Chapter 78
Parathyroid Glands

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ANATOMY

Typically, a person has four parathyroid glands—two superior and two inferior (Fig. 78.1). The normal parathyroid glands are flat, ovoid, and red-brown to yellow. They are 5 to 7 mm × 3 to 4 mm × 0.5 to 2 mm and weigh between 30 and 50 mg each. The lower glands are usually larger than the upper glands. The superior glands are most often embedded in the fat on the posterior surface of the upper thyroid lobe near the site where the recurrent laryngeal nerve enters the larynx. The inferior glands are usually more ventral and lie close to or within the portion of the thymus gland that extends from the inferior pole of the thyroid gland into the chest. Although this anatomy is fairly consistent, substantial variations from the norm can occur, and it is essential that the surgeon have a thorough understanding of these anatomic variations.

Variations in parathyroid anatomy are primarily caused by differences in patterns of embryogenesis. During the fourth and fifth weeks of fetal development, a series of four pharyngeal pouches develop (Fig. 78.2). The superior parathyroid arises from the fourth pharyngeal pouch in conjunction with the lateral thyroid, and the inferior gland arises from the third pouch along with the thymus. The derivatives of each pouch then migrate together so that the superior parathyroid usually remains in close association with the upper pole of the thyroid, although it may occasionally be loosely attached by a long vascular pedicle, migrating caudad along the esophagus into the posterior mediastinum. Occasionally, a gland may be totally embedded in the thyroid parenchyma. The inferior parathyroid descends with the thymus, but this migration is extremely variable. Inferior glands can be found anywhere from the pharynx to the mediastinum. Regardless of their location, they usually adhere to the
thymus or are within the thyrothymic ligament. Supernumerary glands can be identified in up to 15% of patients, most often in association with the thymus. Autopsy studies suggest that four parathyroid glands are virtually always present.

The arterial supply to both the superior and inferior parathyroid glands is usually from the inferior thyroid artery, although it may arise from the superior thyroid or thyroidea ima arteries or from the rich anastomosis of vessels supplying the larynx, trachea, and esophagus. It has been suggested that a mediastinal parathyroid gland that descended during embryonic development usually receives its blood supply from either the internal mammary artery or small arteries within the thymus. In adults, however, an enlarged parathyroid gland that migrates into the mediastinum usually carries with it the corresponding branch of the inferior thyroid artery. The inferior, middle, and superior thyroid veins, which drain the parathyroid glands, empty into the internal jugular vein or the innominate vein.

Histologically, the normal adult parathyroid is about half parenchyma and half stroma, including fat cells (Fig. 78.3). In children, the gland is almost entirely composed of parenchymal chief cells. Beginning at puberty, adipocytes appear and, with age, occupy an increasing proportion of the gland. Also with increasing age, acidophilic, mitochondria-rich oxyphil cells are present in increasing numbers and are intermixed with the glycogen-laden, polygonal, water-clear cells. The functional significance of the various cell types remains unclear, although the water-clear cells and oxyphil cells are probably derived from the chief cells and secrete parathyroid hormone (PTH).

**PHYSIOLOGY**

The primary physiologic role of the parathyroid gland is the endocrine regulation of calcium and phosphate metabolism. Average daily exchanges of these ions from the gastrointestinal tract, bone, and kidney are shown in Fig. 78.4.

**Calcium**

Calcium ion plays a critical role in all biologic systems. It participates in enzymatic reactions and is a mediator in hormone metabolism. Calcium is intimately involved in the physiology of neurotransmission, muscle contraction, and blood coagulation. It is the major cation in bone and teeth. It represents about 2% of the average body weight, and almost all calcium is contained in the skeleton. The normal range of serum calcium is 9 to 10.5 mg/dL (4.5 to 5.2 mEq/L), and the daily variation in a normal person is generally less than 10%. About half of the total serum calcium
is in an ionized, biologically active form; 40% is bound to serum protein, mainly albumin, and 10% forms compounds with organic ions, such as citrate. The total serum calcium concentration is a function of the serum protein content, and because hydrogen ion competes with calcium for the same binding sites on albumin, the body fluid pH is important. In general, for every change of 1 g/dL in the serum albumin level, a direct alteration of 0.8 mg/dL occurs in the serum calcium concentration. Almost all the physiologically important activity of calcium is represented by the unbound, or free, fraction.

Calcium is absorbed in its inorganic form from the duodenum and proximal jejunum. The rate of absorption is precisely regulated according to body calcium status. The calcium in the extracellular fluid is constantly being exchanged with that in the intracellular fluid, the exchangeable bone, and the glomerular filtrate. Calcium reabsorption by the kidney is closely related to that of sodium, and about 99% of the filtered load is reabsorbed under normal conditions.

**Phosphate**

Phosphate anion is also an integral component of most biologic systems. It is critical to the pathways of glycolysis and is the functional group for a number of high-energy transfer compounds, including adenosine triphosphate. It is also the major anion in crystalline bone. Normal levels of plasma phosphate range from 2.5 to 4.3 mg/dL, and the level varies inversely with the serum level of calcium. The relation is such that the product of plasma calcium and phosphate is constant and ranges between 30 and 40 mg/dL. When it increases above this level, a potential develops for the precipitation of calcium phosphate in body tissues.
In contrast to the percentage of calcium absorbed, the percentage of phosphate absorbed from the diet is relatively constant, and excretion usually provides the major mechanisms for regulating phosphate balance (Fig. 78.4). Unlike stores of calcium, the readily exchangeable soft-tissue stores of phosphate, such as those in muscle, are large.

**Regulation of Calcium and Phosphate Metabolism**

The maintenance of calcium and phosphate homeostasis depends on major contributions from three organ systems—the gastrointestinal tract, the skeleton, and the kidneys—with minor contributions from the skin and liver. The primary hormonal regulators of this metabolism are PTH, vitamin D, and calcitonin. The actions of each of these hormones in the organs are summarized in Table 78.1.
**FIGURE 78.2**  
(A) Pharyngeal arches in a 5-week embryo. The corresponding pouches extend from within the pharynx into each arch.  
(B) Schematic representation of the differentiating epithelium of the respective pharyngeal pouches. (After Langman J. *Medical embryology and human development: normal and abnormal*. Baltimore: Williams & Wilkins, 1975, p. 262.)

**FIGURE 78.3** A normal adult parathyroid is composed of about half parenchyma and half fat (3150).
Parathyroid Hormone

Parathyroid hormone (PTH) is the single most important hormonal regulator of calcium and phosphate metabolism in humans. It has direct effects on the skeleton and kidney and indirect effects on the intestine, mediated through vitamin D. In target tissues, PTH binds first to membrane receptors, activating adenyl cyclase to generate cyclic adenosine monophosphate (cAMP), which regulates other intracellular enzymes.


**TABLE 78.1** HORMONAL REGULATION OF CALCIUM AND PHOSPHATE METABOLISM
In bone, the effects of PTH are complex, stimulating both resorption and the formation of new bone. However, sustained elevations of PTH stimulate osteoclasts and inhibit osteoblasts. Osteocytes, in the matrix of cortical bone, may also act to reabsorb matrix in response to PTH, a process referred to as osteocytic osteolysis. Calcium and phosphate mobilization in response to PTH occurs in two phases. Initially, mineral is mobilized from areas of rapid equilibrium. This phase is followed by a more sustained release mediated by newly synthesized lysosomal and hydrolytic enzymes. In the kidney, PTH increases the reabsorption of extracellular fluid calcium at any given concentration, although excess secretion, because of hypercalcemia, increases the net daily amount of urinary calcium excretion. Reabsorption in the proximal tubule and loop of Henle is linked with sodium transport such that factors that alter sodium transport concomitantly alter calcium reabsorption. In contrast, reabsorption in the distal nephron is independent of sodium and directly influenced by PTH. PTH also increases phosphate excretion. This action is accompanied by enhanced bicarbonate secretion. PTH probably has only indirect effects on the gastrointestinal tract, by stimulating the hydroxylation of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D in the kidney.

PTH is synthesized initially as a precursor, preproPTH, which is
sequentially cleaved in the parathyroid gland to proPTH and then to PTH (Fig. 78.5). Secretion of this 84-amino acid molecule is controlled by a negative feedback loop with extracellular fluid calcium. Most PTH is secreted in this form and then cleaved in the liver into N- and C-terminal fragments. The N-terminus contains most of the biologic activity and is rapidly degraded by the liver, whereas the inactive C-terminus is slowly metabolized by the kidney.

**FIGURE 78.5** The parathyroid gland produces a precursor of parathyroid hormone (PTH), prepro-PTH, that is sequentially cleaved to pro-PTH and PTH. PTH secretion is controlled by the extracellular fluid volume. (After Klee GG, Kao PC, Heath H. Hypercalcemia. *Endocrinol Metab Clin North Am.* 1988;17:573.)

**Vitamin D**
Vitamin D acts at two major sites. It increases intestinal absorption of calcium and phosphate. In addition, in the skeleton, it promotes mineralization and enhances PTH-mediated mobilization of calcium and phosphate. It probably has no direct effect on the kidney.

Vitamin D₃, or cholecalciferol, is produced normally by the action of sunlight on 7-dehydrocholesterol in the skin (Fig. 78.6). It is then hydroxylated in the liver (25 position) and kidney (1 position) to form the active 1,25-dihydroxyvitamin D₃ (calcitriol). Vitamin D₂ is normally present in yeast and fungi but not in humans. It is the major pharmacologic source of vitamin D. Pharmaceutical preparations include vitamin D₂ (ergocalciferol), 25-hydroxycholecalciferol (calcifediol), and 1,25-dihydroxycholecalciferol (calcitriol). 1-Hydroxycholecalciferol and dihydrotachysterol are synthetic preparations that require only 25-hydroxylation for activity and so are useful for supplementation in patients with renal failure, who lack the 1-hydroxylase.

**FIGURE 78.6** Schematic illustration of the synthesis of vitamin D₃. Ergosterol, 1α-hydroxyvitamin D₃, and dihydrotachysterol are synthetic
Calcitonin

Calcitonin is a 32-amino acid protein produced by the parafollicular C (calcitonin) cells of the thyroid. The C cells are embryologically derived from the neural crest and, in lower animals, are found in the ultimobranchial bodies, which are glandular structures derived from the lowest branchial pouch. In humans, these structures are incorporated into the superior and lateral aspects of the thyroid lobes.

Total thyroidectomy, with removal of all the C cells, is well tolerated. It appears that calcitonin is not essential for the normal control of calcium metabolism in adult humans. It does inhibit bone resorption and can produce hypocalcemia in experimental animals. It also increases urinary calcium and phosphate excretion. These effects are mediated primarily through cAMP. Several secretagogues for calcitonin have been identified, including catecholamines, gastrin, and cholecystokinin, but the most potent appear to be calcium and pentagastrin. Calcitonin can be useful pharmacologically, to reduce serum calcium levels.

