Parathyroid Glands

The parathyroid glands are derived developmentally from pharyngeal pouches that also give rise to the thymus. They are most commonly located in close proximity to the upper and lower poles of each thyroid lobe but may be found anywhere along the pathway of descent of the pharyngeal pouches, including the carotid sheath, the thymus, and elsewhere in the anterior mediastinum. Most of the gland is composed of *chief cells* which have secretory granules containing *parathyroid hormone (PTH). Oxyphil cells* are found throughout the normal parathyroid either singly or in small clusters. They are slightly larger than the chief cells, have acidophilic cytoplasm, and are tightly packed with mitochondria.

Parathyroid glands are key regulators of calcium homeostasis. The activity of the parathyroid glands is controlled by the level of free (ionized) calcium in the blood, rather than by trophic hormones secreted by the hypothalamus and pituitary. Normally, decreased levels of free calcium stimulate the synthesis and secretion of PTH, which has the following effects on its target tissues, the kidneys and the bones:

- Increased renal tubular reabsorption of calcium
- Increased urinary phosphate excretion, thereby lowering serum phosphate levels (since phosphate binds to ionized calcium)
- Increased conversion of vitamin D to its active dihydroxy form in the kidneys, which in turn augments gastrointestinal calcium absorption
- Enhanced osteoclastic activity (i.e., bone resorption, thus releasing ionized calcium), mediated indirectly by promoting the differentiation of osteoclast progenitor cells into mature osteoclasts

The net result of these activities is an increase in the level of free calcium in the blood, which inhibits PTH secretion from chief cells. Abnormalities of the parathyroids include both hyperfunction and hypofunction. *Tumors of the parathyroid glands, unlike thyroid tumors, usually come to attention because of excessive secretion of PTH, rather than mass effects.*

HYPERPARATHYROIDISM

Hyperparathyroidism occurs in two major forms, *primary* and *secondary,* and, less commonly, as *tertiary* hyperparathyroidism. The first condition represents an autonomous, spontaneous overproduction of PTH, while the latter two conditions typically occur as secondary phenomena in patients with chronic renal insufficiency.

Primary Hyperparathyroidism

Primary hyperparathyroidism is a common endocrine disorder and an important cause of hypercalcemia. There was a dramatic increase in the detection of cases in the latter half of the 20th century, mainly due to routine performance of serum calcium assays in hospitalized patients. The frequency of occurrence of the various parathyroid lesions underlying primary hyperparathyroidism is as follows:

- Adenoma—85% to 95%
- Primary hyperplasia (diffuse or nodular)—5% to 10%
- Parathyroid carcinoma—1%

Pathogenesis

Abnormalities in two genes are commonly associated with parathyroid tumors:

- *Cyclin D1 gene rearrangements*. Cyclin D1 is a positive regulator of the cell cycle. An inversion on chromosome 11 repositions the *cyclin D1* gene (normally on 11q), so that it resides adjacent to genomic elements that regulate the *PTH* gene (on 11p). These elements drive abnormal expression of cyclin D1 in PTH-producing cells, leading to increased proliferation of these cells. Between 10% and 20% of adenomas have this acquired genetic defect. Cyclin D1 is overexpressed in approximately 40% of parathyroid adenomas, indicating the existence of additional mechanisms that lead to its dysregulation.
- *MEN1 mutations*. Approximately 20% to 30% of sporadic parathyroid tumors have mutations in both copies of the *MEN1* tumor suppressor gene (see later). The spectrum of *MEN1* mutations in the sporadic tumors is virtually identical to that in familial parathyroid adenomas.

