia, dyspnea, or dysphonia. The female-to-male ratio is 1.5:1. About 70 percent of the patients have sporadic disease, and age at presentation typically is between 50 and 60 years, though patients with familial disease present at a younger age.

Tumors may secrete a variety of peptides including calcitonin, calcitonin gene–related peptide, CEA, histaminases, prostaglandins E2 and F2- alpha, and serotonin. Patients with extensive metastatic disease frequently develop diarrhea, which can be debilitating. The reason for this is unclear, although increased intestinal motility, impaired intestinal water and electrolyte flux might be responsible.
Between 2 and 4 percent of patients with MTC develop Cushing's syndrome as a result of ectopic production of ACTH. Kidney stones occur in patients with primary hyperparathyroidism, and hypertension occurs in those with pheochromocytoma.

**Diagnosis**

Diagnosis of MTC is established by history, physical examination, raised serum calcitonin or CEA levels, and FNAC of the thyroid mass. Attention to family history is important. Since it is not possible to distinguish sporadic from familial disease at initial presentation, all new patients with MTC should be screened for RET point mutations and for pheochromocytoma by measuring 24-h urinary levels of vanillylmandelic acid (VMA), catecholamine, and metanephrine. Serum calcium level also should be observed. A coexisting pheochromocytoma should be ruled out, because operation on a patient with an undiagnosed pheochromocytoma can result in a hypertensive crisis and death.

**Familial Disease**

MTC is sporadic (70 percent of new cases) or familial (30 percent of new cases). Familial MTC occurs as MEN IIA, as MEN IIB, or as familial MTC without other endocrinopathies. It also may occur in association with papillary thyroid cancer.

**MEN IIA**

These patients have a syndrome characterized by MTC, pheochromocytoma, or adrenal medullary hyperplasia and hyperparathyroidism. C-cell hyperplasia is present in all of them and normally is detectable by screening before the development of pheochromocytoma. Bilateral pheochromocytomas are detectable in more than 50 percent of the patients with the syndrome and occasionally is the presenting feature. Hyperparathyroidism (25 percent), Hirschsprung's disease, and cutaneous amyloidosis are present in some patients.

**MEN IIB**

MTC, bilateral pheochromocytomas, and ganglioneuromas affecting mucosal surfaces are found in patients with this condition. Patients have a characteristic facies with a thickened tongue and lips (Fig. 36-27). Marfanoid features, slipped epiphysis, and pectus excavatum also may occur. Patients with MEN IIB have the most aggressive medullary thyroid cancers; patients with familial MTC without other endocrinopathies have the least aggressive thyroid cancers.

Screening of patients with familial MTC for RET point mutations on chromosome 10 has replaced using provocation testing with pentagastrin or calcium-stimulated calcitonin levels to make the diagnosis. Calcitonin and CEA are used to identify patients with persistent or recurrent MTC. The specific phenotypes of MTC are also associated with specific RET mutations (familial MTC, 768 and 804; MEN IIA, 609, 611, 618, 620, and 634; MEN IIB, 918).

**Treatment**

Most clinicians agree that total thyroidectomy is the treatment of choice for patients with MTC because of the high incidence of multicentricity and the more aggressive course. Because tumors are of C-cell origin, radioiodine therapy and levothyroxine sodium TSH suppression therapy usually are not helpful. The central compartment nodes from carotid sheath to trachea frequently are involved early in the disease.
process and always should be meticulously cleared along with paratracheal nodes (central neck node dissection). In patients with palpable cervical nodes or involved central neck nodes, ipsilateral or bilateral, bilateral modified radical neck dissection is recommended. Similarly, patients with MTCs larger than 2 cm should undergo ipsilateral prophylactic modified radical neck dissection, because more than 60 percent of these patients have nodal metastases.

If superior mediastinal lymph nodes are noted at operation they also should be removed, although it is rarely necessary to perform a median sternotomy. Surgeons should be prepared to sacrifice the recurrent laryngeal nerve when it is involved in the tumor mass. Though this does not occur frequently, the possibility should be discussed with the patient preoperatively.

Tumor debulking in cases of metastatic disease or local recurrence should be undertaken. This frequently ameliorates symptoms of flushing and diarrhea, and it helps in decreasing the risk of death resulting from recurrent central neck disease.

External-beam radiotherapy for patients with tumors at resection margins or unresectable tumors is controversial. It is recommended for patients with unresectable residual or recurrent tumor, although the results are debatable. There is no effective chemotherapy regimen.

When patients have associated conditions such as pheochromocytoma or hyperparathyroidism, these conditions also require careful evaluation. Pheochromocytomas should be operated on first, before thyroidectomy is performed. In most cases pheochromocytomas can be removed laparoscopically. In patients who have hypercalcemia at the time of thyroidectomy, the parathyroid glands should be identified and, when abnormal, selectively removed. In patients with normocalcemia, efforts should be made to preserve the parathyroid glands, which should be marked with a stitch or clip in patients with MEN IIA. When a normal parathyroid cannot be maintained on a vascular pedicle, it should be removed, biopsied to confirm that it is a parathyroid, and then autotransplanted to the forearm of the nondominant arm.

Postoperative Follow-up and Prognosis
Patients should be assessed at regular postoperative intervals, and serum calcitonin and CEA levels should be monitored regularly. Calcitonin level is more sensitive for detecting persistent or recurrent disease, and CEA for predicting outcome. In a study of 123 patients with MTC, Russell and colleagues reported that 67 percent of the patients whose MTC was confined to the thyroid were clinically and biochemically (calcitonin) free of disease (mean follow-up time 5.5 years), compared to only 8 percent of patients who had extrathyroidal spread. A later paper from the same group reported on 31 patients who, despite having adequate primary operations for MTC, had persistently raised calcitonin levels. The 5- and 10-year survival rates for these patients were 90 percent and 86 percent, respectively, with only two patients dying from MTC. Postoperatively raised calcitonin levels are frequently encountered and are a cause for concern signaling the need for evaluation.

When recurrent or metastatic MTC is suspected and suggested by rising calcitonin levels, localization studies for occult or clinically apparent disease should be used. The investigative tools available include CT, MRI of the neck and mediastinum,
ultrasound examination, and selective venous catheterization (with calcitonin assay), including hepatic vein and jugular sampling after pentagastrin stimulation. An increase in the hepatic veins before an increase in the cervical veins indicates hepatic metastases. Nuclear imaging studies with 131I metaiodobenzylguanidine (MIBG), dimercaptosuccinic acid (DMSA), and 99mTc-sestamibi all have been used but are only occasionally helpful. Positron-emission tomography (PET) scanning appears to be useful in selected patients. Some clinicians examine the liver laparoscopically to rule out liver metastases.

Ultimately prognosis is related to disease stage. The 10-year survival rate is approximately 80 percent, and only 45 percent in those patients with lymph node involvement. Survival also is significantly influenced by disease type. It is best in patients with familial non-MEN medullary thyroid cancer, followed by those with MEN IIA, then those with sporadic disease, and it is worst in patients with MEN IIB. Patients with tumors that stain poorly for calcitonin and with a heterogeneous antibody uptake do worse than patients in whom calcitonin staining is increased and homogeneous.

With the identification and localization to chromosome 10 of the gene that causes MTC, it is now possible to screen family members and identify children at risk of developing MTC. Performing thyroidectomy at the C-cell-hyperplasia stage or before, after the age of 5 years, will prevent MTC and improve survival rates. Patients with MEN IIA and MEN IIB are at risk for pheochromocytoma.

Anaplastic Carcinoma
This tumor is one of the most aggressive malignancies, with few patients surviving 6 months beyond diagnosis. The incidence of anaplastic carcinoma has dropped to about 1 percent of thyroid carcinomas in the United States. The decrease in incidence is probably a result of the decrease in iodine-deficient (endemic) goiter, which was a precursor for this condition. Most anaplastic carcinomas arise from differentiated thyroid cancers. There is a female-to-male ratio of 1.5:1, and the majority of tumors present in the seventh and eighth decade of life. Presentation before the age of 50 years is rare.

Pathology
Tumor growth is extremely rapid, with macroscopic invasion of surrounding tissues. Lymph node involvement frequently is present. Microscopically, sheets of cells are seen, with marked heterogeneity. Cells may be spindle-shaped, polygonal, or large, multinucleated cells. Foci of more differentiated cells may be seen, either follicular or papillary in pattern. Anaplastic tumors originally described as small-cell are recognized to be lymphomas or less commonly medullary carcinomas of the thyroid gland and should be treated as such.

Clinical Manifestations
Patients typically are elderly females with a history of a lump in the neck that has been present for some time before rapidly enlarging and becoming painful. Associated symptoms such as dysphonia, dysphagia, and dyspnea are common. The tumor is hard and may be fixed to surrounding structures or may be ulcerated (Fig. 36-28). Lymph nodes usually are palpable at presentation. Evidence of metastatic spread also may be
present. Diagnosis is confirmed by FNAC revealing characteristic giant and multinucleated cells. Incisional biopsy to confirm the diagnosis rarely is necessary.

Treatment
All forms of treatment have been disappointing. Tennvall and colleagues reported on 33 patients treated prospectively over an 8-year period with initial hyperfractionated radiotherapy with doxorubicin, then debulking thyroidectomy, followed by completion of radiotherapy and chemotherapy. Using this regimen, only four patients (12 percent) survived more than 2 years, and few patients died of suffocation because of central neck disease. Although the overall survival rate remains very poor, this treatment is recommended until better treatment results are documented.

Lymphoma
Approximately 1 percent of thyroid malignancies are lymphomas, and most of the primary thyroid lesions are of the non-Hodgkin's B-cell type. Although the disease can arise as part of a generalized lymphomatous condition, most thyroid lymphomas develop in patients with chronic lymphocytic thyroiditis (Hashimoto's thyroiditis). Chronic antigenic lymphocyte stimulation has been suggested to result in lymphocyte transformation.