Mineral Homeostasis

Under normal conditions, serum calcium and phosphate levels vary minimally during the course of the day. Regulation occurs primarily through PTH but also through a series of feedback loops involving vitamin D and calcitonin (Fig. 78.7). A fall in serum ionized calcium increases PTH secretion and stimulates the production of 1,25-dihydroxyvitamin D₃. Conversely, increases in serum calcium inhibit PTH secretion and the formation of active calciferol.

Pathophysiology

Diseases of the parathyroid glands present almost exclusively as disorders of calcium metabolism. Hypercalcemia is the most common manifestation, and in the patient who presents with an elevated serum calcium level, the differential diagnosis can be complex. A thorough understanding of both hypercalcemia and hypocalcemia is essential for the successful treatment of patients undergoing parathyroid surgery. Primary disorders of plasma phosphate are not usually related to surgical disease and are not discussed in detail here.
HYPERCALCEMIA
Hypercacemia is a relatively common clinical problem. In the general population and in hospital outpatients, the incidence is between 0.1% and 0.5%. Most patients in this group have primary hyperparathyroidism. In contrast, hypercalcemia is identified in almost 5% of hospitalized patients, and nearly two thirds of them have a malignancy.

Clinical Manifestations
The symptoms of hypercalcemia are varied and nonspecific (Table 78.2). Severity is a function of both the magnitude and rapidity of onset of the hypercalcemia. Many of the manifestations are subtle and are evident only in retrospect, after the patient has been successfully treated for the cause of the elevated calcium. Specific symptoms and diagnostic tests are addressed in more detail in the section on hyperparathyroidism.

Differential Diagnosis
Although the diagnosis of primary hyperparathyroidism can, after appropriate investigation, be established with confidence in most patients, all causes of hypercalcemia must be considered and excluded. The multiple causes of hypercalcemia are listed in Table 78.3.

Etiology
Hyperparathyroidism
The diagnosis of hyperparathyroidism is discussed in detail later. Patients typically have elevated plasma concentrations of calcium and PTH, increased urinary excretion of calcium, and a low plasma concentration of phosphate.

Malignancy
Generally, patients with hypercalcemia and malignancy (humoral hypercalcemia of malignancy) can be classified into two groups. Patients with solid tumors, such as lung carcinoma (25% of all cases of humoral hypercalcemia of malignancy); breast carcinoma (20%); squamous cell carcinoma of the head, neck, esophagus, or female genital tract (19%); or renal cell cancer (8%), account for three fourths of all cases. Humoral hypercalcemia of malignancy in this setting generally appears late in the disease, with nearly all patients having known, or readily evident, malignancy. These patients have elevated levels of serum calcium, low levels of serum phosphorus, and elevated levels of urinary cAMP, consistent with increased PTH activity but normal or low serum PTH.
The hypercalcemia is now known to be caused by PTH-related protein secreted by the tumor, rather than by the bony metastases that many of these patients have because of the advanced nature of their cancers. In the second group, accounting for one fourth of cases, are patients with hematologic malignancies, such as multiple myeloma, certain lymphomas and leukemias, and a subset of the patients with breast cancer. These patients have elevated levels of serum calcium, but in contrast to most patients with solid tumors and humoral hypercalcemia of malignancy, they have elevated levels of serum phosphate and low levels of urinary cAMP. These patients always have lytic bony lesions and histologically demonstrate increased osteoclast bone resorption adjacent to tumor cells. This osteoclast-activating activity is an effect of cytokines, mainly interleukin-1 beta and tumor necrosis factor-beta (lymphotoxin). These cytokines promote local net bone resorption and thus produce hypercalcemia and hyperphosphatemia.
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<th>Neurologic</th>
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<tr>
<td>• Lethargy</td>
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<td>• Confusion</td>
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<td>• Coma</td>
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<td>• Headache</td>
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<td>• Paranoia</td>
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<td>• Muscle weakness</td>
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<td>• Hyporeflexia</td>
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<td>• Incontinence</td>
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<td>• Memory loss</td>
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<td>• Hearing loss</td>
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<td>• Ataxia</td>
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<td>• Anorexia</td>
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<td>• Nausea and vomiting</td>
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<td>• Polydipsia</td>
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<td>• Weight loss</td>
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<td>• Pancreatitis</td>
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<td>• Peptic ulcer</td>
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<td>• Abdominal pain</td>
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<td>• Bradycardia</td>
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<td>• Heart block</td>
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<td>• Hypertension</td>
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<td>• Polyuria</td>
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<td>• Uremia</td>
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<td>• Renal colic</td>
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<td>• Nephrocalcinosis</td>
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<th>Other</th>
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<tr>
<td>• Band keratopathy</td>
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• Conjunctivitis
• Change in vision
• Pruritus
• Thrombosis
• Myalgia

**TABLE 78.3 ETIOLOGY: CAUSES OF HYPERCALCEMIA**

- Hyperparathyroidism
- Malignancy
- Vitamin A or D intoxication
- Thiazide diuretics
- Hyperthyroidism
- Milk-alkali syndrome
- Sarcoidosis and other granulomatous diseases
- Familial hypocalciuric hypercalcemia
- Immobilization
- Paget disease
- Lithium therapy
- Addisonian crisis
- Idiopathic hypercalcemia of infancy

**Vitamin D and Vitamin A Intoxication**

When administered in excess, vitamins A and D can produce hypercalcemia. Affected patients tend to have normal or elevated serum phosphate levels associated with a low PTH level. Metastatic calcification may occur.

**Thiazide Diuretics**
Thiazides may increase serum calcium levels to a mild degree, primarily through hemoconcentration and decreased renal excretion. Serum phosphate may also be depressed. It often takes several weeks for the hypercalcemia to resolve after the medication is discontinued.

**Hyperthyroidism**

Hyperthyroidism is associated with increased bone resorption. Often, the plasma PTH is low, and a history of other thyrotoxic symptoms can be elicited. The hypercalcemia usually resolves as the patient becomes euthyroid.

**Milk-Alkali Syndrome**

Typically, the milk-alkali syndrome occurs in patients with peptic ulcers who consume large quantities of milk and absorbable antacids. Usually, some degree of renal failure is present. PTH levels are low. This syndrome has become much less common with the increased use of nonabsorbable antacids and histamine 2-receptor antagonists.

**Sarcoidosis and Other Granulomatous Diseases**

These syndromes are associated with hypersensitivity to vitamin D. Apparently, the granulomas can convert the inactive vitamin D to its active form. Patients have elevated plasma globulins and low PTH levels. The administration of large doses of cortisone for 10 days usually reduces the hypercalcemia. Biopsy of lymph nodes or the liver may confirm the diagnosis.

**Familial Hypocalciuric Hypercalcemia**

This disease is an asymptomatic, autosomal dominant condition characterized by mild to moderate hypercalcemia, hypocalciuria, and normal or only slightly elevated PTH levels. It develops in people heterozygous for a mutation in the calcium-sensing receptor. The mutation causes an increase in the set point for extracellular calcium concentration, so that the “normal” calcium level is higher in these people than in the normal population. No treatment is necessary, although people with this disease should receive genetic counseling. Neonatal severe hyperparathyroidism, which can be fatal, develops in children homozygous for mutations in this receptor. Treatment for neonates with this disease is controversial, but they appear to benefit from early surgical management.
**Immobilization**

Immobilization produces hypercalcemia by increasing the ratio of bone resorption to bone formation. These patients can usually be distinguished by history, although on laboratory evaluation they have elevated serum levels of calcium and phosphate and a decreased serum concentration of PTH. Often, hypercalciuria is present, which may lead to the development of renal stones. Treatment is early mobilization and forced diuresis.

**Other Causes**

A variety of other diseases may produce hypercalcemia. For example, Paget disease (osteitis deformans) typically causes mild elevations in serum calcium. Paget disease can be diagnosed on the basis of the characteristic radiographic lesion. Adrenal insufficiency may be associated with hypercalcemia, although the symptoms are typically those of the primary abnormality. Lithium therapy appears to produce hypercalcemia by altering the parathyroid set point for inhibition by calcium, and, over long courses of therapy, may also be associated with hyperparathyroidism. Idiopathic hypercalcemia of infancy is a rare disorder that is probably the result of hypersensitivity to vitamin D. It occurs in infants with mental retardation and is satisfactorily treated with glucocorticoids. Other causes include aluminum-induced renal osteomalacia and a host of analytic errors related to improper specimen collection with prolonged tourniquet times, tube contamination, and instrument drift.

**Medical Treatment**

Although the choice of therapy is tailored to the cause of the hypercalcemia, several general measures can prove effective.7

For the patient with mild hypercalcemia, a trial of a decrease in dietary calcium is indicated. A reduction in intake of milk and other dairy products is suggested, along with discontinuation of thiazide diuretics and vitamin D preparations. Mobilization prevents bone demineralization.

Patients with more marked hypercalcemia or severe symptoms should be admitted to the hospital for treatment, with careful observation and monitoring. In the patient with severe hyperparathyroidism, although the definitive therapy is surgical, it is unwise to proceed with neck exploration until the calcium has been reduced to near-normal levels. The mainstay of therapy is intravenous hydration, preferably with normal saline solution in sufficient quantities to maintain the urine output above 100 mL per hour. These patients are often dehydrated before therapy, and fluid can be administered intravenously at a rate of 200 mL per hour. Caution must be
exercised in older patients, whose cardiac reserve may be marginal. This therapy exploits the parallel handling of calcium and sodium by the kidneys. The diuretic furosemide also increases sodium and calcium excretion but should not be used until the patient is well hydrated.

The end points of therapy are a decrease in the serum calcium level and a reduction of symptoms. Diuresis with saline solution is usually effective when the hypercalcemia results from hyperparathyroidism or a benign cause. In contrast, the hypercalcemia of malignancy may produce severe symptoms associated with extremely high serum calcium levels that are difficult to control. In this setting, a variety of other measures may be considered (Table 78.4). Some of the agents used to treat hypercalcemia cause significant toxicity, and close patient monitoring is required during treatment. Calcitonin is a fairly weak hypocalcemic agent, but it acts rapidly and is associated with less toxicity than many of the other drugs. Salmon calcitonin is the most potent preparation. Glucocorticoids may be particularly efficacious in patients with sarcoidosis and other granulomatous diseases. Plicamycin has proved useful in patients with hypercalcemia of malignancy, but it causes a cumulative toxicity (thrombocytopenia, hepatotoxicity, and nephrotoxicity). Biphosphonates inhibit osteoclast activity directly. These agents are given intravenously and are particularly efficacious, although long-term use may be associated with significant osteomalacia. Prostaglandin synthetase inhibitors were initially considered useful, but their efficacy has proved to be limited. Intravenous phosphates and chelating agents have largely been abandoned because of their severe toxicity; however, oral phosphates may be beneficial in patients requiring prolonged therapy.