MORPHOLOGY

The morphologic changes in primary hyperparathyroidism include those in the parathyroid glands and in other organs affected by hypercalcemia. In 75% to 80% of cases, one of the parathyroid glands harbors a solitary **adenoma.** The typical parathyroid adenoma is a well-circumscribed, soft, tan nodule, invested by a delicate capsule. **By definition, parathyroid adenomas are confined to a single gland** (Fig. 20.19). The other glands are normal in size or somewhat shrunken, as a result of feedback

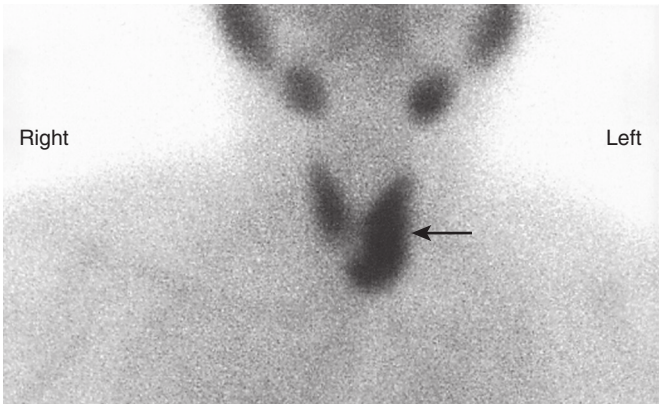

Fig. 20.19 Technetium-99 radionuclide scan demonstrates an area of increased uptake corresponding to the left inferior parathyroid gland *(arrow)*. This proved to be a parathyroid adenoma. Preoperative scintigraphy is useful in localizing and distinguishing adenomas from parathyroid hyperplasia, in which more than one gland will demonstrate increased uptake.

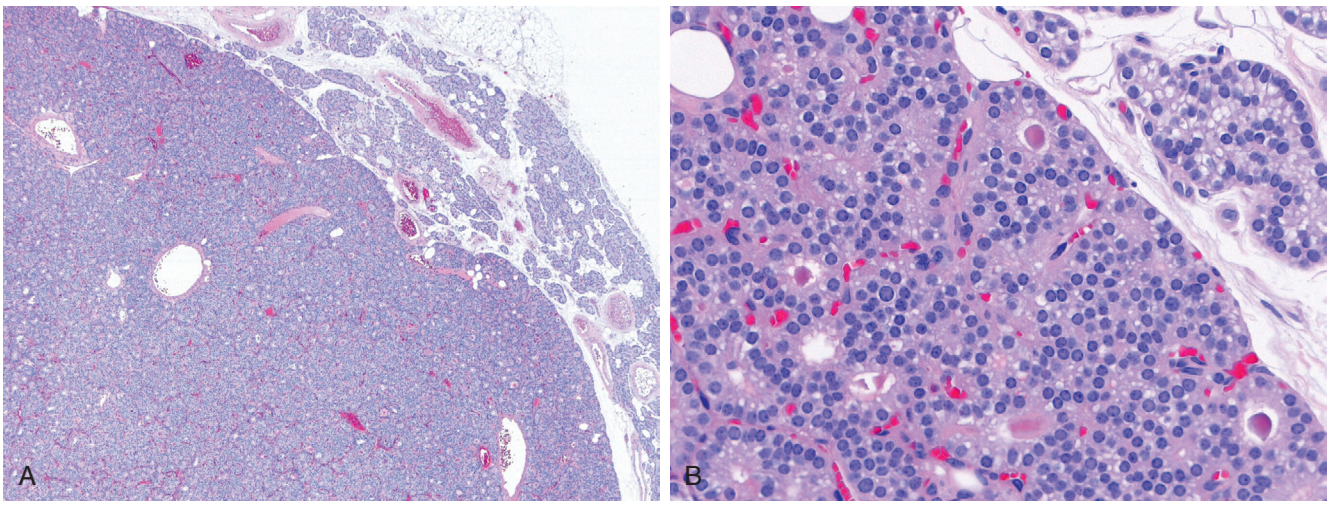

Fig. 20.20 Chief cell parathyroid adenoma. (A) In this low-power view, a solitary hypercellular adenoma is delineated from the residual normocellular gland on the upper right. (B) High-power detail shows minimal variation in nuclear size and occasional follicle formation. *(Courtesy of Dr. Nicole Cipriani, Department of Pathology, University of Chicago, Chicago, Illinois.)*

inhibition by elevated serum calcium. Most parathyroid adenomas weigh between 0.5 and 5 g. On microscopic examination, parathyroid adenomas are composed predominantly of chief cells (Fig. 20.20). A rim of compressed, non-neoplastic parathyroid tissue, generally separated by a fibrous capsule, often is visible at the edge of the adenoma. The chief cells of the adenoma are larger and show greater nuclear size variability than normal chief cells. Cells with bizarre and pleomorphic nuclei are often seen within adenomas (so-called "**endocrine atypia**") and must not be taken as a sign of malignancy. Mitotic figures are rare. In contrast with the normal parathyroid parenchyma, adipose tissue is inconspicuous within adenomas.