Patients usually present with symptoms similar to those of patients with anaplastic carcinoma, although the rapidly enlarging neck mass often is painless. Because there is frequently coexisting Hashimoto's thyroiditis, patients may be clinically hypothyroid or may already be receiving thyroxine treatment. Most patients presenting with thyroid lymphoma are elderly women. The diagnosis usually is suggested by FNAC, although needle-core or open biopsy may be necessary for definitive diagnosis. When nodal dissection is being performed, taking a biopsy sample of lymph node often helps to clarify the diagnosis.

Patients with thyroid lymphoma usually respond rapidly to chemotherapy (CHOP—cyclophosphamide, doxorubicin, vincristine, and prednisone), and combined treatment with radiotherapy and chemotherapy is often recommended. Thyroidectomy and nodal resection are used to alleviate symptoms of airway obstruction in patients who do not respond quickly to chemotherapy or chemotherapy and radiotherapy.

Prognosis depends on the histologic grade of the tumor and whether the lymphoma is confined to the thyroid gland or is disseminated. The overall 5-year survival rate is about 50 percent; patients with extrathyroidal disease have markedly lower survival rate compared to those with intrathyroidal disease—40 percent versus 85 percent. Although there are no prospective studies, similar remission rates have been reported for patients who underwent diagnostic biopsy plus adjuvant therapy alone (85 percent), compared to debulking surgery plus adjuvant therapy. These findings support the argument for chemotherapy and radiotherapy for most patients.

Metastatic Carcinoma
The thyroid gland is a rare site of metastases from other cancers, including kidney, breast, lung, and melanoma; the most common metastatic tumor to the thyroid is hypernephroma. Approximately 3 percent of bronchogenic carcinomas metastasize to the thyroid, and these metastases account for 20 percent of secondary metastases to the thyroid.
Clinical examination and the history often suggest the source of the metastatic disease, and FNAC usually provides definitive diagnosis. Resection of the thyroid, usually lobectomy, may alleviate symptoms in symptomatic cases.

SURGERY OF THE THYROID
Patients who have had any change in voice or any previous neck surgery should have a preoperative vocal cord assessment, by direct or indirect laryngoscopy. Patients should be euthyroid at operation. On the operating table, a sandbag should be placed between the patient's shoulder blades, the head supported by a ring, and the neck extended to provide optimal exposure.

Operative Technique
A Kocher transverse collar incision is sited in a skin crease about 1 cm below the cricoid cartilage and carried through the platysma muscle (Fig. 36-29). The length of the incision varies, typically around 5 cm, and it should be symmetrical. Longer incisions are necessary in patients with larger tumors, in patients with a short, fat neck or whose neck cannot be extended, and in patients with low-lying thyroid glands. The upper flap is dissected in an avascular subplatysmal plane anterior to the anterior jugular veins and deep to the platysma muscle, to the level of the thyroid cartilage. The lower flap is then mobilized in a similar manner, to the suprasternal notch. Skin towels and a self-retaining retractor are applied. Meticulous hemostasis in thyroidectomy facilitates the identification of the parathyroid glands and the recurrent laryngeal nerves, reducing the possibility of inadvertent damage.

The thyroid gland is exposed via a midline incision through the superficial layer of the deep cervical fascia between the sternohyoid and sternothyroid muscles (Fig. 36-30). Care should be taken not to disrupt the veins on the thyroid surface. On the side to be dissected first, the more superficial sternohyoid muscle is separated from the deeper sternothyroid muscle by blunt dissection. The dissection proceeds laterally until the ansa cervicalis is noted on the lateral edge of the sternohyoid muscle and the medial aspect of the internal jugular vein. The deeper sternothyroid muscle is dissected free from the thyroid gland by blunt or sharp dissection, exposing the middle thyroid vein or veins laterally. The thyroid lobe is retracted anteromedially by finger traction and the lateral tissues swept posterolaterally by a pledget. The middle thyroid veins are divided and ligated. In rare cases the strap muscles must be divided in order to gain access to a large thyroid tumor. When this maneuver is necessary, the muscles should be divided high so that innervation from the ansa hypoglossal nerve is preserved. Occasionally a thyroid cancer invades the strap muscles; in this situation the involved muscles should be removed en bloc with the thyroid.

The superior thyroid pole is identified by retracting the thyroid inferiorly and medially. The tissues lateral to the upper pole of the thyroid and medial to the carotid sheath can be mobilized quickly by blunt dissection, because there are no nerves in that region. The upper pole of the thyroid is then mobilized caudally and laterally. The dissection plane should be close to the thyroid to avoid possible injury to the external branch of the superior laryngeal nerve. An effort should be made to identify and preserve the branch of the external laryngeal nerve that supplies the cricothyroid muscle. The branch is visible in about 80 percent of patients on the cricothyroid
muscle (Fig. 36-31). The superior pole vessels are then individually identified, skeletonized, and doubly ligated low on the thyroid gland.

When the superior pole vessels have been ligated and divided, the tissues posterolateral to the superior pole can be swept away from the thyroid gland in a posteromedial direction. The direction is important because it reduces the chances of damaging the vessels supplying the upper parathyroid glands. The recurrent laryngeal nerves enter the larynx at the level of the cricoid cartilage, passing under or through Berry's ligament and entering the larynx deep to the cricothyroid muscle (Fig. 36-32).

At this point it should be possible to identify the upper parathyroid gland. The upper gland usually is situated at the level of the cricoid cartilage. The lower parathyroid gland is found most commonly just below where the inferior thyroid artery and recurrent laryngeal nerve cross. In approximately 80 percent of patients the glands are located within 1 cm of the artery. The lower parathyroid gland usually is situated anterior to the recurrent laryngeal nerve, and when it is not, it is usually located in the thymus or in parathymic fat (Fig. 36-33).

The thyroid is completely mobilized by gently sweeping dorsally all tissue along the posterolateral border away from the thyroid. All vessels are ligated and divided on the thyroid capsule to minimize the possibility of devascularizing the parathyroids. No tissue should be clamped or divided that might be or contain a recurrent laryngeal nerve.

Parathyroids that are ischemic, or are situated very anteriorly on the thyroid gland, or have been removed along with the thyroid lobe, should be examined after removal. They should be biopsied and confirmed by frozen-section examination, minced into 1-mm cubed pieces, and implanted into a small pocket in the ipsilateral sternohyoid muscle, with a silk suture or clip marking the site.

The recurrent laryngeal nerves should be identified; the nerve is located more medially on the left and runs more obliquely on the right. The most difficult part of the operation usually is during the dissection where the recurrent nerve passes through Berry's ligament. It is here that the nerve is in close proximity to the thyroid, tethered down by the ligament, through which runs a small artery, and it is here that the nerve is most commonly injured. If bleeding occurs at this site it should be controlled by gentle pressure before identification of the nerve to avoid injury, and then the vessels are all ligated. Use of electrocautery to control bleeding should be strictly avoided.

A pyramidal lobe is present in about 80 percent of patients and should be dissected free superiorly to the level of the thyroid cartilage or higher and removed in continuity with the thyroid lobe and the isthmus. One or more lymph nodes are often present just cephalad to the isthmus of the thyroid gland (Delphian node) and should be removed with the thyroid.

When lobectomy is performed, the isthmus is divided flush with the contralateral gland and oversewn. When total thyroidectomy is performed, the same procedure is followed on the contralateral side. If a subtotal thyroidectomy is being performed (for Graves' disease or multinodular goiter), normal practice is to perform a total lobectomy on one side and a subtotal lobectomy on the other side. Removing all
thyroid tissue on one side has the advantage of obviating the need to reoperate on one side in cases in which reoperation may be necessary, and the possibility of damage to the recurrent laryngeal nerve and parathyroid on that side during future procedures is reduced.

Subtotal lobectomy is achieved in a similar fashion to lobectomy, but after division of the superior thyroid pole, arterial clamps are placed along the length of the lobe, anterior to the insertion of the inferior thyroid artery, usually leaving approximately 1 to 2 cm³ (4 to 8 g) of thyroid tissue. The thyroid is oversewn and secured to the lateral tracheal fascia to encourage hemostasis. Suction drains rarely are necessary. They can be used when there is a large space, e.g., after removing a large substernal goiter. Strap muscles are reapproximated with absorbable sutures, as is the platysma, and the skin is closed with subcuticular sutures or clips.

Surgical Removal of Intrathoracic Goiter
In 99 percent of the patients, intrathoracic goiter can be removed via a collar incision in the neck rather than resorting to a sternotomy. Patients with substernal goiters who have had previous thyroid operations, some with invasive malignant tumors, and patients with no thyroid tissue in the neck may require a median sternotomy.

Vascular connections in the neck are identified, ligated, and divided. The superior pole vessels and the middle thyroid veins are identified and ligated first. Dividing the isthmus may help with subsequent mobilization of the substernal goiter from beneath the sternum.

Several large 1-0 or 00 sutures are placed deeply into the goiter, and through a combination of traction and blunt dissection the thyroid usually can be delivered into the neck from its substernal location. In patients with a very large colloid goiter, the colloid occasionally may be evacuated to permit delivery, but this maneuver usually is unnecessary, and it is contraindicated if cancer is present. Although 1 percent of goiters contain cancer, the frequency of cancer in substernal goiter is as high as 10 percent in some series.

In approximately 1 percent of patients, part or all of the thyroid gland is intrathoracic. This usually is a consequence of extension or migration of the thyroid into the mediastinum rather than aberrant glandular tissue. The blood supply usually originates in the neck rather than the mediastinum. These goiters are more difficult to remove because it is difficult to apply traction.

Substernal goiters occasionally are too large to deliver via a neck incision, and a sternotomy is required. In patients in whom thyroid cancer is suspected or demonstrated in an intrathoracic gland, attempts should be made to avoid rupture of the thyroid capsule.

Because the blood supply to the thyroid gland, thymus gland, and lower parathyroids primarily is derived from the inferior thyroid arteries in the neck, median sternotomy usually is unnecessary. Sternotomy is indicated in patients in whom the intrathoracic gland is cancerous and mediastinal node involvement or metastatic cancer deep in the mediastinum has been demonstrated by scanning. When sternotomy is indicated, the sternum usually should be divided to the level of the third intercostal space and then
laterally on one side at the space between the third and fourth ribs (Fig. 36-34). Median sternotomy provides excellent exposure of the upper mediastinum and lower neck.