**TABLE 78.4 TREATMENT: TREATMENT OF HYPERCALCEMIA**

<table>
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<tr>
<th>Therapy of Primary Disease</th>
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<td>- Tumor resection (hypercalcemia of malignancy)</td>
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<td>- Parathyroidectomy (primary hyperparathyroidism)</td>
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<th>Expansion of extracellular volume</th>
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<tr>
<td>- Infusion of saline solution</td>
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<td>- Enhancement of urinary calcium excretion</td>
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<td>- Extracellular volume expansion</td>
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<td>- Loop diuretics (furosemide and ethacrynic acid)</td>
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Hypocalcemia can occur as a consequence of various acquired and hereditary diseases. Generally, these disorders produce a deficiency or defect in the action of either PTH or vitamin D. It is most commonly a significant clinical problem after neck operation for thyroid disease. Vitamin D deficiency is associated with compensatory PTH excess. The end result is rickets in children or osteomalacia in adults.

**Clinical Features**

The major signs and symptoms of hypocalcemia are a direct consequence of the reduction in plasma levels of ionized calcium, which increases neuromuscular excitability (Table 78.5). The earliest clinical manifestations are numbness and tingling in the circumoral area, fingers,
and toes. Mental symptoms are also common. Patients become anxious, depressed, and occasionally confused. Tetany may develop, characterized by carpopedal spasm, tonic-clonic convulsions, and laryngeal stridor. The magnitude of symptoms at any given plasma concentration of ionized calcium varies from patient to patient. On physical examination, contraction of the facial muscles is elicited by tapping anterior to the ear, over the facial nerve (Chvostek's sign), although this sign may be present in 10% of normal patients. Trousseau's sign is elicited by occluding blood flow to the forearm for 3 minutes. The development of carpal spasm indicates hypocalcemia, although the test is unpleasant and clinically impractical.

<table>
<thead>
<tr>
<th>TABLE 78.5 DIAGNOSIS: CLINICAL FEATURES OF HYPOCALCEMIA</th>
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<tr>
<td>Neurologic</td>
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<tr>
<td>• Circumoral paresthesia</td>
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<td>• Anxiety</td>
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<td>• Confusion</td>
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<td>• Chvostek's sign</td>
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<td>• Trousseau's sign</td>
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<td>• Irritability</td>
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<td>• Laryngeal spasm</td>
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<td>• Electrocardiogram changes (prolonged QT interval, T-wave peaking)</td>
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<tr>
<td>• Arrhythmia</td>
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<td>• Tachycardia, hypotension</td>
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</table>
**Etiology**

Some of the causes of hypocalcemia are listed in Table 78.6. The most common cause of hypocalcemia by far is excision of or damage to the parathyroid glands during thyroid surgery.

**Postoperative Hypoparathyroidism**

Postoperative hypoparathyroidism commonly develops after total thyroidectomy for malignancy. Most patients undergoing operation on the thyroid experience some alteration in serum calcium, although they often are asymptomatic; the low calcium probably represents contusion or temporary alteration of the blood supply to the parathyroid glands. The hypocalcemia is usually transient and is not treated unless significant symptoms develop. Occasionally, in hyperparathyroid patients who have parathyroidectomy and significant bone disease, a marked skeletal deposition of calcium and symptomatic hypocalcemia occurs, so-called bone hunger. The plasma calcium usually reaches its nadir at 48 to 72 hours after surgery and then slowly returns to normal within several days. These patients may require calcium and vitamin D therapy for weeks or months after parathyroidectomy.

**TABLE 78.6 ETIOLOGY: CAUSES OF HYPOCALCEMIA**

- Hypoparathyroidism
- Vitamin D deficiency

- Lenticular cataracts
Idiopathic Hypoparathyroidism
A less common form of hypoparathyroidism is idiopathic lack of function. It occurs both sporadically and in families. In some cases, it develops as part of a polyglandular disorder and is thought to have an autoimmune basis. DiGeorge syndrome is a congenital disorder involving the branchial pouches that produces agenesis of the thymus and parathyroid glands. Hypoparathyroidism may also develop in newborns as a result of prenatal suppression of the fetal parathyroid glands as a consequence of maternal hypercalcemia. It is also common in otherwise normal but premature infants.

Vitamin D Deficiency
Vitamin D deficiency may occur as a result of dietary deficiency or lack of exposure to the sun. Likewise, renal disease produces a decrease in the 1-hydroxylase activity necessary for the formation of active vitamin D₃. The result is a decrease in calcium absorption and an increased secretion of PTH by the stimulated parathyroid glands. Osteomalacia, abnormal fractures, and the deformities of rickets may result.

Pseudohypoparathyroidism
Pseudohypoparathyroidism is a familial disease characterized by a rotund appearance, shortening of the extremities, and sometimes mental deficiency. The defect is not in PTH secretion; in fact, most patients have elevated plasma levels of PTH with evidence of increased bone resorption. Rather, the kidney is unresponsive to the hormone, and as a consequence, hypocalcemia and hyperphosphatemia develop. The deficit appears to be
in the renal adenyl cyclase system.

**Hypomagnesemia**

This unusual deficit may result from chronic alcoholism, malabsorption, parenteral nutrition, or increased renal clearance during therapy with aminoglycosides. The deficit appears to block the physical response to PTH in addition to its release from the parathyroid gland.

**Other Causes**

In short-gut syndrome, after extensive small-bowel resection or bypass, vitamin D and calcium may be absorbed in insufficient quantities. In pancreatitis, the massive soft-tissue destruction and saponification that occur with hemorrhagic disease may sequester significant amounts of calcium in the retroperitoneum. Some undefined systemic factor also appears to contribute to hypocalcemia in these patients. Hypoalbuminemia causes a reduction in the total plasma calcium level, although the level of ionized calcium remains within the normal range and patients are asymptomatic. Circulatory substances, such as the citrate used to anticoagulate banked blood and radiographic contrast media, may bind to calcium. In patients with osteoblastic metastases, particularly associated with prostate carcinoma, hypocalcemia has been attributed to increased calcium flux into the lesions. Toxic shock syndrome is sometimes associated with hypocalcemia, but the mechanism has not been defined. Acute hyperphosphatemia, as a consequence of exogenous administration of phosphate or during the cytolytic chemotherapy of highly responsive tumors (e.g., Burkitt lymphoma and acute lymphoblastic leukemia), may produce symptomatic hypocalcemia associated with soft-tissue calcification.

<table>
<thead>
<tr>
<th><strong>TABLE 78.7 TREATMENT: TREATMENT OF HYPOCALCEMIA</strong></th>
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<tr>
<td><strong>Symptom or goal</strong></td>
</tr>
<tr>
<td>Symptomatic hypocalcemia</td>
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</table>

http://gateway.ut.ovid.com/gwl/ovidweb.cgi
Treatment

The treatment of hypocalcemia is summarized in Table 78.7. For acute symptomatic hypocalcemia, calcium should be administered intravenously. Calcium gluconate is less irritating to the veins than calcium chloride, and the calcium release is slower, without a risk for overcorrection. Usually, 20 to 30 mL of 10% solution is infused over a 15- to 20-minute period, and then 50 to 100 mL is administered over the next 12 hours in adults. A practical guide after an initial bolus dose includes 60 mL of 10% calcium gluconate in a 500 mL bag of dextrose 5% in water, infused at 1 mL/kg/h, and adjusted every 4 hours based on the serum level of calcium and patient symptoms. Bicarbonate precipitates any calcium infused through the same intravenous line. Serum magnesium should always be measured, and hypomagnesemia should be corrected if present. In patients with convulsions from advanced tetany, diphenylhydantoin therapy is useful, but symptoms should never be allowed to progress to this point.

Long-term therapy is gauged on the basis of symptoms. In the postoperative patient, the continued stimulus of mild hypocalcemia to any remaining parathyroid tissue may prove useful. Concomitant therapy with calcium and vitamin D is effective in a timely fashion. A starting dose of 2 g of oral calcium carbonate per day in divided doses is usually well tolerated. Vitamin D can be administered as calcitriol, a synthetic vitamin D analogue. Most adults respond to a dose of 0.5 to 2.0 mg per day;
reduced doses may be necessary for patients with renal dysfunction.

HYPERPARATHYROIDISM

Definitions
Parathyroid neoplasms are rarely identified by physical enlargement but rather are sought because of the peripheral effects of excess hormone. Primary hyperparathyroidism develops spontaneously, without apparent cause but possibly in response to exogenous stimuli. When the normal control of serum calcium is disturbed and the autonomous production of PTH is increased, the state is referred to as primary hyperparathyroidism. This category includes both benign single- and multiple-gland enlargements and the much rarer parathyroid carcinoma. In some cases, the disease is familial. In contrast, secondary hyperparathyroidism occurs when a defect in mineral homeostasis leads to a compensatory increase in parathyroid function. This occurs most commonly in response to renal disease but may also develop as a consequence of the hypocalcemia associated with some diseases of the gastrointestinal tract, bones, or other endocrine organs. Occasionally, with prolonged secondary stimulation, the hyperfunctioning glands are no longer physiologically responsive to an increase in ionized calcium. This uncommon (affecting about 2% of patients after renal transplantation), relatively autonomous state referred to as tertiary hyperparathyroidism, develops most commonly after renal transplantation when the defect in calcium homeostasis is corrected.

Incidence
The advent in the 1970s of the widespread assessment of serum calcium as part of automated multichannel analysis has considerably altered our understanding of hyperparathyroidism. Before that time, primary hyperparathyroidism was thought to be a relatively rare condition. Most patients presented with symptoms of disease, usually renal stones or bony manifestations. Today, most patients are asymptomatic or have only vague symptoms or signs that can be related to hyperparathyroidism. Occasionally, patients recognize that they had symptoms only after their well being improves following parathyroidectomy. Incidence varies with both age and gender (Table 78.8), but hyperparathyroidism is believed to develop in about 50 to 100 people per 100,000 in the general population, with approximately 50,000 new cases occurring annually in the United States. Marked variations have been noted worldwide; the reasons for these differences remain unclear.
Etiology
The cause of primary hyperparathyroidism is not known. Although the sequence of progression from secondary to tertiary disease in response to chronic stimulation has a logical appeal, it is difficult to draw parallels with primary disease. Most patients with primary hyperparathyroidism have disease of a single rather than of multiple glands, which is not what might be predicted if an external stimulus were part of the pathophysiology. Hyperparathyroidism is most common in postmenopausal women, the population group with the highest incidence of osteoporosis and the most significant alterations in calcium and phosphate metabolism. Loss of renal function with aging is associated with elevations in PTH and decreases in phosphate clearance. It has been suggested but not demonstrated that a renal calcium leak, if sufficient, might result in a chronic calcium deficit stimulating the parathyroid glands.

<table>
<thead>
<tr>
<th>New cases per 100,000</th>
</tr>
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<tbody>
<tr>
<td>Age (y)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>5 &lt;39</td>
</tr>
<tr>
<td>26 40–50</td>
</tr>
<tr>
<td>92  &gt;60</td>
</tr>
<tr>
<td>18  Total</td>
</tr>
<tr>
<td>56</td>
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</table>

Genetic studies of parathyroid adenomas have described an oncogene (PRAD1) that may be one step in the path to neoplasia in these tumors. Ongoing research indicates that overexpression of the normal PRAD1 gene, also known as cyclin D1, allows progression of the cell cycle from the G1 phase to the S phase, thus promoting cellular growth and division. PRAD1 is overexpressed in only a subset of parathyroid adenomas; further research may reveal other genetic alterations that contribute to the neoplastic growth.\textsuperscript{10,11}

Hyperparathyroidism occurs in several familial forms. It is a major component of the multiple endocrine neoplasia (MEN) syndromes types I and IIA. The parathyroid disease of MEN-1 syndrome is multiple parathyroid adenomas that appear with increasing frequency over the patient's lifetime.\textsuperscript{12} In other families, hyperparathyroidism is inherited in an autosomal dominant fashion without other manifestations of MEN-I or MEN-II; some have osseous abnormalities (tumor-jaw syndrome) and some apparently have isolated disease.
**Pathology**

**Single-gland versus Multiple-gland Disease**

Microscopically, the cell most commonly involved in primary hyperparathyroidism is the chief cell. Less frequently, the oxyphil cell is the predominant cell type. Diseased glands typically have an increase in the proportion of stromal cells and a reduction in the proportion of stromal fat. Single diseased glands, or adenomas, have been classically described with a predominance of chief cells centering in a single focus, with a compressed rim of surrounding normal tissue (Fig. 78.8). In contrast, parathyroid hyperplasia has been characterized as a diffuse proliferation of clear cells in multiple glands, with little remaining normal tissue (Fig. 78.9). These criteria have proved totally unreliable. Although pathologic studies can usually distinguish parathyroid glands from other tissue, they may not prove useful beyond this capacity. Intraoperative decisions frequently depend on recognizing disease of one or more parathyroid glands, and in this regard, the histologic description of adenoma or hyperplasia is generally unreliable in primary hyperparathyroidism.

**FIGURE 78.9** Primary parathyroid hyperplasia. The normal adipose tissue of the gland has been replaced by sheets and trabeculae of
Patients with multiple-gland disease may have one gland that appears to be an adenoma and another that appears diffusely involved or even histologically normal with gross enlargement. Other methods of identifying normal glands, including staining of intracellular fat, measurement of glandular density, and flow cytometric analysis of cellular DNA content, have all been used with some reported success, although none provides unequivocal differentiation between normal and abnormal glands.

The most reliable index of abnormality is the determination of glandular enlargement by visual inspection. The incidence of single- and multiple-gland enlargement as judged by visual inspection in 66 consecutive patients with hyperparathyroidism is shown in Table 78.9. The visual assessment and judgment of the experienced surgeon have proved to be an effective basis for intraoperative decisions. This approach requires that all four parathyroid glands be evaluated at the time of operation. However, the recent ability to rapidly measure PTH during operation has provided a method to assess gland function rather than size. This

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Patient, n</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Adenoma</td>
<td>50</td>
<td>76%</td>
</tr>
<tr>
<td>Double adenoma</td>
<td>4</td>
<td>6%</td>
</tr>
<tr>
<td>Hyperplasia</td>
<td>12</td>
<td>18%</td>
</tr>
</tbody>
</table>


Patients with multiple-gland disease may have one gland that appears to be an adenoma and another that appears diffusely involved or even histologically normal with gross enlargement. Other methods of identifying normal glands, including staining of intracellular fat, measurement of glandular density, and flow cytometric analysis of cellular DNA content, have all been used with some reported success, although none provides unequivocal differentiation between normal and abnormal glands.

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experience indicates that there may be more enlarged glands than there are hyperfunctioning glands.\textsuperscript{14}

**Carcinoma**

Parathyroid carcinoma is a rare entity, and the histologic diagnosis can be exceedingly difficult. The surgeon may suspect the diagnosis when dense invasion and scarring are encountered, although this may also be secondary to some other inflammatory disease in the neck. Pathologic criteria include marked mitotic activity, dense fibrous stroma, and evidence of local invasion into the capsule or surrounding vessels. Malignant-appearing tumors, however, may pursue an apparently benign clinical course; the converse is less frequently true. An aneuploid pattern by flow cytometric analysis of tumor DNA content may help to distinguish carcinoma from atypical adenoma in borderline cases.\textsuperscript{15} The only reliable criteria of malignancy are metastases, most commonly to the lymph nodes, lung, or liver, and true local invasion.

**Systemic Effects**

The use of automated technology for determining serum calcium has changed not only the estimated incidence of hyperparathyroidism but also the usual mode of presentation.\textsuperscript{16} Before screening, three fourths of patients presented with renal disease, particularly nephrolithiasis; one third to one half had skeletal manifestations, and rare patients had both. Most recent series suggest that at least half of the patients in whom hyperparathyroidism is diagnosed do not have renal or osseous disease and many are minimally symptomatic or asymptomatic. Manifestations of the disease are protean but generally nonspecific, and they may be difficult to elicit in the history. A significant proportion of patients present without a readily quantifiable index of disease severity. This finding has created some controversy about the need for surgery in the asymptomatic patient and particularly for the elderly or high-risk patient.\textsuperscript{17,18}

The earliest complaints are often the vague symptoms of hypercalcemia. These vary with the magnitude of plasma calcium elevation and can include muscle weakness, anorexia, nausea, constipation, polyuria, and polydipsia. These nonspecific symptoms may or may not cause the patient to seek medical attention.\textsuperscript{19} Some symptomatic patients have evidence of chronic disease involving the kidney or skeleton. Usually, only one of these systems is significantly involved in any individual patient. The treatment of hyperparathyroidism is designed to eliminate or halt the progression of the complications of the disease. Symptomatic patients can be divided into two groups. Members of the first group have renal manifestations, a slower onset of symptoms, and generally lower serum
calcium concentrations. Patients in the second group have a more rapid onset of symptoms, higher serum calcium levels, and significant bone disease. No recognizable histologic or physiologic characteristics distinguish patients with renal disease from those with bone disease.

**Renal Manifestations**

Renal complications develop because the hypercalcemia leads to an increase in urinary calcium excretion and because PTH increases the excretion of phosphate and produces urinary alkalosis. Both these events predispose to stone formation. Urinary stones may be treated surgically or with lithotripsy, and subsequent definitive treatment of the hyperparathyroidism reduces the rate of re-formation. Of patients who present for the first time with renal colic, 5% to 10% are found to have primary hyperparathyroidism. Nephrocalcinosis (Fig. 78.10) is calcification of the renal parenchyma and occurs in 5% to 10% of patients with hyperparathyroidism. It causes more significant renal damage than nephrolithiasis does. In general, the more severe the renal damage, the less likely it is that nephrocalcinosis will regress after parathyroidectomy.

**FIGURE 78.10** Abdominal film demonstrating nephrocalcinosis, or
The incidence of hypertension in hyperparathyroidism increases with the degree of renal impairment. Hypertension may be a significant cause of the morbidity associated with hyperparathyroidism, but although a decrease in blood pressure has been demonstrated in some patients after parathyroidectomy, the correlation between the two conditions is not clear.

**Skeletal Manifestations**
Parathyroid bone disease in its most classic and severe form, osteitis fibrosa cystica, is seldom encountered; however, 5% to 15% of patients with parathyroid bone disease present with significant symptoms of skeletal disease. Most commonly, these symptoms include bone pain and pathologic fractures.

Bone changes are often demonstrable on detailed plain radiographs of the hands (Fig. 78.11). Characteristically, subperiosteal resorption is evident on the radial aspect of the middle phalanx of the second or third finger. Because of tufting of the distal phalanges, clubbing may be evident on physical examination. Other findings that typically involve the skull and long bones include bone cysts, “brown” tumors (i.e., localized proliferations of osteoclasts), and diffuse demineralization or granularity. More subtle bone loss can be detected by iliac crest bone biopsy or dual energy x-ray absorptiometry scan. The risk of bone fracture increases with increasing severity of bone loss.

**Gastrointestinal Manifestations**
Hypercalcemia is clearly associated with nonspecific gastrointestinal complaints, including nausea, vomiting, constipation, and anorexia, but attempts to demonstrate a definite relation between hyperparathyroidism and either peptic ulcer disease or pancreatitis remain unconvincing. Hypercalcemia stimulates gastric acid secretion experimentally and clinically and has been associated with pancreatitis. Therefore, a theoretic rationale for the complex of hyperparathyroidism and gastrointestinal symptoms does exist.
Neuromuscular Manifestations

Neurologic and muscular complaints are those of hypercalcemia in general. Fatigability and proximal muscle weakness are among the most debilitating manifestations. Atrophy of type II muscle fibers, consistent with a neuropathic and not a myopathic cause, has been demonstrated. Sensory complaints include dysesthesia, a reduced vibratory sense, and stocking-glove sensory deficits.

Psychological Manifestations

The emotional disturbances of hyperparathyroidism are often subtle and
difficult to quantify. As with other forms of hypercalcemia, they range from depression or anxiety to psychosis and coma. Patients undergoing parathyroidectomy frequently experience a sense of well-being and relief from fatigue and dullness postoperatively, even if they may have had no noticeable complaints preoperatively.

Other Manifestations
A variety of signs and symptoms of soft-tissue calcification have been described. Nonspecific arthralgia, particularly involving the proximal interphalangeal joints of the hands, is characteristic. The incidence of chondrocalcinosis is increased. Pruritus, vascular and cardiac calcification, and band keratopathy of the cornea have all been noted. Several reports have suggested an increased incidence of malignancy, but they remain unsubstantiated.

Physical Findings
Except in patients with the classic deformities of advanced bone disease, the physical examination is seldom helpful. Diseased parathyroid glands are infrequently palpable, except in patients with parathyroid carcinoma. A mass in the anterior neck in a patient with primary hyperparathyroidism is most commonly a thyroid nodule.

Laboratory Findings
Tests for calcium, PTH, phosphate, bicarbonate, and magnesium, in addition to other laboratory tests, are useful to establish the diagnosis of hyperparathyroidism.