Neck Dissection for Nodal Metastases
Lymph nodes in the central compartment (medial to the carotid sheath) are frequently involved in metastatic spread in patients with papillary, medullary, and Hürthle cell carcinomas. In these patients all central neck nodes should be removed at the time of the primary procedure, preserving the recurrent laryngeal nerves and, when possible, the parathyroid glands, autotransplanting them when necessary, after histologic confirmation, into the sternocleidomastoid muscle. Removal of all central nodes is important in patients with medullary and Hürthle cell carcinoma because of the high frequency of microscopic tumor spread and because these tumors do not take up radioiodine and cannot be ablated with 131I.

In patients with thyroid cancer with palpable cervical lymph nodes or in cases of medullary carcinoma when the thyroid lesion is larger than 2 cm, a modified radical neck dissection usually should be performed. This operation is possible via extension of the collar incision laterally to the anterior margin of the trapezius muscle (MacFee incision). The internal jugular vein, the spinal accessory nerve, and the sternocleidomastoid muscle are preserved unless they are invaded or adhered to tumor. During dissection all tissue in the anterior triangle of the neck from the hyoid bone to the clavicle is removed. Dissection along the spinal accessory nerve is most important because this is a frequent site of metastatic disease. The deep dissection plane is the anterior scalenus muscle, the brachial plexus, and the medial scalenus muscle. The phrenic nerve is preserved on the scalenus anterior muscle, as are the cervical sensory nerves in most patients.

Complications of Thyroid Surgery
The mortality rate from thyroidectomy is low. In two large series, Gould and colleagues reported no mortality in more than 1000 consecutive patients. Similarly, Colcock reported no deaths in his personal series after 1954. Morbidity is approximately 13 percent. Serious morbidity occurs in fewer than 2 percent of patients. Complications specifically attributable to thyroidectomy include nerve damage or respiratory problems, bleeding with hematoma formation, hypoparathyroidism, wound infection, keloid formation, and, rarely, thyroid storm.

Injury of the Recurrent Laryngeal Nerve
Permanent recurrent laryngeal nerve injury is a relatively uncommon event, with a rate of approximately 1 percent; the rate is probably lower in patients with benign disease and higher in patients with large, invasive, or recurrent thyroid carcinomas. Injuries may be temporary, caused by traction or stretching of the nerve, or permanent, caused by division or ligation of the nerve. Injuries may be unilateral or bilateral. Recurrent laryngeal nerve injury leads to vocal cord paralysis, with the vocal cord assuming a paramedian position. In cases of bilateral nerve damage, the cords may obstruct the airway and lead to acute respiratory distress immediately after extubation. Reintubation and, occasionally, subsequent tracheostomy are needed. Unilateral nerve damage leads to paralysis of the ipsilateral vocal cord, with the cord lying in a paramedian position, usually resulting in a hoarse or husky voice. Because
the nerve also is sensory to the larynx and because the vocal cords do not approximate, patients also describe choking and coughing when drinking fluids.

When damage is temporary, vocal cord function usually returns within 6 months, but it may take 1 year. When function has not returned by 6 to 12 months, injection lateral to the cord with Teflon mobilizes the cord to the midline and improves the voice. Occasionally the contralateral cord compensates and vocal cord paralysis may be unnoticed, so all patients should have direct or indirect laryngoscopy to evaluate vocal cord function before reoperation. Speech therapy also helps some patients with vocal cord dysfunction and should be done before Teflon injection.

Identification of the recurrent laryngeal nerves during surgery has been shown to decrease the incidence of permanent damage, although transient paralysis is more common. When nerves are not identified, transient paralysis is reduced, but the incidence of permanent damage is three or four times higher. Disease-specific risk factors for permanent nerve damage, in order of frequency, include recurrent thyroid cancer or recurrent goiter, thyroid cancer, large substernal goiters, chronic lymphocytic thyroiditis, Graves' disease, and euthyroid nodular goiter.

A rare cause of injury to a laryngeal nerve is that it is a nonrecurrent laryngeal nerve. This anomaly occurs in about 0.5 percent of patients and is almost always encountered on the right side. Awareness of this possibility reduces the risk of nerve injury when the recurrent nerve cannot be identified at the usual site.

Meticulous hemostasis, precise dissection between the thyroid capsule and sheath, and care dissecting Berry's ligament, where injuries are most likely to occur, all help to reduce the possibility of damage. The right recurrent laryngeal nerve takes a more oblique course in the neck as it loops around the subclavian artery, whereas the left recurrent laryngeal nerve loops around the ligamentum arteriosum and assumes a more midline position in the tracheoesophageal groove. Either nerve may branch before it enters the larynx posterior to the cricothyroid muscle at the level of the cricoid cartilage.

Injury of the External Branch of the Superior Laryngeal Nerve
Injury to the external laryngeal nerve results in difficulty shouting or singing high notes (the nerve is also called the “high note nerve”). The risk of injuring the nerve can be greatly reduced by retracting the strap muscles laterally to provide adequate visualization of the superior thyroid pole. A plane is opened by blunt dissection between the thyroid pole and the cricothyroid muscle bed. In about 80 percent of patients the nerve can be seen on the cricothyroid muscle. The superior thyroid vessels are individually ligated and divided low on the thyroid gland, rather than taken all together in one large bloc to avoid injury to the external laryngeal nerve. If these steps are followed, injury to the nerve is uncommon (2 percent).

Hypoparathyroidism
The chances of permanent hypoparathyroidism after thyroidectomy vary with the size and degree of invasion of the tumor, the type of pathology, the extent of the procedure, and the experience of the surgeon. Total thyroidectomy and central neck compartment clearance in medullary thyroid carcinoma has a higher incidence of subsequent hypoparathyroidism than does subtotal thyroidectomy for multinodular.
goiter (2 percent versus 0.5 percent), because all of the central neck fibroadipose and lymphatic tissue should be removed in patients with medullary carcinoma. After most operations the serum calcium level falls by about 1 mg/dL. Symptomatic postoperative hypoparathyroidism after thyroidectomy usually is transient and resolves in most cases within a few days without treatment and with calcium supplementation when treatment is necessary. When the serum phosphorus level is low or normal, there is less concern in the hypocalcemic patient than when it is high, because the latter suggests hypoparathyroidism.

In most instances, postoperative hypoparathyroidism is a result of parathyroid ischemia from bruising and partial interruption of parathyroid blood supply. This situation can be avoided by dissection along the thyroid capsule and gently teasing the parathyroid gland on a broad plane of tissue away from the thyroid gland in a posterolateral direction. This decreases the risk of disruption of the parathyroid blood supply, derived from the inferior and superior thyroid arteries. Hypoparathyroid patients usually exhibit early tingling and numbness around the lips, followed by the same sensation in the fingers. A positive Chvostek's sign (twitching of the lips after tapping over the facial nerve) is usually present. When hypocalcemia is not treated, patients may progress to carpopedal spasm. Symptoms occur when the calcium level falls below 8 mg/dL. Hypocalcemia also increases anxiety and respiratory alkalosis. Hyperventilation can cause tetany with or without associated hypocalcemia. Patients with postoperative hypocalcemia are treated initially with approximately 1 g of calcium every 4 h if symptomatic. When the serum calcium level remains low, intravenous calcium (1 to 10 ampoules of calcium gluconate or calcium chloride) can be given over several hours. Extravasation into the subcutaneous tissues can cause tissue necrosis. Treatment with calcitriol (Rocaltril) 0.25 to 1.0 mg twice daily is occasionally necessary. In patients with persistent symptoms, the serum magnesium level should be evaluated.

Postoperative Management of Differentiated Thyroid Cancer
Thyroid Hormone
After thyroid surgery for carcinoma, patients should be placed on thyroxine. This is necessary as replacement therapy in patients who have undergone total thyroidectomy but has the additional effect of suppressing TSH and reducing the growth stimulus to any possible residual thyroid cancer cells. TSH suppression reduces tumor recurrence rates, particularly in patients with papillary cancer. Thyroxine should be administered to ensure that the patient remains euthyroid, with circulating TSH levels about 0.1 mU/L in low-risk patients or less than 0.1 mU/mL in high-risk patients.

Thyroglobulin Measurement
Thyroglobulin levels in patients who have undergone total thyroidectomy should be below 2 ng/mL when the patient is taking thyroxine, and below 3 ng/ml when the patient is not taking thyroxine. A thyroglobulin level above 3 ng/mL is highly suggestive of metastatic disease or persistent normal thyroid tissue, especially if it increases when TSH levels increase when thyroid hormone treatment is discontinued in preparation for radioiodine scanning. In this situation, radioiodine scan should be performed.

About 95 percent of patients with persistent or recurrent thyroid cancer of follicular cell origin will have thyroglobulin levels higher than 3 ng/mL. High-risk patients...
should also have a CT or MRI scan of the neck and mediastinum for early detection of any persistent or recurrent disease.

Radioiodine Therapy
Metastatic differentiated thyroid carcinoma can be detected and treated by radioactive iodine in about 75 percent of patients. Screening and treatment are facilitated by the removal of all normal thyroid tissue, which effectively competes for iodine uptake and is the most compelling arguments in favor of total thyroidectomy for differentiated thyroid carcinoma. Radioiodine is more effective in young patients, even with occult pulmonary metastases, and less effective in older patients with less well differentiated thyroid cancers.

Most follicular carcinomas concentrate iodine. One exception is the Hürthle cell carcinomas, of which only about 10 percent take up iodine. Screening with radioactive iodine is a more sensitive test of metastatic disease than chest x-ray or CT but less sensitive than serum thyroglobulin determination. Micrometastases in the chest are detectable by radioiodine scanning even when chest x-rays show no evidence of disease. Approximately 75 percent of these patients have been successfully treated after receiving ablative doses of 131I for micrometastases, especially when total thyroidectomy has been performed. The success rate of treating macro–pulmonary metastases with 131I is less than 10 percent. TSH suppression with thyroxine after treatment with 131I should be used.