Calcium.
Hypercalcemia is the single most important diagnostic finding; however, particularly in early or mild cases, serial analysis may show fluctuations in and out of the normal range. Coexistent hypoalbuminemia and acidosis may produce an apparently normal total serum calcium, even though the ionized fraction is actually elevated. Serum concentrations of ionized calcium may be helpful in the patient with intermittent or mild hypercalcemia.

Parathyroid Hormone.
In the United States, PTH measurement has become an important method for establishing the diagnosis of hyperparathyroidism. Because of the heterogeneity of the various circulating forms of PTH, conflicting and confusing results were often obtained during the initial clinical experience
with radioimmunoassays. The methodology continues to be refined, and most current assays are sufficiently sensitive, specific, and reliable and are in wide clinical use. Intact hormone assays and whole molecule assays, as opposed to amino terminus or carboxyl terminus assays, are the most dependable. The demonstration of an elevated plasma PTH concentration alone does not establish the diagnosis of hyperparathyroidism. With a simultaneous elevated serum calcium level, this finding is virtually diagnostic (Fig. 78.12).

![FIGURE 78.12](image)


**Phosphate.**

PTH increases renal phosphate excretion and, in about half of patients, produces hypophosphatemia. In the presence of renal disease, however, the serum phosphate levels may be normal or significantly elevated.

**Bicarbonate**
PTH also increases bicarbonate excretion, so that a hyperchloremic metabolic acidosis may develop. It has been suggested that the finding of an elevated serum chloride-to-phosphate ratio may be helpful in the differential diagnosis of hypercalcemia. A ratio greater than 30 is considered highly suggestive of hyperparathyroidism.

**Magnesium.**

Hypomagnesemia develops in 5% to 10% of patients with hyperparathyroidism. After parathyroidectomy, if both hypocalcemia and hypomagnesemia are present, it may be difficult to correct the calcium until the serum magnesium has been corrected.

**Other Diagnostic Tests.**

A variety of special diagnostic tests for hyperparathyroidism are available. None is more specific than the measurement of serum concentrations of calcium and PTH, although they may be useful in equivocal cases. For example, the 24-hour urinary calcium excretion is usually elevated in patients with hyperparathyroidism, although the finding is not specific for this disease. This test is helpful in identifying patients with familial hypercalcemic hypocalciuria, in whom the rate of urinary calcium excretion is low. Measurements of tubular reabsorption of phosphate below 30% suggest primary hyperparathyroidism. Urinary cAMP is generated specifically as a consequence of PTH activation of renal tubular adenyl cyclase. Increased urinary concentrations are identified in most patients with primary hyperparathyroidism. These measurements are rarely necessary because of the reliability of the intact PTH measurement.

**Localization with Imaging Techniques**

In order to try to simplify the operative approach to hyperparathyroidism, attempts have been made to localize enlarged glands preoperatively. In the hands of an experienced surgeon, the cure rate for hyperparathyroidism at the initial operation without preoperative localization exceeds 95% with the conventional full neck exploration. However, recent technologic developments have led surgeons to pursue alternatives to the full neck exploration. These innovations are increasingly accurate preoperative localization with $^{99m}$technetium sestamibi scintigraphy or high-resolution ultrasound and intraoperative intact PTH measurement that allows termination of the operation without visualization of all four parathyroid glands. Surgeons have used these technologies in various combinations to limit the extent of the neck exploration. All the current alternative strategies, however, depend on a preoperative parathyroid localization study to direct the exploration.
The study most frequently used for imaging previously unoperated patients is $^{99m}$technetium sestamibi scintigraphy (Fig. 78.13). Sestamibi scanning can identify the site of abnormal tissue in 75% to 80% of patients but has limitations in patients with small adenomas or multiple-gland disease. Sestamibi was originally developed for cardiac imaging. It also images parathyroid tissue on delayed scans and has been used recently for noninvasive parathyroid imaging. The use of a single nuclide with a short half-life and a high-energy profile has advantages in lateral, oblique, and three-dimensional imaging that technetium-thallium scanning, which was formerly used, does not provide.

FIGURE 78.13 $^{99m}$Technetium sestamibi scan of a patient with a parathyroid adenoma. The radionuclide is present in both thyroid and parathyroid tissue on the 10-minute film; however, by 2 hours, the radionuclide has washed out of the thyroid and remains only in the right-sided parathyroid gland. This scan shows a 794-mg right upper parathyroid adenoma (arrow).
FIGURE 78.14 Ultrasound views of parathyroid adenomas. (A) Saggital image of the upper pole of the right lobe of the thyroid
High-resolution ultrasound examination of the neck has been used increasingly for localization of abnormal parathyroid tissue, particularly when it is available for use by the clinician. The current machines scan at high frequencies (10 to 13 MHz) that allow demonstration of small abnormalities in the neck (Fig. 78.14). The examination is best done by a clinician in real time, as that allows the most complete assessment of the neck, rather than scans performed by a technician for later review of still pictures by the physician. The sensitivity of cervical ultrasound for abnormal parathyroid glands is about the same as for sestamibi scanning. Ultrasonography is an operator-dependent technique. It is rapid and relatively inexpensive and can direct fine-needle aspiration for cytologic confirmation and immunoassay for PTH.

In patients with persistent or recurrent hyperparathyroidism, preoperative imaging is important to guide the exploration. High-resolution real-time ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), and sestamibi scanning all appear to have comparable sensitivities of 50% to 60%. The results of these examinations may be less successful at centers without significant experience in their use.

Computed tomography is more expensive but less operator-dependent than ultrasonography. It clearly is superior in identifying deeper structures and for examining the retrosternal mediastinum. MRI is considerably more expensive than CT and has not been shown to be superior. Most surgeons prefer to have results of two or more imaging tests that confirm an abnormality before exploration in the reoperative setting.

**Treatment**

**Indications for Surgery**

Generally, the only practical therapeutic option is surgery. Nephrolithiasis, bone disease, and neuromuscular symptoms all respond well to surgical intervention. In contrast, surgery in patients with renal failure,
hypertension, and psychiatric symptoms is not so uniformly successful, although it benefits some patients and is usually indicated in all except those at highest risk. The question of how to manage the large group of patients with apparently asymptomatic disease requires particularly careful consideration.

**Management of Asymptomatic Hyperparathyroidism**

A large proportion of patients with the diagnosis of hyperparathyroidism are minimally symptomatic or asymptomatic. The appropriate treatment for these patients remains controversial. Although little evidence indicates that irreversible complications, such as renal failure, eventually develop in patients with asymptomatic mild disease, the natural history of the disease remains incompletely defined. Many of the manifestations of this disease may go unrecognized until they are corrected surgically. Still unanswered is the question of how much asymptomatic disease may contribute to generalized osteopenia in this predominantly postmenopausal female population.

One study followed a group of 142 asymptomatic patients without operation. At the end of the 10-year study, more than 20% of the patients had required surgery for an increase in serum calcium to above 11 mg/dL or for specific complications attributable to the disease. Another 20% were lost to or declined follow-up. The remaining patients either died of unrelated causes or had persistent asymptomatic disease. The authors concluded that because of the large percentage (about 40%) of patients who either required operation or were lost to follow-up, they could not reliably recommend conservative management.

A more recent report detailed the 10-year natural history of 121 patients with asymptomatic hyperparathyroidism. Operation was recommended for those in whom symptoms or findings developed, according to the guidelines of the National Institutes of Health Consensus Conference (see later). During the monitoring period, indications for operation developed in 27% of the patients, and biochemical normalization and increased bone mass were observed in those who underwent surgery. However, although the patients who did not undergo operative correction continued to have biochemical abnormalities, renal stones or fractures did not develop in any of them. These data confirm the impression of most clinicians that mild hyperparathyroidism rarely takes a precipitously worsening clinical course; thus the risks and discomforts of management must remain appropriate to the disease.

In October 1990, a National Institutes of Health Consensus Development Conference reviewed the available evidence regarding the management of
asymptomatic primary hyperparathyroidism. After interval developments, a panel of experts reconvened in 2002, and revisited this issue. The panel agreed that operation is the indicated treatment for all patients with symptoms; however, they recognized a subgroup of patients who have no symptoms attributable to hyperparathyroidism, and their conclusions included several indications for surgical intervention in these asymptomatic patients (Table 78.10).

The panel mandated close (every 6 months) follow-up for those patients not treated by operation. In addition, they recommended surgery for cases in which medical surveillance is neither desirable nor suitable, such as when a patient requests surgery, consistent follow-up is unlikely, coexistent illness complicates management, or a patient is younger than age 50 years.

![Table 78.10 Indications/Contraindications: National Institutes of Health Consensus Development Conference's Indications for Surgical Intervention in Patients with Asymptomatic Primary Hyperparathyroidism](image)

This remains an area of considerable controversy, and complete resolution of the question requires a randomized, controlled trial. The complication rate of operation by an experienced surgeon is very low. Within a short period, the financial cost of medical follow-up exceeds that of treatment by operation. Based on these considerations, most patients should undergo operation, and those who do not must be closely followed.

**Principles of Surgical Correction**
Although neck exploration for hyperparathyroidism may be straightforward, it sometimes becomes an arduous procedure requiring considerable patience because of the variability in both the location and the number of diseased glands. Persistent hyperparathyroidism and the necessity for reexploration can usually be avoided by a meticulous initial procedure. Reoperation is predictably more difficult than the initial operation, and the risks for damage to the recurrent laryngeal nerves and hypoparathyroidism are greater during reoperation.

It is essential that the surgeon be confident of the preoperative diagnosis and prospectively discuss the procedure with the patient. The potential complications of damage to either the recurrent laryngeal nerve or the superior laryngeal nerve and the development of hypocalcemia require discussion. Likewise, the possibility of an unsuccessful initial operation must be explained, and the patient should recognize that re-exploration, including median sternotomy, may be required. Although alternatives to full neck exploration are often now applied, no patient should be explored by a surgeon who is unfamiliar with the principles and techniques of the conventional full neck exploration.

For a full neck exploration, the patient is placed under general anesthesia with a roll beneath the shoulders and the neck extended. The neck is opened through a transverse incision overlying the thyroid isthmus, and the platysma is similarly divided. Superior and inferior flaps are developed. The strap muscles are separated in the midline and retracted laterally; division is unnecessary. One lobe of the thyroid is chosen and rotated medially. Important landmarks include the tracheoesophageal groove, the recurrent laryngeal nerve, the inferior and superior thyroid arteries, and the middle thyroid vein (Fig. 78.15). In most patients, the nerve lies in the tracheoesophageal groove or just laterally. Occasionally, it may be situated more anteriorly. Uncommonly, it may originate directly from the vagus without passing around the right subclavian artery. Both these variations make the recurrent nerve more susceptible to injury. The external branch of the superior laryngeal nerve, which innervates the cricothyroid muscle, usually lies medial to the superior thyroid vessels and should be carefully preserved.
For a full neck exploration, all four glands should be identified at the initial exploration because of the possibility of multiple-gland disease. Supernumerary glands may be present and should be sought at the initial procedure. Although frozen section has not been helpful in differentiating diseased from normal glands, it is generally reliable for confirming the presence or absence of parathyroid tissue. Small, thin biopsy specimens are sharply incised from the gland, with extreme care taken to avoid damaging its delicate blood supply. Most surgeons use frozen section selectively to confirm suspected abnormal parathyroid tissue or to document difficult or confusing situations.\textsuperscript{25}

The upper glands are usually located far dorsally on the surface of the thyroid lobe at the level of the upper two thirds of the gland. The lower glands are less constant and may be located anywhere from well above the thyroid to the anterior mediastinum. The lower glands are most typically in the region where the thyrothymic ligament attaches to the lower pole of the thyroid lobe. If the inferior glands cannot be localized, the thymic pedicle should be carefully examined and mobilized. Because of their common embryologic origin, the inferior gland is frequently associated with the thymic remnant. Parathyroid glands within the mediastinum sometimes can be removed by mobilizing the thymus through the cervical incision. If this technique is unsuccessful in identifying the parathyroid gland, the thyroid lobe on the side of the missing gland is mobilized and palpated. Intraoperative ultrasonographic
examination may identify an intrathyroidal parathyroid gland. As a last resort, excision of the thyroid lobe may be indicated.

If after meticulous exploration of all these areas three or four parathyroid glands have been identified, none of which is enlarged, most surgeons would favor terminating the operation.

**Limited Surgical Exploration**

With the availability of accurate preoperative localization methods, it has become routinely possible to identify abnormal parathyroid glands prior to operation for most patients. This allows the surgeon to know where to start the exploration. Then, intraoperative PTH measurement can be used to confirm removal of all hyperfunctioning parathyroid tissue, that is, when to stop the operation. This strategy of directed, limited neck exploration is applicable to about 75% of initial parathyroid explorations, and has about the same success rate as full neck exploration.26,27,28,29,30 The preoperative localization can be done by either 99m technetium sestamibi nuclear medicine scan or by high-resolution ultrasound. The intraoperative PTH measurement is first assessed at the outset of the procedure, and/or immediately preceding parathyroid gland excision (the pre-excision baseline). Blood samples are obtained at time intervals after parathyroid gland resection. A decrease of the PTH level by 50% from the higher of the incision or pre-excision baseline predicts long-term normocalcemia.28 Other investigators use more sensitive criteria for the detection of multigland disease, including reduction of the PTH level into the normal range and kinetic assessments of the rate of PTH decrease.31 This increase in sensitivity comes with the cost of decreased specificity, however. Blood samples can be obtained either centrally or peripherally.32,33,34

The limited nature of this operative approach also makes it easier to perform this operation under regional or local anesthetic in an ambulatory setting. However, because of the possibility of multiple gland disease or inaccurate preoperative localization, all surgeons undertaking this approach should also be skilled in the full neck exploration for hyperparathyroidism.33,35,36

**Extent of Resection**

The operative procedure performed has been based on the number of enlarged glands identified for full neck explorations, however, with the use of intraoperative PTH monitoring, it has become clear that not all enlarged parathyroid glands are hyperfunctioning.14,37 In contrast, nearly all hyperfunctioning glands are enlarged and hypercellular. The full neck exploration experience has demonstrated that removing all enlarged...
glands is a highly successful approach to curing hyperparathyroidism, and in the absence of PTH monitoring, this remains an accepted approach. Typically, single-gland disease has been treated by simple excision, whereas any combination of two- or three-gland enlargement is treated by resecting the diseased tissue and leaving the normal glands in place. The question of whether two- or three-gland enlargement implies the presence of disease in all glands (hyperplasia) has not been resolved. If one gland is large and the remaining three are normal in size, resection of the single parathyroid cures virtually all patients. Of 76 patients with two- or three-gland disease treated by excising the large glands and leaving the normal glands, only eight (10.5%) had recurrent hypercalcemia, which tended to be mild (follow-up of 12 to 140 months postoperatively). This approach seems satisfactory in most patients.\textsuperscript{38}

Treating patients with four-gland disease has been more difficult. In many of these patients, the disease occurs as a component of one of the familial syndromes, particularly MEN-I. Patients with four-gland parathyroid hyperplasia can be treated by subtotal parathyroidectomy (removing three and a half glands) or by total parathyroidectomy with autotransplantation of some parathyroid tissue into the nondominant forearm. Both operations depend on meticulous identification of all parathyroid tissue for adequate results. The putative advantage of the subtotal parathyroidectomy is that it leaves the remaining parathyroid tissue with its native blood supply. Total parathyroidectomy with autograft has the advantage of removing all the abnormal parathyroid tissue from the neck and placing it in a site where reoperation for recurrent hyperparathyroidism is simpler.

The reported incidence of recurrent hypercalcemia after subtotal parathyroidectomy for nonfamilial parathyroid hyperplasia is 0 to 16%; the incidence of permanent hypoparathyroidism is 4% to 5%. Total parathyroidectomy with autograft is associated with a similar risk for permanent hypoparathyroidism in the sporadic setting (5%) and a higher reported risk for recurrent hypercalcemia (20%). Reoperation for recurrent hypercalcemia is greatly simplified by the approach of total parathyroidectomy with autotransplantation. Thus, given the current data, sporadic parathyroid hyperplasia can be acceptably treated by either operation.\textsuperscript{38,39,40} In patients with MEN-I, the disease is not the same as sporadic hyperplasia. Rather, defects in the MEN-1 gene cause multiple parathyroid adenomas that arise independently over the life of the patient.\textsuperscript{41} The operative results reflect this independent capability of all parathyroid tissue in these patients to become neoplastic. The hypercalcemia recurrence rate is 26% to 36% with long-term follow-up after subtotal parathyroidectomy, and similar after total...
parathyroidectomy with autograft. However, the incidence of permanent hypoparathyroidism after autograft in MEN-1 is also significant (reported as high as 46%). While both approaches are currently accepted, most experienced centers now advocate subtotal parathyroidectomy as the initial operation in MEN-1 hyperparathyroidism, and anticipate that recurrent disease is likely, manageable, and less problematic than permanent hypocalcemia.42,43,44,45,46

**Technique of Parathyroid Autotransplantation**

The parathyroid gland is sliced into 15 to 20 pieces and autografted into a forearm muscle bed. The sites are marked with silk sutures. This location permits easy subsequent access under local anesthesia if recurrent hypercalcemia develops. Function of the autograft is documented by (a) normocalcemia, with the autograft as the only source of PTH, (b) by measuring higher concentrations of hormone in the antecubital vein draining the graft bed than in the corresponding vein in the opposite arm, or (c) “transient parathyroidectomy,” by placing a venous occlusive tourniquet on the arm above the graft, and measuring changes over several minutes in the PTH levels drawn from the contralateral arm.47 Lack of function is unusual outside of the MEN-1 patients; hypoparathyroidism develops in about 5% of patients. Glands should also be viably frozen in dimethyl sulfoxide and serum. If in the postoperative period it becomes clear that the patient is aparathyroid, the cryopreserved tissue can be reimplanted under local anesthesia.

**Special Situations**

**Persistent or Recurrent Hyperparathyroidism**

Persistent hyperparathyroidism occurs in fewer than 5% of patients after exploration by an experienced surgeon. Most commonly, it is the result of a single diseased gland remaining in the neck or the mediastinum. Recurrent disease develops after an interval of normocalcemia and may be the result of regrowth of diseased tissue, implantation from a tumor broken at the initial procedure, or even recurrent parathyroid carcinoma.

In the evaluation of these patients, it is essential to document that the initial diagnosis was correct. Familial hypocalciuric hypercalcemia should be excluded by measuring urinary calcium excretion.

Reviewing the original operative notes and pathology reports may provide clues to the position of missed glands. The locations of parathyroid tumors not found at the initial operation but identified on subsequent exploration in one large series are shown in Fig. 78.16.
It is generally agreed that localization studies do have a place in the management of recurrent disease. Noninvasive methods are used first, and if these are unsuccessful in identifying the diseased gland, selective angiography and venous sampling for PTH are used. The utility of the techniques vary across institutions, dependent on local experience, expertise and preference. Selective angiography localizes 50% to 80% of parathyroid glands that cannot be detected by any other modality. Venous sampling may also be helpful in some patients, although interpretation can be complicated by the collateralization that occurs postoperatively. Because it provides no direct image but indicates the side of the neck where the hyperfunctioning tissue is located, it may help to direct the exploration to one or the other side of the neck. Both these invasive radiographic techniques require considerable expertise. Transient cortical blindness, transverse myelitis, and cerebrovascular accidents have all been reported as complications of arteriography. Angiographic ablation of mediastinal parathyroid tissue with large doses of ionic contrast has been successful in selected patients. This technique may be used in some patients with mediastinal parathyroid adenomas who are at increased surgical risk and who have other functional parathyroid tissue remaining.48
Surgical reexploration can be a difficult procedure. The neck should almost always be reexplored first. If the thymic remnant has not already been removed, it should be excised at this time. Two adjunctive techniques, intraoperative ultrasonography to locate glands and intraoperative measurement of PTH to document the adequacy of resection, may be useful in patients undergoing operation for persistent disease.49

If the gland is not identified in the neck by means of the maneuvers described, the mediastinum is examined; most surgeons do this only if there is imaging evidence of disease in the mediastinum, rather than blind explorations. Median sternotomy and exploration are necessary in only 1% to 2% of patients with hyperparathyroidism. Successful transcervical mediastinal exploration is sometimes possible with use of the Cooper thymectomy retractor, a substernal retractor that permits more extensive mediastinal exploration and thymectomy through a cervical incision.50 Any remaining thymic tissue is first isolated and examined. Inferior parathyroid glands most commonly migrate into the anterior mediastinum. If the results of this exploration are negative, the area posterior and lateral to the trachea is then explored. The location of superior parathyroid glands may be as far posterior as the esophagus and as far superior as the pharynx.

Surgical reexploration is successful in experienced hands in 60% to 80% of cases. The incidence of complications is increased. Unilateral recurrent nerve injury occurs in 5% to 10% of patients postoperatively, and permanent hypoparathyroidism in 10% to 20% of patients. Cryopreservation of excised tissue is an important component of the management of these patients because it allows later autotransplantation if the patient becomes hypoparathyroid postoperatively. The risks of these complications must be clearly outweighed by the clinical improvement in patients with advanced disease. Reoperation in asymptomatic patients with mild disease is controversial.