Radioactive iodine scanning and treatment follow a standard protocol after initial or completion total thyroidectomy. Patients should have their levothyroxine therapy discontinued for approximately 8 weeks before the scanning with 131I. During the first 6 weeks of this time they are given a synthetic triiodothyronine (T3); this decreases the period (and discomfort) of hypothyroidism, because T3 has a half-life of about 1 day, whereas T4 has a half-life of about 1 week. The T3 is then discontinued for remaining 2 weeks, which allows TSH levels to rise. A low-iodine diet also is recommended during these 2 weeks immediately before scanning.

In most centers, a screening dose of about 2 mCi of 131I is administered and the uptake is measured at 24 h. The uptake in most patients should be less than 1 percent, with no “hot” spots in the neck or elsewhere (remnant normal thyroid or metastases). The most frequent cause of a hot spot in the neck after initial screening is residual thyroid tissue in the thyroid bed. If there is significant uptake (>1 percent), then a therapeutic dose of 131I, 30 to 50 mCi in low-risk patients and 100 to 200 mCi in high-risk patients, is recommended. Some physicians omit the scanning dose of 131I for patients who are thyroglobulin positive, especially if the thyroglobulin level increases when the patient is hypothyroid in preparation for scanning or treatment. For these patients a scan should be performed 5 to 7 days after the treatment dose; about one-third will become thyroglobulin and radioiodine-uptake negative, which documents a therapeutic benefit.

After scanning and treatment, patients are placed again on levothyroxine (normal dose is about 125 mg/day) and observed over follow-up with serum thyroglobulin determinations and physical examination at regular intervals. Patients with previously positive scans and patients with serum thyroglobulin levels over 3 ng/mL usually need another 131I treatment after 6 to 12 months. The maximum dose of radioiodine that
can be administered at one time is approximately 200 mCi with a cumulative dose of 1000 mCi.

External Beam Radiotherapy and Chemotherapy
External beam radiotherapy is required occasionally to control unresectable locally invasive or recurrent disease. It also is of value for the treatment and control of pain from bony metastases when there is no appreciable radioiodine uptake.

Multidrug chemotherapy and adriamycin have been used with little success in disseminated thyroid cancer; remission sometimes occurs, but cure is rare. Taxol has been reported recently to be of some value in patients with incurable disease.
Parathyroid

Historical Background Anatomy Pathology Physiology of Calcium Homeostasis 
Primary Hyperparathyroidism Persistent and Recurrent Hyperparathyroidism 
Secondary Hyperparathyroidism Tertiary Hyperparathyroidism Multiple Endocrine Neoplasia and Hyperparathyroidism Hypercalcemic Crisis Parathyroid Carcinoma

HISTORICAL BACKGROUND

In 1849 Sir Richard Owen, curator of the London Zoological Gardens, performed an autopsy on a rhinoceros that had been given to the London Zoo by the government of India (Fig. 36-35). Owen's original description of the mysterious structures he found within the neck of the rhinoceros remains an accurate assessment of the normal parathyroid gland—"a small, yellow, glandular body … attached to the thyroid at the point where the veins emerge." In 1879 Anton Wölfer documented the relationship between total thyroidectomy and the ensuing tetany in the first such patient operated on by C.A. Theodor Billroth. The first description of the parathyroid glands in human beings was that by Ivar Sandström, a medical student in Uppsala, Sweden, in 1880 (Fig. 36-36). He suggested that these glands be named the glandulae parathyroideae. The function of these structures was unknown at that time.

Friedrich von Recklinghausen, in 1891, described the fibrocystic disease of bone produced by hyperparathyroidism. The first association of hyperparathyroidism with osteitis fibrosa cystica (von Recklinghausen's disease) was made by Askanazy in 1903. In the same year, Erdheim recorded the coexistence of a parathyroid tumor and a pituitary tumor, foreshadowing the description of multiple endocrine neoplasia almost 50 years later. In 1909 serum calcium level determination became possible, and the association between serum calcium level and the parathyroid glands was established.

The first patient to be operated on for a parathyroid abnormality was a 38-year-old male who underwent a successful parathyroidectomy in 1925 by Felix Mandl. The patient had severe bone pain secondary to advanced osteitis fibrosa cystica. His condition dramatically improved after the operation, and he lived for another 7 years before dying of recurrent hyperparathyroidism or renal failure. In 1926, at the Massachusetts General Hospital, Edward Churchill, assisted by an intern named Oliver Cope, operated for the seventh time on the famous sea captain Charles Martell (Fig. 36-37) for severe primary hyperparathyroidism. No parathyroid abnormalities were identified in any of Captain Martell's previous six cervical explorations. It was only at the time of the seventh operation that an ectopic adenoma was found in the substernal position. Captain Martell died 6 weeks after the successful seventh operation, most likely from laryngeal spasm after a subsequent surgical procedure to relieve ureteral obstruction secondary to stones.

The first successful parathyroidectomy for hyperparathyroidism based on an accurate preoperative biochemical diagnosis was performed in 1928 by Isaac Y. Olch at the Barnes Hospital in St. Louis, Missouri, on a 56-year-old female. At operation, a 3 × 3
cm adenoma was found attached to the left lower lobe of the thyroid gland. Postoperatively the patient developed life-threatening tetany, with her serum calcium dropping as low as 4.5 mg/dL. The patient recovered and lived for many years, although she required lifelong supplemental oral calcium lactate.

ANATOMY
The superior parathyroid glands arise from the fourth branchial pouch in conjunction with the ultimobranchial bodies. Because of this association, the superior parathyroid glands remain in close proximity to the posterior portion of the upper thyroid lobes. This position is fairly constant, and superior parathyroid glands located in ectopic sites are less common in comparison to the inferior glands. When the superior glands enlarge, they tend to “descend by gravity” into or along the tracheoesophageal groove and may be inferior to the inferior parathyroid glands (Fig. 36-38). When true embryologic descent of the superior glands does occur, the descent is in a posterior plane (Fig. 36-39). When such glands descend, they can be located in the posterior or middle mediastinum, with the aortopulmonary window being the most common site. The superior parathyroid glands usually are found in close association with the posterior aspect of the middle and upper thirds of the thyroid gland (Fig. 36-40). In this position, they are in close proximity to the cricothyroid membrane entrance of the recurrent laryngeal nerve and usually cephalad to the superior thyroid artery.

The inferior parathyroid glands arise from the third branchial pouches in conjunction with the thymus. Given this important association, and since the embryologic journey is a longer one, ectopic sites for the inferior glands are more common and more widely distributed than ectopic sites for superior glands (Fig. 36-41). With rare exceptions, thymic tissue is intimately related to inferior glands in ectopic locations. Ectopic sites range from an intrathymic parathyroid gland located in the anterior-superior mediastinum to an undescended inferior parathyroid gland (parathymus) located superior to the superior parathyroid gland. Undescended inferior glands are most often found at the angle of the mandible anterior to the carotid artery but may be seen as high as the base of the skull.

The normal inferior glands are more variable in location than superior glands (see Fig. 36-40 B). The most common site (approximately 60 percent) for inferior parathyroids is within a circle 2 cm in diameter centered on a point that is on the posterolateral aspect of the lower pole of the thyroid gland. The majority of the remaining normal inferior parathyroid glands will be found in the thyrothymic tongue of tissue (thyrothymic ligament), which extends inferiorly from the lower pole of each thyroid lobe to the thymus gland, usually located in the anterior mediastinum (Fig. 36-42).

A normal parathyroid gland usually weighs less than 50 mg, measures approximately 3 × 3 × 3 mm, and may be difficult to differentiate from adjacent fatty tissue. Parathyroid glands are more yellow-brown than normal fatty tissue, and close observation will invariably reveal small “grains of salt” on their surface, an observation that aids in differentiation from surrounding fatty tissues. Normal glands have more clearly defined margins, which aids in this differentiation and which has led to their being described as looking like “the tongue of a jaundiced hummingbird.

PATHOLOGY
Primary hyperparathyroidism may be due to parathyroid adenoma(s), hyperplasia, or, rarely, carcinoma. Of these causes, a parathyroid adenoma is by far the most common, accounting for 90 percent of cases. In almost 2 percent of patients with adenomatous disease, double adenomas are present. Parathyroid hyperplasia (multiglandular disease) may be found in nearly 8 percent of patients with sporadic hyperparathyroidism. The incidence of hyperplasia increases markedly and may be universal in patients with hyperparathyroidism that occurs in families with multiple endocrine neoplasia (MEN) type I or II, and in patients with non-MEN familial hyperparathyroidism. Parathyroid hyperplasia is seldom equal or even symmetrical. This “unequal hyperplasia,” if misinterpreted by the surgeon, may lead to a mistaken diagnosis of single versus multiglandular disease. Parathyroid carcinoma, as a cause for hyperparathyroidism, is exceedingly rare, occurring in less than 1 percent of patients with this disease.

Differentiation between the causes of hyperparathyroidism is of paramount importance, because the selection of appropriate surgical treatment depends on it. This delineation is made primarily by the operating surgeon identifying the pathology encountered at the time of surgical exploration. A structure that looks like a little kidney in the neck or mediastinum is virtually pathognomonic for single-gland disease. Finding multiple enlarged glands somewhat “paler than a normal kidney” suggests multiglandular disease. The pathologist can be of great help to the surgeon, and vice versa. Unequivocal histologic identification of the causes of primary hyperparathyroidism can be difficult without the surgeon's description of the gross characteristics of all glands. With small biopsy specimens alone of parathyroid glands, it can be extremely difficult for the pathologist to accurately differentiate histologically between a truly normal gland, a parathyroid adenoma, or a hyperplastic parathyroid gland. Our own preference is to avoid taking biopsy specimens of normal-appearing glands and to rely on visual inspection of the remaining glands and the histology of the excised abnormality to determine the diagnosis.

Normal parathyroid glands contain primarily chief cells, with occasional oxyphil cells. An adenoma is typically defined as an enlarged parathyroid gland that is made up of solid sheets of chief cells, oxyphil cells, or varying combinations of both with a rim of compressed normal parathyroid tissue (Fig. 36-43). This compressed rim of normal tissue is present in only 20 to 30 percent of parathyroid adenomas. The histology of parathyroid hyperplasia may be difficult to discern unless the nature of the other parathyroid glands is placed in context (Fig. 36-44). Histologically, the presence or absence of parathyroid fat cells has been believed by some authorities to be of help in the diagnosis of parathyroid hyperplasia; the higher the percentage of fat cells, as demonstrated by fat staining, the lower the chances of hyperplasia, and vice versa.

The macroscopic appearance of the parathyroid glands, as visualized by an experienced parathyroid surgeon, continues to be the most accurate means of identifying the various types of parathyroid pathology.

PHYSIOLOGY OF CALCIUM HOMEOSTASIS

(Parathyroid Hormone (PTH)

In patients with primary and tertiary hyperparathyroidism, the secretion of parathyroid hormone is abnormal and excessive. In secondary hyperparathyroidism, PTH...
secretion is increased, but appropriately so. The effect of PTH in human beings is to increase serum calcium concentration (Fig. 36-45). Hypercalcemia occurs because the principal actions of PTH involve the following:

1. Increase of bone osteoclast and osteoblast activity
2. Increase in rate of conversion of 25-hydroxycholecalciferol (25-hydroxyvitamin D3) to 1,25-dihydroxycholecalciferol (1,25-dihydroxyvitamin D3) in the kidneys by stimulation of 1α-hydroxylase activity
3. Increase of gastrointestinal absorption of calcium by enhancing vitamin D synthesis
4. Increased excretion of bicarbonate by the kidney
5. Decrease in serum phosphate level by increasing the excretion of urinary phosphate

PTH is a single-chain polypeptide of 84 amino acids. The entire polypeptide is referred to as intact PTH, a hormone that has a half-life of 2 to 5 min. The N-terminal PTH portion (1–34), also called the amino (N) terminal, is biologically active, with a half-life of 2 min. The C-terminal PTH portion (35–84) or carboxyl (C) terminal, is biologically inactive, with a half-life of approximately 30 min. Among other effects, PTH acts to promote bone resorption and to increase calcium absorption from filtered urine in the renal tubule.

Calcium
Calcium is the principal regulator of parathyroid hormone release. This regulation is mediated by calcium receptors or other receptors on the parathyroid cell surface. A membrane protein that has been proposed to constitute such receptors (calcium ion-sensing receptor [CaR]) demonstrates reduced expression in hyperparathyroidism and seems causally related to the relative insensitivity of the secretion to external calcium in pathologic parathyroid cells. This protein consequently may be an important cause for the hypercalcemia of this disorder. Modulating the functions of such proteins comprises interesting means of future therapy in several disorders of mineral metabolism. Increased knowledge of these proteins and parathyroid pathophysiology may clarify the presence of relevant mutations, secretory derangements, and propensity for cell growth, from which accurate classification of parathyroid diseases and improved treatment strategies might evolve.

Calcium is the most abundant cation in human beings, and its distribution within cells is essential for virtually all physiologic functions. Calcium balance in a normal individual is tightly regulated. The body contains approximately 1000 g of calcium, with minimal variations from day to day in serum calcium concentration (Fig. 36-46). Total serum concentrations, as tested by routine laboratory analysis, are accurate as long as serum protein concentrations are normal. Total calcium level must always be considered in its relationship to plasma protein levels, especially serum albumin (for each gram per deciliter of alteration of serum albumin above or below 4.0 mg/dL, there is a 0.8 mg/dL increase or decrease in protein-bound calcium and thus in total serum calcium.
Vitamin D
Vitamin D3 (cholecalciferol) is vital to calcium homeostasis. It is absorbed through the gastrointestinal tract and synthesized in the skin and is converted by the liver to 25-hydroxycholecalciferol, which is subsequently converted to its active form, 1,25-dihydroxycholecalciferol in the kidneys by the enzyme 1a-hydroxylase. Vitamin D3 increases the absorption of calcium from the gastrointestinal tract and promotes phosphate retention; it elevates serum calcium and phosphate levels and in turn .enhances the mineralization of bone

A fall in serum calcium concentration stimulates secretion of PTH, which, among other effects, results in a rise in vitamin D3synthesis. Vitamin D3 then acts peripherally to raise the serum calcium concentration toward normal. Vitamin D3 promotes bone resorption and enhances absorption of calcium and phosphorus from the gut. An elevation of the serum calcium level reduces PTH secretion and the formation of vitamin D3. Both effects tend to lower serum calcium concentration

PRIMARY HYPERPARATHYROIDISM
Primary hyperparathyroidism is the hypercalcemic condition generated as a result of overproduction of PTH by one or more parathyroid glands. PTH enhances gastrointestinal absorption of calcium, stimulates the production of vitamin D3, and inhibits renal calcium excretion. PTH secretion from the parathyroid glands is inversely related to serum calcium levels and is tightly regulated. In primary hyperparathyroidism, the normal negative feedback loop is altered, and inappropriately elevated PTH levels occur in the face of hypercalcemia

The incidence of primary hyperparathyroidism in the United States is estimated to be 1:700, with a female-to-male ratio of nearly 3:1. Primary hyperparathyroidism is the most common cause of hypercalcemia observed. Only advanced malignancy is a more common cause of hypercalcemia in hospitalized patients in the United States. Of the nearly 100,000 cases diagnosed yearly in the United States, most occur in postmenopausal women, in whom the incidence is nearly 1:200. The incidence of this disease appears to have decreased over the past decade, for unknown reasons

Etiology
While the exact cause or stimulus that brings about the autonomous production of PTH remains unclear, pathologically the disease is manifested by three separate entities. Most commonly, primary hyperparathyroidism is caused by the benign enlargement of one (90 percent) or, occasionally, two (2 percent) parathyroid glands, a condition referred to as benign parathyroid adenoma(s). Less common is the occurrence of multiple gland enlargement (8 percent), which is referred to as multiglandular hyperplasia. Parathyroid carcinoma is a rare (less than 1 percent), often lethal, cause of hyperparathyroidism

Clinical Manifestations
Before calcium levels were routinely included in serum chemistry analysis in the late 1960s, and before their routine use in the 1970s as an adjunct for general medical examinations, the diagnosis of primary hyperparathyroidism was rarely considered, typically only in patients with renal stones, bony abnormalities, or severe mental changes. Patients with primary hyperparathyroidism had variable symptoms: renal
stones (64 percent), bone disease (20 percent), peptic ulcer disease (12 percent), and hypertension (4 percent). Walter St. Goar, in 1957, first used the mnemonic “Hyperparathyroidism is a disease of stones, bones, and abdominal groans” to remind physicians to consider this diagnosis in patients with varied complaints. With time, the triad of St. Goar has been extended to include other nonspecific regional symptoms of hypercalcemia pertaining to the abdomen, kidney, bone, constitutional, .(and neurologic manifestations (Fig. 36-47

Over half of all patients diagnosed with primary hyperparathyroidism are asymptomatic, and the disease is discovered by routine serum chemistry analysis showing hypercalcemia. After successful surgical management of primary hyperparathyroidism, nearly all patients realize that they had in fact been symptomatic.

Evaluation
The diagnosis of primary hyperparathyroidism is most commonly one of exclusion. It is most commonly considered when serum chemistry analysis reveals hypercalcemia. A focused history in symptomatic and asymptomatic patients is important to rule out medicinal use that might cause hypercalcemia and obscure the diagnosis—most commonly thiazide diuretics, but also lithium and excessive ingestion of vitamin A or vitamin D. Consumption of extraordinary amounts of milk or antacids might alert the clinician to the diagnosis of the milk-alkali syndrome. Questions regarding renal failure, dehydration, immobilization, and Paget's disease can lead to identifying the cause of the hypercalcemia. Endocrine abnormalities such as adrenal insufficiency, and either hyperthyroidism or hypothyroidism are similarly rare causes of hypercalcemia. Granulomatous diseases such as sarcoidosis, tuberculosis, coccidiodomycosis, histoplasmosis, and berylliosis can elevate serum calcium levels. It is to critical to evaluate hypercalcemic patients for previous or current malignancy with possible bony metastases. The malignant causes of hypercalcemia include renal cell carcinoma, multiple myeloma, and squamous or small cell lung cancer. Over 90 percent of patients with hypercalcemia have primary hyperparathyroidism or malignancy, most commonly metastatic from the prostate or breast, as the source of .their elevated serum calcium levels.

A family history of multiple endocrine neoplasia or benign familial hypocalciuric hypercalcemia (BFHH) is critical. MEN and BFHH usually occur in younger patients with a known genetic predisposition. BFHH involves sufficient retention of calcium to cause hypercalcemia. Unlike patients with primary hyperparathyroidism, BFHH patients have unusually low urinary calcium excretion. Cervical exploration in these patients is of no benefit and is contraindicated.

Physical examination of patients with primary hyperparathyroidism is rarely of diagnostic aid, but it is important to assess for neck masses, voice abnormalities or hoarseness, cervical lymphadenopathy, and mobility of the cervical spine. Neck masses most commonly represent benign thyroid nodules but could be the rare parathyroid cancer. Hypercalcemia coupled with a firm cervical mass with hoarseness or a recent change in voice would indicate involvement of a recurrent laryngeal nerve secondary to this rare malignancy. As a corollary, parathyroid adenomas, regardless of their size, are rarely palpable. While cervical lymphadenopathy can be observed with parathyroid carcinoma, this finding would more likely represent a recent upper
respiratory infection or a more common malignant process such as metastatic lung, thyroid, or oropharyngeal cancer. Assessing cervical mobility is important if the patient eventually becomes a surgical candidate with the need for neck extension to facilitate surgical exposure.

While band keratopathy is easily detectable in most patients undergoing ophthalmologic examination with hyperparathyroidism, keratopathy and other ocular changes are not specific; all patients with hypercalcemia show ocular changes. Most patients with primary hyperparathyroidism have no other signs or symptoms; the only likely physical findings of interest would be those to help exclude the diagnosis or to create the suspicion of malignancy as the source of hypercalcemia.