**Hypercalcemic Crisis**
Occasionally, patients with hyperparathyroidism become acutely hypercalcemic with severe symptoms. The pathogenesis appears to involve a vicious cycle of uncontrolled PTH secretion followed by hypercalcemia and secondary polyuria, dehydration, and reduced renal function, which exacerbate the hypercalcemia. Serum calcium concentrations may reach the range of 16 to 20 mg/dL, and the syndrome is manifested by rapidly developing muscle weakness, nausea and vomiting, lethargy, fatigue, and even coma. If the diagnosis of hyperparathyroidism is in question, ultrasonography or CT may help to identify the enlarged gland.

Definitive treatment involves resecting the diseased parathyroid tissue, which is almost always curative. Generally, however, it is safer to lower the serum calcium level before operation.

**Hyperparathyroidism in Pregnancy**
Hyperparathyroidism in pregnancy is a rare disorder that not only causes hypercalcemia in the mother but also is associated with increased morbidity and mortality rates in the fetus. Even the newborn is at risk for the development of tetany. The risk for fetal complications is higher if the hyperparathyroidism is left untreated. The mother should undergo operation in the second trimester.51,52,53,54

**Neonatal Hyperparathyroidism**
Neonatal hyperparathyroidism occurs in infants who are homozygous for a mutation of the calcium-sensing receptor and is characterized by hypotonia, poor feeding, constipation, and respiratory distress.6 Each parent of these children is affected by familial hypocalciuric hypercalcemia. The 1-year survival rate in children with symptoms is less than 50%, and patients without symptoms appear to have significant bone disease. Total parathyroidectomy with autotransplantation is the treatment of choice.55

**Secondary Hyperparathyroidism**
Secondary hyperparathyroidism develops as a consequence of chronic renal failure. Phosphate retention and hyperphosphatemia reduce the serum calcium levels. This effect is aggravated by the reduction in 1-hydroxylase activity in the kidney, necessary for the activation of vitamin D₃. The secondary increase in PTH levels to compensate for the hypocalcemic effects is exacerbated by aluminum accumulation in bone. Aluminum, present both in the dialysate water and in phosphate-binding medications, contributes to the osteomalacia (renal osteodystrophy) that develops in all these patients after several years of dialysis. Therapy
includes controlling the hyperphosphatemia with dietary restriction and phosphate-binding gels, calcium supplementation orally and in the dialysate bath, correction of acidosis, administration of vitamin D sterol, and reduction in aluminum intake in both the dialysate and the diet. Therapy should be initiated carefully because metastatic soft-tissue calcification may occur. Indications for surgical therapy include persistent, symptomatic hypercalcemia that cannot be controlled medically, particularly in prospective renal transplant patients; bony pain and abnormal fractures; ectopic calcification; and intractable pruritus. Subtotal parathyroidectomy and total parathyroidectomy with heterotopic autotransplantation both appear to be acceptable options, although reexploration for recurrent disease is less complicated after total parathyroidectomy with autotransplantation. Parathyroidectomy can actually enhance aluminum deposition, so any excess should be corrected preoperatively through chelation.

**Parathyroid Carcinoma**

Parathyroid carcinoma is a rare condition, accounting for less than 1% of all cases of hyperparathyroidism. Histologic criteria remain controversial, and the diagnosis is securely made only on the basis of local invasion or distant metastases. In comparison with patients with benign disease, these patients tend to be somewhat younger and more symptomatic. In contrast to the marked female predominance in benign disease, the male-to-female ratio in carcinoma is equal. Serum calcium, PTH, and alkaline phosphatase levels are relatively more elevated, and patients often have an elevated level of human chorionic gonadotropin. Patients may have manifestations of both renal and bone disease. The affected gland is palpable in almost half of patients.

Initial treatment should include radical resection of the involved gland, ipsilateral thyroid lobe, and regional lymph nodes. Neither chemotherapy nor radiation therapy has shown any benefit. If the disease recurs, resection should be attempted because without treatment these patients usually succumb to uncontrolled hypercalcemia. The long-term prognosis is poor, and the opportunity for survival depends on complete initial resection.\(^{56}\)

**MULTIPLE ENDOCRINE NEOPLASIA**

Although these familial disorders are typically characterized by a predisposition to the development of tumors of multiple endocrine organs, the parathyroid is characteristically involved in two of them. The disorders are all inherited in an autosomal dominant
fashion, and the tumors tend to be multicentric. The tumors may be benign or malignant and may occur metachronously or synchronously. MEN-I is characterized by the concurrence of parathyroid hyperplasia, pancreatic islet cell tumors, and pituitary adenomas. MEN-IIA consists of medullary thyroid carcinoma (MTC), pheochromocytoma, and parathyroid hyperplasia. MEN-2B includes MTC, pheochromocytoma, mucosal neuromas, and a distinctive marfanoid habitus. Together these syndromes encompass much of the spectrum of endocrine neoplasia.

**Pathogenesis**

A unifying hypothesis for the MEN syndromes was offered by Pearse based on both embryologic and cytochemical studies. He suggested that these tumors arise in cells that embryologically derive from the neural crest and are characterized by amine precursor uptake and decarboxylase activity. According to this theory, some defect in the development of the neural crest might explain the development of multicentric tumors in multiple organs. Although the theory could account for the development of MTC, pheochromocytomas, pituitary tumors, and the widespread nervous system hypertrophy of MEN-IIB, the endocrine cells of the parathyroid and pancreas do not appear to be of neural crest origin. Another unifying hypothesis, developed subsequently, whereby a tumor in one organ secretes endocrine products that secondarily stimulate neoplasia in other glands, has not been accepted. Although some evidence has suggested the presence of a mitogenic factor in the serum of patients with MEN-I, direct attempts to define the pathophysiology have not proved rewarding. As a result, investigators in this area have taken a different approach, attempting to map the diseased gene through modern molecular genetic techniques.

The genetic abnormality in MEN-I has been identified and described in detail. As a tumor-suppressor gene, the first mutation is inherited and becomes unmasked only when a second mutation, in some cases a deletion, develops in susceptible tissues. The resulting complete loss of the tumor suppressor allows neoplasia to develop. The occurrence of multiple second mutations explains the characteristic multicentric involvement of these diseases. Direct genetic testing is now available for some families with known mutations.

Mutations of the *RET* protooncogene are the cause of MEN-IIA. Genetic testing is now available to identify affected family members and provide the opportunity for early treatment of MTC in affected persons.

**Clinical Features and Management of Multiple Endocrine Neoplasia Type I**
Characteristically, MEN-I develops in the third and fourth decades, without any gender predilection.\textsuperscript{62} The gene is transmitted with nearly complete penetrance, and autopsy studies suggest that all three organs are affected in more than 90\% of patients. The phenotype varies, however; more than 90\% of patients have hyperparathyroidism, but evidence of islet cell neoplasms (30\% to 80\%) and pituitary tumors (15\% to 50\%) is less common. The cause of death in carriers of the MEN-I mutation is related to MEN-I in about 45\% of patients and often caused by malignant islet cell or carcinoid tumors.\textsuperscript{63}

**Parathyroid Disease**

Hypercalcemia secondary to hyperparathyroidism is usually the first biochemical abnormality detected in MEN-I and represents the best screening study for members of affected kindreds until direct genetic screening is available. Many of these patients are asymptomatic and have relatively mild hypercalcemia. When symptoms do develop, they typically involve the urinary tract rather than the skeleton.

Typically, the patients have four-gland disease, which may be particularly difficult to manage. The disease is characterized by metachronous development of multiple parathyroid adenomas.\textsuperscript{41} There is no curative operation; the two accepted approaches (subtotal parathyroidectomy and total parathyroidectomy with autograft) each have faults (see earlier). Over time, the subtotal parathyroidectomy approach is becoming the preferred choice by most surgeons.

**Pancreatic Tumors**

In patients with pancreatic tumors, multicentric and diffuse hyperplasia of the pancreatic islets may occur in areas distant from any grossly evident tumor. The management of these tumors is controversial because although some patients have aggressive, malignant tumors, many patients have a fairly benign course. No reliable criteria are available to detect malignant tumors. Tumor size is often cited as a useful marker of prognosis, but substantial overlap has been noted between the sizes of primary benign and malignant tumors (Fig. 78.17).\textsuperscript{64} Because of the difficulty in identifying the more aggressive subset, some authors have chosen a liberal policy of early operation to try to prevent metastasis and death.\textsuperscript{65,66} The detection of these tumors can also be difficult; testing with meal stimulation can be used if an intervention plan supports the diagnosis at this early phase.\textsuperscript{67} Some evidence indicates that measuring serum concentrations of pancreatic polypeptide may provide a general screening measure for a variety of islet cell tumors.\textsuperscript{68} Pancreatic tumors are typically multicentric and frequently malignant. Somatostatin receptor
Scintigraphy can be a useful imaging technique to demonstrate the extent of tumor\(^{69}\) (Fig. 78.18).

Gastrinoma is the most common functional tumor in MEN-I; typically, a severe ulcer diathesis (Zollinger-Ellison syndrome) develops that is associated with secretory diarrhea. Serum gastrin levels are usually markedly elevated (>100 pg/mL); when levels are equivocal (250 to 1,000 pg/mL), provocative testing with secretin (2 m/kg) may be useful. An absolute serum gastrin increase of 200 pg/mL is diagnostic. The primary tumors are often in the submucosa of the duodenal wall.

**FIGURE 78.17** Scatter plot of largest primary tumor size versus metastatic status in 43 patients with pancreatic islet cell tumors associated with multiple endocrine neoplasia type I. Each point represents a single patient. Tumor size is not correlated with the presence of liver or lymph node metastases. (From Lowney JK, Frisella MM, Lairmore TC, et al. Islet cell tumor metastasis in multiple endocrine neoplasia type I: correlation with primary tumor size. *Surgery* 1998; 124:1043-1049.)
Biochemical cure of these gastrinomas is almost never possible, as it is in sporadic gastrinomas, although exploration can reduce the need for antisecretory medications and may reduce the risk for liver metastasis. Histamine 2-receptor antagonists or proton pump inhibitors are effective in controlling acid secretion, although very high doses may be necessary; the malignant disease is often indolent. Total gastrectomy is no longer ever necessary to eliminate acid secretion.70,71

Insulinoma is the next most common pancreatic neoplasm. These tumors are usually small and multicentric. Patients present with a history of sweating, dizziness, confusion, and syncope, consistent with neuroglycopenia; these symptoms are relieved by consuming carbohydrates. The diagnosis is verified by documenting fasting hypoglycemia associated with inappropriately elevated plasma insulin levels. Preoperative tumor localization is usually achieved by a combination of CT and arteriography. Calcium is injected into various pancreatic arteries and plasma insulin levels in the hepatic vein plasma

FIGURE 78.18 Somatostatin receptor scintigraphy in a patient with multiple endocrine neoplasia type I. This scintiscan detected an otherwise unrecognized metastasis to the left lateral segment of the liver (white arrow), which was resected along with the small primary tumor (black arrow).
are measured to detect a gradient after the injection of specific pancreatic arteries.