Formerly, a solitary test result showing hypercalcemia was repeated to verify the hypercalcemic state. Today, given the accuracy of serum calcium determination, a single analysis is cost effective and sufficient. After a thorough history and physical examination of an otherwise healthy patient with no risk factors for hypercalcemia, the diagnosis of primary hyperparathyroidism is virtually certain if hypercalcemia exists and the serum PTH level is inappropriately high. “Inappropriately high” does not necessarily mean outside the normal serum range (usually 1 to 5 pmol/L). Given a normally functioning feedback loop, serum PTH levels in an otherwise healthy patient with hypercalcemia should be virtually zero. Nearly 20 percent of patients with primary hyperparathyroidism have an inappropriately normal level of PTH in the presence of hypercalcemia. Serologic testing of patients with primary hyperparathyroidism usually generates consistent results: hypophosphatemia, hypercalcemia, and elevated PTH levels (Fig. 36-48). In any patient in whom the diagnosis of primary hyperparathyroidism is not secure, additional testing is mandatory. Some examples include:

- Intravenous pyelography or ultrasonography to rule out renal cell carcinoma (a rare cause of hypercalcemia resulting from the secretion of a parathyroid hormone related protein PTHep)
- Protein gel electrophoresis to rule out multiple myeloma and sarcoidosis
- 24-h urine collection for calcium determination to eliminate BFHH-24
- Chest x-ray to exclude sarcoid, fungal diseases, or a malignancy of the lungs or mediastinum
- Mammography in postmenopausal women

Imaging
Radiologic studies are unnecessary unless previous neck operations have been undertaken. Some advocate the use of preoperative ultrasonography in the hopes of avoiding bilateral exploration and minimizing operative time and morbidity, but surgical exploration remains the most accurate localization modality. Use of ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), venous sampling, and nuclear scintigraphy is not cost effective for initial cervical exploration in patients with primary hyperparathyroidism.
In patients who are undergoing reoperation, in whom dissection is more hazardous, ultrasonography of the neck is helpful to the operating surgeon. Similarly, technetium-99m-sestamibi (Cardiolite) scanning has great sensitivity in identifying missed parathyroid tissue in the neck as well as in the mediastinum. Venous sampling, CT, and MRI are helpful in identifying aberrantly located glands, but they are expensive and less accurate. Our preference when performing a reoperation is to use ultrasonography with fine-needle aspiration of any suspicious cervical masses. If ultrasonography is equivocal, we proceed with technetium-99m-sestamibi scanning.

Treatment

With success rates higher than 98 percent for initial operations, the indication for surgical intervention is the diagnosis of primary hyperparathyroidism. Given the negligible operative mortality and minimal morbidity associated with first-time parathyroidectomy, virtually all patients who have no prior neck operations should be offered exploration. Given the safety and success of primary cervical exploration, concomitant surgical procedures ranging from minor (breast biopsy, dilatation and curettage) to major (cardiopulmonary bypass and cholecystectomy) may be considered. With success rates of roughly 90 percent in operative cases, repeat exploration for recurrent or persistent hyperparathyroidism is generally indicated if the offending gland has been localized in imaging studies.

Solitary parathyroidectomy, without biopsy of other glands, is sufficient treatment for solitary adenomas. Instances of double adenomas require both offending glands to be removed. Therapy for four-gland or multiglandular hyperplasia is controversial; our preference is three and one-half gland parathyroidectomy. Total parathyroidectomy with reimplantation of approximately 50 mg in the neck or forearm is another viable option. The use of the rapid (15 min) intact immunoreactive parathyroid hormone (iPTH) assay allows intraoperative assurance of removal of the offending (or sufficient) tissue. The indications for such intraoperative serological testing are rare.

Postoperative laboratory analysis reveals normocalcemia within 24 to 72 h in nearly all cases. Transient hypocalcemia is common with removal of large adenomas, resections involving four-gland hyperplasia, and in patients who have had prolonged hyperparathyroidism. The cause of postoperative hypocalcemia is invariably bone hunger or hypoparathyroidism. Bone hunger and hypoparathyroidism are differentiated by analysis of the serum phosphate and PTH levels. Bone hunger is identified by low phosphate levels associated with transient hypocalcemia after parathyroidectomy. PTH levels are within the normal range. The parathyroid state is diagnosed by elevated phosphate levels and abnormally low PTH levels.

Hospitalization of patients without complications usually is an overnight stay. Serum calcium levels should be checked to demonstrate the equilibration of calcium before discharge. Obtaining a follow-up serum calcium level is appropriate in 1 or 2 months and yearly thereafter to assess for persistent or recurrent hyperparathyroidism.

The goals of cervical exploration in patients with primary hyperparathyroidism are as follows:

Identification of the pathology. In practice, this most commonly consists of the identification of a solitary adenoma (90 percent). A less common occurrence is
multiglandular disease (8 percent) involving diffuse hyperplasia, which may be unequal. Identification of dual adenomas (2 percent) or parathyroid carcinoma (1 percent) is rare.

Removal of sufficient pathologic tissue to restore normocalcemia. The ideal postoperative result in these patients is a normocalcemic state with no need for supplemental calcium or vitamin D therapy. Transient hypocalcemia is sometimes unavoidable if severe osteopenia is present preoperatively, with ensuing postoperative bone hunger. Postoperative hypocalcemia or hypercalcemia may be caused by errors in cervical exploration: not finding the offending pathology (most often in single-gland disease); finding the diseased tissue but excising insufficient amounts of it (multiglandular hyperplasia), with resultant hypercalcemia; overly aggressive exploration with biopsies and possible injury to normal glands in single-gland disease; or excising too much hyperplastic tissue in multiglandular disease, with resulting hypocalcemia.

Minimal postoperative morbidity and mortality. The operative mortality in most reported series is less than 1 percent, which attests to the safety of cervical exploration. Complications and morbidity involve wound infection, cervical hematoma, injury to the inferior or superior laryngeal nerves, postoperative hypocalcemia, and, perhaps most commonly, poor cosmesis. All such complications should occur in less than 1 percent of patients.

To achieve these goals, cervical exploration should be undertaken with the conviction that parathyroid pathology exists and requires identification and removal. Cervical exploration should not be undertaken to make or confirm the diagnosis of hyperparathyroidism. A gentle technique that delivers a bloodless operative field is imperative. Poor visualization may result in disruption or fracture of parathyroid tissue with subsequent functional regrowth, the so-called parathyromatosis. The surgeon who is unfamiliar with parathyroid embryology should not undertake cervical exploration for hyperparathyroidism. It is important be unhurried when performing this procedure. The surgical adage “The slower one operates, the sooner the operation is over” applies to this operation.

Technique
Although cervical exploration for primary hyperparathyroidism can be performed under regional blockade supplemented by intravenous sedation and local anesthesia, general anesthesia with endotracheal intubation is preferable in most patients. After induction of general anesthesia, both arms are tucked at the patient's sides with careful attention to any interference with the previously placed intravenous lines and with particular attention to possible pressure points on the patient's elbows and wrists. The midline placement of a folded surgical towel beneath the patient's scapulae and a 5- to 10-degree downward tilt of the head of the operating table facilitates exposure of the lower portion of the neck. Cervical extension should be minimized in older patients to avoid undue postoperative neck pain. It is prudent to ask all patients to demonstrate the degree of extension they can achieve voluntarily without discomfort. Sandbags are placed alongside the patient's head to avoid any side-to-side movement during the operation.
It is important for cosmesis that the patient's chin, thyroid cartilage, and suprasternal notch be aligned vertically before an incision is made. Failure to establish this alignment may result in an asymmetric and unsightly incision. A thyroid surgical drape is placed with tie-tapes passing behind each earlobe and anchored at the head of the table with a single hemoclip (see Fig. 36-49).

A collar incision is made approximately two fingerbreadths above the suprasternal notch, which usually means the incision is situated over the cricoid cartilage. The surgeon should look carefully for obvious skin creases slightly above or below this site; if there are any, they should be used for improved cosmesis. The length of the incision is approximately 10 cm. The planned site should be marked in a linear fashion by applying pressure to the imaginary line with a suture. The course of the incision extending laterally above both clavicles should be carefully inspected and equalized, ensuring cosmesis. An incision that is higher on one side than the other is noticeable and troublesome to the patient. The table is positioned with the patient's head and chest elevated approximately 15 to 20 degrees to the horizontal.

The skin incision is made and, with use of electrocautery, the platysma muscle is identified and divided. This muscle is extremely thin, usually measuring no more than 1 to 2 mm in thickness. The avascular plane, just deep to the platysma, should be searched for. If the dissection at this stage is carried too deep, there will be unnecessary bleeding because of injury to the anterior jugular veins. By placing sharp rake retractors and t -ens the platysma anteriorly, the avascular plane immediately beneath the muscle can be easily developed superiorly to the level of the thyroid cartilage. There should be no bleeding during this stage of the operation. Minimal dissection is required inferiorly, usually just enough to allow placement of a self-retaining retractor (Fig. 36-50).

The midline is readily identified by finding the thin, avascular fascial plane connecting right and left strap muscles. This plane is divided with electrocautery. This dissection is carried posteriorly until the thyroid isthmus is clearly identified. Occasionally, small veins cross this midline space; if these are encountered, they should be isolated, ligated, and divided. A meticulous and bloodless operative technique is mandatory. Even minimal bleeding will render identification of parathyroid glands, particularly normal glands, extremely difficult. Once the thyroid isthmus has been identified, traction is applied laterally to the strap muscles with retractors that work against digital medial retraction of the thyroid lobe.

Anterior and medial displacement of the thyroid lobe brings the middle thyroid vein into view. The vein is isolated, ligated, and divided. The carotid sheath should appear in the posterior aspect of the dissection. Clamps are placed on the inferior and superior aspects of the thyroid lobe, and the thyroid gland is elevated anteriorly, superiorly, and eventually medially. This elevation of the thyroid lobe is required for accurate identification of the parathyroid glands (Fig. 36-51).

The superior parathyroid glands usually are found in close association with the posterolateral aspect of the superior pole of the thyroid lobe. The superior thyroid pole seldom needs to be taken down to visualize the superior parathyroid gland as long as there is anterior and medial displacement of the thyroid lobe. The inferior parathyroid gland, in contrast, is intimately involved with the inferior aspect of the thyroid gland...
and the thyrothymic tongue of fat (thyrothymic ligament) that extends inferiorly toward the mediastinum. Many inferior parathyroid glands are subcapsular, i.e., attached to the inferior aspect of the thyroid lobe and covered by a thin layer of fibrous tissue. This does not represent an intrathyroid parathyroid gland, as is often erroneously assumed. To be truly intrathyroid, the parathyroid gland should be circumferentially surrounded by thyroid parenchyma.

If the superior parathyroid gland is not visualized, the tracheoesophageal groove should be explored digitally. Enlarging superior parathyroid adenomas often descend into this groove and can be palpated accurately by inserting a finger into the avascular space immediately superior to the inferior thyroid artery (Fig. 36-52). Such glands are often located inferior to the inferior parathyroid glands. The parathyroid glands can be found from as high as the angle of the mandible or the base of the skull (undescended parathyroid) to as low as an intrathymic location in the anterior mediastinum or in the aortopulmonary window in the posterior mediastinum.

In the hands of an experienced surgeon, a negative exploration usually is the result of an unusual variation in embryologic descent. The following rule is useful in this situation: If the superior parathyroid gland is not found in its conventional position, the surgeon should search inferior to the inferior parathyroid gland for the superior parathyroid gland (tracheoesophageal groove); conversely, if the inferior parathyroid gland is not found inferior to the superior parathyroid gland, the surgeon should search superior to the superior parathyroid gland for the inferior parathyroid gland (undescended parathyroid). If these simple maneuvers are unsuccessful, the surgeon should become suspicious that the offending parathyroid gland might be in one of the following locations:

1. In the thymus. A fairly complete transcervical thymectomy should be performed to search for the missing inferior gland.

2. Within the thyroid. Truly intrathyroid glands are exceedingly rare. Most so-called intrathyroid parathyroid glands are inferior parathyroid glands located beneath the thin veil of the thyroid capsule and can be easily teased off the thyroid.

3. In the carotid sheath. This is extraordinarily rare, but opening the carotid sheath should be considered when all other possibilities have been ruled out.

4. Lateral to the carotid sheath. This location is even more unusual than in the carotid sheath, but the parathyroid gland can hide laterally.

Routine bilateral exploration is recommended in all patients. If a single adenoma is identified, excision of this adenoma, without biopsy of normal glands, is suggested. If hyperplasia is documented, all but approximately 50 mg of clearly viable parathyroid tissue is excised and routine transcervical thymectomy is performed. With the approach outlined, surgical success should approach 99 percent. Permanent laryngeal nerve palsy or hypoparathyroidism occurs in less than 1 percent of patients.

Persistent and Recurrent Hyperparathyroidism
Almost twenty years ago, Wexler stated, “Persistent hypercalcemia in suspected hyperparathyroidism is due to an improperly performed primary operation.”
Persistent hyperparathyroidism is defined as elevated serum calcium levels that do not return to normal after an operation for biochemically proved hyperparathyroidism; this situation should be differentiated from the less common situation of recurrent hyperparathyroidism in which at least 6 months of well-documented normocalcemia occurs after cervical exploration for hyperparathyroidism before hypercalcemia is documented again.

The results of reoperation for recurrent or persistent hyperparathyroidism do not parallel those achieved for the initial operation. Regardless of the surgical expertise involved, reoperative cure rates are uniformly 10 to 20 percent lower (i.e., 80 to 90 percent success rates) than those obtained in first-time operations (95 to 99 percent). In addition, postoperative morbidity involving recurrent laryngeal nerve palsies, postoperative hematomas, and permanent hypocalcemia are three to five times higher than the rates anticipated after first-time explorations (<1 percent).

The principal factors contributing to persistent or recurrent hyperparathyroidism are varied (Table 36-4). A systematic, logical approach to management is required (Fig. 36-53), with a concerted effort by all members of a multidisciplinary team.

The initial step is to reconfirm the diagnosis of hyperparathyroidism. In particular, the possibility of benign familial hypocalciuria hypocalcemia must be excluded, because cervical exploration is of no benefit to patients with BFHH. This diagnostic trap may be avoided by obtaining a 24-h urine collection for calcium determination. The clinician must be concerned with the hypercalcemic patient who has 24-h urine calcium levels of less than 100 mg. If diagnostic uncertainty persists, the urine calcium-to-creatinine ratio should be calculated. In BFHH patients, this ratio invariably is less than 0.01. The formula for calculating this ratio, the fractional excretion of calcium, is:

\[
\text{FE Ca}^2+ = \frac{\text{Urinary Ca}^2+ (\text{mg/total volume}) \times \text{serum creatinine (mg/dL)}}{\text{Serum Ca}^2+ (\text{mg/dL}) \times \text{urinary creatinine (mg/total volume)}}
\]

Although the indication for operation for primary hyperparathyroidism is the diagnosis itself, this is not the case in patients who are undergoing reoperation. Risk assessment in this situation is of great importance. Objective data that are helpful in evaluating the anesthetic risks can be obtained. The criteria most often used are those of the American Society of Anesthesiologists physical status classification (Table 36-5) and of the Goldman multivariate index of cardiac risk (Table 36-6).

While cervical exploration invariably is well-tolerated, if the operative risk is unacceptably high, consideration should be given to nonsurgical means of parathyroid tissue ablation. The two most commonly used modalities are angiographic embolization and ultrasound-guided alcohol ablation; the latter technique is somewhat safer in the high-risk patient and is gaining worldwide acceptance.

When repeat exploration is warranted, the surgeon should review the prior operative report. It is important to know what tissue was removed and from which site.
Additional clues may be obtained regarding the thoroughness of the previous operation. Statements in the report may lead to finding pathologic tissue in more common locations rather than in unusual hiding places.

The pathologist should review previously excised tissue to ascertain whether it was in fact parathyroid tissue and not thyroid or lymphatic tissue and whether any histologic evidence is present to suggest single-gland versus multiglandular disease or parathyroid carcinoma.

The radiologist should be consulted regarding the most appropriate localizing modality for the patient under consideration. In contrast to primary operations for hyperparathyroidism, in which preoperative localization is not indicated, localization in the reoperative setting is crucial. A wide variety of localizing modalities are in use (Table 36-7). The most popular modalities are radionuclide scanning with technetium-99m-sestamibi and ultrasonography (Fig. 36-54). Sestamibi scanning reaches sensitivity rates of over 90 percent and is particularly useful for parathyroid tissue located in the mediastinum (Fig. 36-55). A powerful adjunct to ultrasonography is liberal use of ultrasound-guided fine-needle aspiration (Fig. 36-56), not only for cytologic review but also for the measurement of iPTH. A high level confirms that the image seen is parathyroid tissue.

If all localizing modalities are negative, blind exploration should not be performed. Clinical and biochemical monitoring with interval reevaluation is the more prudent course to follow.

Although a repeat cervical or mediastinal exploration is considerably more difficult than a primary exploration, accurate preoperative localization enables the surgeon to perform a more focused exploration (e.g., unilateral cervical exploration, lateral cervical approach, thoracoscopic mediastinal exploration, mediastinal exploration, or a Chamberlain parasternal approach). Imaging studies of the abnormally located parathyroid gland minimize surgical morbidity and increase success rates. A recent adjunct in these difficult scenarios is the rapid iPTH assay, which can be performed and completed before finishing the operation. The assay is especially helpful for reexplorations in patients with multiglandular disease.

SECONDARY HYPERPARATHYROIDISM

Secondary hyperparathyroidism is an uncommon clinical disorder that develops in patients with chronic renal failure or intestinal malabsorption. PTH secretion appropriately increases because of hypocalcemia caused by hyperphosphatemia (renal failure) or dysfunctional calcium and vitamin D absorption (malabsorption).

Etiology

Calcium and phosphorus levels are inversely related. As chronic renal failure worsens and hypocalcemia occurs secondary to rising phosphate levels, the parathyroid glands secrete PTH in an attempt to counteract the hypocalcemic effects of renal failure. Compounding the problem is abnormal renal function that causes diminished 1α-hydroxylase activity, which is necessary for proper vitamin D production. Because of the high content of aluminum in renal dialysate and the need to take phosphate-binding medications, patients on hemodialysis or oral phosphate binders can develop dire consequences.
aluminum accumulation in bone, (aluminum intoxication), which contributes to osteomalacia and further PTH stimulation.

The cause of PTH stimulation with malabsorption syndromes is that calcium and vitamin D absorption is hindered to the point of hypocalcemia. Although PTH elevation is significant in renal failure and malabsorption, calcium regulation remains tight, and patients with either disease remain normocalcemic.

Clinical Manifestations
The diagnosis of secondary hyperparathyroidism often is made serologically before any symptoms are identified by the patient. When symptomatic, the most problematic feature for patients with secondary hyperparathyroidism usually is severe bone pain related to renal osteodystrophy. Less commonly, patients complain of soft-tissue calcifications (calcium tachyphylaxis) or pruritus. Others may develop bony fractures secondary to bone reabsorption.

Treatment
Initial therapy of secondary hyperparathyroidism is nonsurgical. In renal failure, dietary restriction of phosphate along with consumption of oral phosphate binders counteracts the underlying cause, hyperphosphatemia. In renal failure and malabsorption, oral calcium supplementation along with vitamin D ingestion is helpful. Altering the dialysate to minimize aluminum content and maximize calcium content is beneficial in renal failure patients.

Removing three and one-half parathyroid glands or total parathyroidectomy with reimplantation of a portion of tissue is indicated in secondary hyperparathyroidism for: (1) uncontrollable bone pain, (2) bone fractures, (3) intractable pruritus, (4) symptomatic ectopic calcifications, or (5) intractable disease that cannot be controlled medically. The preference is to excise three and one-half parathyroid glands and leave in situ approximately 50 mg of clearly viable parathyroid tissue.

TERTIARY HYPERPARATHYROIDISM
Tertiary hyperparathyroidism represents the continuation of secondary hyperparathyroidism; parathyroid tissue under the constant stimulation of hyperphosphatemia, and subsequent hypocalcemia, autonomously produces PTH and creates hypercalcemia. This rare situation is seen most commonly in patients with long-standing renal dysfunction who undergo successful renal transplantation.