Because the available medical therapy for insulinoma is limited, patients are treated operatively. Lesions in the tail of the gland can be enucleated if they are small; however, distal pancreatectomy carries little morbidity. Tumors of the head can usually be enucleated, so that pancreaticoduodenectomy can be avoided. In patients with malignant disease, metastases may respond to streptozocin, diazoxide, verapamil, or octreotide may successfully reduce insulin secretion and control symptoms. A diet of complex carbohydrates can also help stabilize serum glucose levels in the hyperinsulinemic patient.\textsuperscript{70,71} Other islet cell lesions occur only rarely in association with MEN-I.

**Pituitary Adenomas**

Prolactin-secreting tumors occur most commonly in this setting, although Cushing disease or acromegaly develops in an occasional patient. Symptoms may result from compression of the optic chiasm, which produces bitemporal hemianopsia, or from prolactin excess, which produces amenorrhea and galactorrhea in female patients and hypogonadism in male patients.

Bromocriptine inhibits prolactin secretion and shrinks many prolactinomas. Refractory tumors and those producing other hormones can be managed by pituitary ablation or radiation.

**Other Tumors**

MEN-I is associated much less frequently with adrenocortical tumors and benign thyroid adenomas. Lipomas and carcinoid tumors may also occur.

**Clinical Features and Management of Multiple Endocrine Neoplasia Type II**

Like MEN-I, the MEN-II syndromes are inherited in an autosomal dominant fashion with complete penetrance but variable phenotype. Bilateral MTC occurs in every affected patient. More frequently than the other syndromes, MEN-IIB may arise as a new mutation that can be transmitted to subsequent generations.

**Medullary Thyroid Carcinoma**

Medullary thyroid carcinoma accounts for about 10% of all thyroid malignancies, and 20% of cases occur in the familial setting of MEN-IIA, MEN-IIB, or familial non-MEN MTC. It is usually the first tumor that develops in these patients and typically appears in the second or third
decade. Tumors are virtually always bilateral and develop in multiple areas of the middle and upper portions of the thyroid lobe (Fig. 78.19). Occasionally, in young people, a diffuse proliferation of parafollicular C cells, termed *C-cell hyperplasia*, is present without frankly invasive carcinoma.\(^7^2\) This finding is highly suggestive of one of the familial MTC syndromes.

Patients typically present with a neck mass and may have hoarseness, dysphagia, or palpable cervical adenopathy. MTC may produce a variety of hormones, including calcitonin, adrenocorticotropic hormone, prostaglandin, and serotonin. The hypercalcitoninemia is often asymptomatic, although severe diarrhea can develop.

**FIGURE 78.19** Medullary thyroid carcinoma. Coronal section of a total thyroid resection shows bilateral involvement by a firm, pale tumor. (From Rubin E, Farber JL. *Pathology*, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 1999.)
By detecting minimal elevations of plasma calcitonin, it is possible to diagnose MTC at a clinically occult stage.\textsuperscript{73} Basal plasma calcitonin levels in normal subjects are in the range of 30 to 100 pg/mL. An increase to levels of 150 to 200 pg/mL occurs, however, after the administration of the potent secretagogues calcium and pentagastrin. The plasma calcitonin levels of patients with MTC show striking increases (>1,000 pg/mL) after provocative testing, so that they can be identified readily. Patients with occult disease may have only minimally elevated basal calcitonin levels that increase in response to secretagogues. The combined infusion of calcium and pentagastrin was the most effective screening test for familial MTC before genetic testing became available. By means of provocative testing in kindred members at risk for disease, MTC was diagnosed at a preclinical stage, and a greater percentage of these patients were cured by surgical therapy. With genetic testing now available, prophylactic thyroidectomy to prevent the development of MTC is possible for all affected people.

Postoperatively, the presence of residual MTC can be readily detected by provocative testing. Recent reports have suggested that meticulous reoperation in patients with recurrent or persistently elevated plasma calcitonin levels postoperatively, including mediastinal dissection on occasion, can normalize elevated plasma calcitonin levels and apparently cure many of them.\textsuperscript{74} For the patient with unresectable metastases, few therapeutic options are available. Neither radiation nor chemotherapy is of significant benefit.

The clinical course of patients with the MEN-II syndromes is determined primarily by the status of their MTC. In the setting of MEN-IIA, the tumors are often indolent and survival prolonged, even in the presence of metastatic disease. By contrast, the tumors in patients with MEN-IIB occur at an earlier age and are generally more aggressive neoplasms. Patients may succumb to the disease at a young age. As a consequence of this aggressiveness, the size of kindreds with the disease is typically small, and usually only a few generations are affected.

**Pheochromocytoma**

Pheochromocytomas are usually detected during the initial screening or follow-up of patients in whom MTC has already been diagnosed. They typically appear in the second or third decade of life, and about 80% are bilateral. Usually, pheochromocytomas are benign but multcentic, and they almost always arise in the adrenal medulla. In patients with MEN-IIA or MEN-IIB, hyperplasia of the adrenal medulla may develop first, grossly characterized by thickening of the medullary tissue in both adrenal glands.
Pheochromocytomas may be asymptomatic, but most commonly, patients have pounding frontal headaches, episodic diaphoresis, palpitations, or anxiety. Hypertension also occurs and is often episodic.

The diagnosis is made by measuring the plasma concentration of metanephrines. Patients with MEN-IIA or MEN-IIB and MTC should be evaluated for pheochromocytoma before they undergo thyroidectomy. If a patient is found to have both lesions, adrenalectomy should be performed first, followed by neck exploration in 1 to 2 weeks. If urinary excretion rates are equivocal, CT of the abdomen can identify lesions 1 cm or larger, and sometimes hyperplasia is recognized. Scintigraphy with $^{131}$I-metaiodobenzylguanidine is used because this agent, which is similar to norepinephrine, is taken up and stored in neurotransmitter vesicles. Normal glands are not demonstrated, whereas about 90% of pheochromocytomas can be imaged. MRI is also sensitive for pheochromocytomas and has the advantage of allowing the differentiation of pheochromocytoma from benign adenoma based on $T_2$-weighted imaging characteristics.

Preoperatively, $\alpha$-adrenergic blockade is induced with phenoxybenzamine. $\beta$-Adrenergic blockade with propranolol may be necessary if tachyarrhythmia subsequently develops, but it should not be initiated until after $\alpha$-adrenergic blockade because of the risk for unopposed vasoconstriction (termed unopposed-$\alpha$ effect). Intraoperative hypertension is controlled with a vasodilator, such as sodium nitroprusside or phentolamine. The abdomen is explored through a bilateral subcostal incision or, more typically, with a laparoscope. Bilateral pheochromocytomas are treated by bilateral adrenalectomy. In patients with MEN-IIA or MEN-IIB and a unilateral pheochromocytoma, only the diseased adrenal gland is removed. In about 30% of patients treated in this manner, a tumor eventually develops in the opposite gland. In the remaining patients, this approach avoids the need for glucocorticoid and mineralocorticoid replacement and the risk for addisonian crisis. After unilateral adrenalectomy, patients are carefully screened at 6-month or 1-year intervals with plasma metanephrine measurements.

Parathyroid Disease

Hyperparathyroidism develops in about one third of patients with MEN-IIA, although it is usually asymptomatic. Occasionally, nephrolithiasis develops. Bone disease is unusual. Frequently, enlarged parathyroid glands are found at operation for MTC, although the patient is still normocalcemic. Multiglandular chief cell hyperplasia is the predominant histologic finding in MEN-IIA. Significant parathyroid disease rarely
develops in MEN-IIB.  

Total parathyroidectomy and heterotopic autotransplantation are performed in hypercalcemic patients with MEN-IIA. In normocalcemic patients with MEN-IIA undergoing thyroidectomy for MTC, a total parathyroidectomy and heterotopic autotransplantation are performed in one session to ensure that the complete thyroidectomy does not compromise the parathyroid blood supply and to avoid reoperation in the neck for subsequent hyperparathyroidism. Evidence suggests that these patients are more easily treated, with a lower incidence of recurrent hyperparathyroidism, than patients with MEN-I.

**Nonendocrine Manifestations of Multiple Endocrine Neoplasia Type IIB**

In addition to MTC and pheochromocytoma, marked abnormalities of the nervous and musculoskeletal systems develop in patients with MEN-IIB. The classic phenotype is characterized by thick lips and a thin, marfanoid habitus (Fig. 78.20 A, B). The incidence of associated skeletal abnormalities is high; these include kyphosis, pectus excavatum, pes planus or cavus, and congenital dislocation of the hip. Diffuse autonomic nervous hypertrophy is another feature. Mucosal neuromas appear on the tongue (Fig. 78.20 C), eyelids, lips, and pharynx. Slit-lamp examination may reveal hypertrophied corneal nerves. Ganglioneuromatosis develops in the submucosal and myenteric plexuses of the gastrointestinal tract. Constipation is common, and radiographic findings may suggest megacolon or Hirschsprung disease.
FIGURE 78.20 (A and B) Characteristic appearance of patients with multiple endocrine neoplasia type IIB, including thick lips. (C) Multiple mucosal neuromas on the tongue of a patient with MEN-IIB. (From Norton JA, Froome LC, Farrell FE, et al. Multiple endocrine neoplasia type 2b: the most

### KEY POINTS

- The normal parathyroid glands are flat, ovoid, and red-brown to yellow. Their dimensions are 5 to 7 mm × 3 to 4 mm × 0.5 to 2 mm, and they weigh between 30 and 50 mg each.

- Parathyroid hormone is the single most important hormonal regulator of calcium and phosphate metabolism in humans with direct effects on the skeleton and kidney and indirect effects on the intestine, mediated through vitamin D.

- The demonstration of an elevated plasma parathyroid hormone concentration alone does not establish the diagnosis of hyperparathyroidism; with a simultaneous elevated serum calcium level, this finding is virtually diagnostic.

- A large proportion of patients with the diagnosis of hyperparathyroidism are minimally or asymptomatic and the appropriate treatment for these patients remains controversial.

- It is routinely possible to identify abnormal parathyroid glands prior to operation for most patients allowing the surgeon to know where to start the exploration; intraoperative parathyroid hormone measurement can be used to confirm removal of all hyperfunctioning parathyroid tissue, that is, when to stop the operation.

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