Surgical removal of parathyroid tissue in tertiary hyperparathyroidism rarely is necessary. Most instances of tertiary hyperparathyroidism are short-lived; PTH levels eventually return to normal under the control of a functioning transplant kidney that corrects or improves hyperphosphatemia. Should persistent, autonomous overproduction of PTH occur with a well-functioning transplanted kidney, operative intervention is indicated.

MULTIPLE ENDOCRINE NEOPLASIA AND HYPERPARATHYROIDISM
Multiple endocrine neoplasia (MEN) is a collection of syndromes with an autosomal dominant pattern of inheritance. Hyperparathyroidism is one factor among many to consider in patients with endocrine abnormalities (Fig. 36-57). The hallmark of the
pathology in all MEN syndromes, regardless of the organ involved, are multicentricity and bilaterality.

MEN I
Formerly known as Wermer's syndrome, MEN I includes pituitary, parathyroid, or pancreatic neoplasms. Given enough time, all patients with MEN I develop primary hyperparathyroidism. Tumors of the pituitary (15 to 50 percent) and pancreas (30 to 80 percent) are less common.

MEN IIA & IIB
All patients with Sipple's syndrome (MEN IIA) develop C-cell hyperplasia and, subsequently, medullary thyroid carcinoma if total thyroidectomy is not performed prophylactically. Adrenal medullary hyperplasia/pheochromocytoma (approximately 50 percent) and parathyroid abnormalities (10 to 25 percent) are less common but important to rule out. Patients with MEN IIB also can develop medullary thyroid carcinoma and adrenal neoplasms along with a marfanoid habitus, a typical facies (Fig. 36-58), and mucosal neuromas (Fig. 36-59). Chief-cell hyperplasia of the parathyroid glands is uncommon. MEN IIB is inherently virulent, and malignancy shortens the patient's life span if prophylaxis is not undertaken.

Clinical Manifestations
Over 75 percent of patients with MEN have a long and classic family history of endocrine abnormalities. The genetic abnormalities appear linked to changes in the long arm of chromosome 11 in MEN I and in the centromeric region of chromosome 10 in MEN II. Medical surveillance and genetic testing can identify abnormalities before they become symptomatic, but with time, patients with MEN present with complaints of visual changes, kidney stones, ulcer pain, or diabetes (MEN I); neck masses and hypertension (MEN IIA); and buccal and lingual nodules, hypertension, (neck masses, and a marfanoid habitus (MEN IIB.

Evaluation
Patients with suspected MEN should undergo serologic surveillance of the appropriate markers of disease (Table 36-8). A classic family history for medullary thyroid carcinoma/hyperplasia warrants genetic testing for the ret-proto-oncogene. Such testing is important in children with normal serum calcitonin levels. Prophylactic thyroidectomy in the face of a positive ret-proto-oncogene and normal calcitonin levels is aggressive but appropriate therapy for these children, who otherwise develop a medullary thyroid malignancy.

Treatment
After a thorough work-up, operative intervention is suggested in order to minimize the ravages of primary hyperparathyroidism. Therapy for this syndrome is often less important than for the associated thyroid, pancreas, or adrenal disorders.

Treatment of primary hyperparathyroidism in MEN patients involves removing all but 50 mg of parathyroid tissue. A true solitary adenoma is unusual in these patients because of their propensity for multiple tumors. Given classic chief-cell hyperplasia, surgical options include a three and one-half gland parathyroidectomy or total parathyroidectomy with autotransplantation of heterotopic tissue. The concept of removing all but 50 mg of viable tissue is most important. Given the propensity of
MEN patients to have more than four functioning glands, a thorough exploration and a transcervical thymectomy should be a routine part of the operation. It is not uncommon for these patients to have five or six parathyroid glands.

HYPERCALCEMIC CRISIS
Hypercalcemic crisis represents the life-threatening systemic condition brought on by elevated serum calcium levels (generally 13.0 mg/dL or higher).

Clinical Manifestations
Symptoms are varied and range from neuromuscular changes with mild fatigue and irritability to coma. Signs of dehydration are prominent. Gastrointestinal manifestations include anorexia, nausea, vomiting, and weight loss. Cardiac dysrhythmias, most commonly secondary to a shortened Q-T interval, may occur and can be lethal. Cancer cachexia may be evident in patients presenting with skeletal metastases. A palpable neck mass in the face of hypercalcemic crisis is considered a parathyroid carcinoma until proved otherwise. Therapy is initiated before attempting to differentiate the cause of hypercalcemia.

The list for the differential diagnosis is theoretically long, with any cause of hypercalcemia included, but in the vast majority (more than 90 percent) of cases it comes from advanced malignancy or primary hyperparathyroidism.

Treatment
Intravenous saline resuscitation is started and advanced to achieve a diuresis of higher than 100 mL/h. Dehydration is prominent with hypercalcemic crisis, and volume resuscitation (often 4 to 5 L) is the cornerstone of therapy. Once the patient appears adequately hydrated and urine output is more than 1 mL/kg/h, loop diuretics are given to stimulate a natriuresis and subsequent calciuresis. Cardiac dysrhythmias typically resolve with hydration and the subsequent decrease in the serum calcium level. Should dysrhythmias persist or become symptomatic, they are treated with standard agents for dysrhythmia. When hypercalcemia persists in the face of aggressive resuscitation and diuresis, the addition of mithramycin, phosphate binders (e.g., pamidronate), vitamin D, estrogen, calcitonin, or steroids may be useful. Hypercalcemia in patients with advanced malignancy and skeletal metastases can be difficult to normalize.

Patients with hyperparathyroidism usually can be stabilized with simple hydration and diuresis. Identification of a cervical mass on physical examination in the face of hypercalcemic crisis foreshadows a diagnosis of parathyroid carcinoma. Vocal cord function should be checked and the diagnosis of malignancy discussed with the patient. Ultrasonography may be useful while resuscitation is under way, or in the rare patient who is critically ill from persistent hypercalcemia. If a large adenoma is identified, hypercalcemia can be resolved quickly with a focused exploration and parathyroidectomy. With hemodynamic stability, regardless of the results of ultrasonography, operative intervention is undertaken early in patients with primary hyperparathyroidism. If the diagnosis of primary hyperparathyroidism is secure, even in comatose patients or in those with hemodynamic instability despite volume resuscitation, operative intervention should not be delayed. Postoperative transient hypocalcemia is common, and frequent calcium assessment is prudent because of the previous instability of these patients.
PARATHYROID CARCINOMA
Carcinoma of the parathyroid glands accounts for less than 1 percent of reported cases of hyperparathyroidism. In one study, 38 of 5010 patients with hyperparathyroidism were found to have parathyroid carcinoma (0.8 percent). Somewhat higher incidences have been reported in Japan, although the reason for this is unknown. The criteria that should alert the clinician to the possibility of this diagnosis can be divided into preoperative, intraoperative, and histopathologic findings.

Preoperative Findings
Palpable neck mass
An identifiable mass is present in 40 to 50 percent of patients with parathyroid carcinoma; this is in striking contrast to the incidence of less than 1 percent of this sign in patients with nonmalignant primary hyperparathyroidism. When found on physical examination, a mass secondary to parathyroid carcinoma has the expected characteristics of malignancy—firmness and fixation to surrounding tissue.

Markedly abnormal biochemistry
In patients with parathyroid carcinoma, the biochemical parameters used for the diagnosis of hyperparathyroidism are highly abnormal. Mean serum calcium levels usually are greater than 13.0 mg/dL (normal range is 8.9 to 10.1 mg/dL), parathyroid hormone levels are elevated tenfold, and alkaline phosphatase levels are elevated threefold. In our practice, any patient found to have a serum calcium level above 13.0 mg/dL is presumed to have a parathyroid carcinoma until proved otherwise.

Complications of hyperparathyroidism
Clear-cut symptoms of hyperparathyroidism should alert clinicians to the possibility of the diagnosis of parathyroid carcinoma. In one study, bone disease, renal insufficiency, and nephrolithiasis occurred in 91 percent, 84 percent, and 56 percent, respectively, of patients with parathyroid carcinoma, which are considerably higher than the rates found in nonmalignant hyperparathyroidism.

Intraoperative Findings
The surgeon should suspect the presence of a parathyroid carcinoma after finding a parathyroid mass that is firmer than the usual soft, friable, nonmalignant parathyroid gland. When a gland has been transformed from the normal bean shape and kidney color to an irregular, pale white and is adherent to any of the surrounding structures, the diagnosis of malignancy is almost certain.

Histopathologic Findings
Most parathyroid carcinomas weigh more than 2000 mg, but weight does not aid in the diagnosis. The hallmark of malignancy histologically are the presence of a thick, fibrous capsule, fibrous septa interdigitating throughout the tumor, and the enlargement, hyperchromasia, and variation of nuclear size. Clear-cut invasion through the capsule to involve adipose tissue, nerves, thyroid gland, or surrounding muscle usually is present (Fig. 36-60).

Treatment
The treatment of choice is en bloc surgical resection of the tumor and the involved surrounding structures. This treatment usually involves a total thyroid lobectomy on
the affected side. Regional nodal metastases are uncommon, but lymph nodes should be assessed and, if involved, surgically treated by appropriate resection, which may include a modified radical neck dissection. Adjuvant external beam radiotherapy or multimodality chemotherapy have been used with limited success. Symptomatic hypercalcemia is controlled with mithramycin and biphosphonates. Malignant recurrence after initial operative resection occurs in at least 66 percent of cases. When recurrent disease is seemingly localized, repeat surgical resection—repeated as often as can be safely performed—is optimal. Nonsurgical treatment modalities are inadequate. Most patients with parathyroid cancer will undergo one or more explorations ranging from cervical exploration to thoracotomy or craniotomy. In a study of 43 patients, the 3-year and 5-year survival rates were 84 and 69 percent, respectively. The cause of death often was attributed to the metabolic consequences of hypercalcemia and not to the local effects of malignancy.

(Bibliography omitted in Palm version)

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