Parathyroid hyperplasia is typically a multiglandular process. In some cases, however, enlargement may be grossly apparent in only one or two glands, complicating the distinction between hyperplasia and adenoma. Microscopically, the most common pattern seen is that of chief cell hyperplasia, which may involve the glands in a diffuse or multinodular pattern. Less commonly, the constituent cells contain abundant clear cytoplasm as a consequence of the accumulation of glycogen—a condition designated water-clear cell hyperplasia. As in the case of adenomas, stromal fat is inconspicuous within foci of hyperplasia.

Parathyroid carcinomas may be circumscribed lesions that are difficult to distinguish from adenomas, or they may be clearly invasive neoplasms. These tumors enlarge one parathyroid gland and consist of gray-white, irregular masses that sometimes exceed 10 g in weight. The cells usually are uniform and resemble normal parathyroid cells. They are arrayed in nodular or trabecular patterns. The tumor mass is usually enclosed by a dense, fibrous capsule. There is general agreement that a **diagnosis of carcinoma based on cytologic detail is unreliable; invasion of surrounding tissues and metastasis are the only definitive criteria.** Local recurrence occurs in one-third of cases, and more distant dissemination occurs in another one-third.

Morphologic changes in other organs:

- **Skeletal changes** include increased osteoclastic activity, which results in erosion of bone matrix and mobilization of calcium salts, particularly in the metaphyses of long tubular bones. Bone resorption is accompanied by increased osteoblastic activity and the formation of new bone trabeculae. In more severe cases, the cortex is grossly thinned and the bone marrow contains increased amounts of fibrous tissue accompanied by foci of hemorrhage and cysts **(osteitis fibrosa cystica)** (Chapter 21). Aggregates of osteoclasts, reactive giant cells, and hemorrhagic debris occasionally form masses that may be mistaken for neoplasms (**brown tumors** of hyperparathyroidism).
- **Renal changes.** PTH-induced hypercalcemia favors the formation of urinary tract stones **(nephrolithiasis)** as well as calcification of the renal interstitium and tubules **(nephrocalcinosis).**
- **Metastatic calcification** secondary to hypercalcemia also may be seen in other sites, including the stomach, lungs, myocardium, and blood vessels.

Clinical Features

Primary hyperparathyroidism usually is a disease of adults and is much more common in women than in men (gender ratio of nearly 4:1). *The most common manifestation of primary hyperparathyroidism is an increase in serum ionized calcium.* In fact, primary hyperparathyroidism is the most common cause of *clinically silent hypercalcemia.* Other conditions also may produce hypercalcemia (Table 20.4). The most common cause of clinically apparent hypercalcemia

Table 20.4 Causes of Hypercalcemia

Increased PTH	Decreased PTH
Hyperparathyroidism	Hypercalcemia of malignancy
Primary (adenoma > hyperplasia)*	Osteolytic metastases
Secondary†	PTH-rP–mediated
Tertiary†	Vitamin D toxicity
Familial hypocalciuric hypercalcemia	Immobilization
	Drugs (thiazide diuretics)
	Granulomatous diseases (sarcoidosis)

PTH, Parathyroid hormone; *PTH-rP,* PTH-related protein.
*Primary hyperparathyroidism is the most common cause of hypercalcemia overall.
†Secondary and tertiary hyperparathyroidism are most commonly associated with progressive renal failure.

in adults is cancer, which can cause hypercalcemia through a variety of mechanisms, including secretion of PTH-like polypeptides and osteolytic bone metastases (Chapter 6). The prognosis for patients with malignancy-associated hypercalcemia is poor, because it often occurs in those with advanced cancers. In individuals with hypercalcemia caused by parathyroid hyperfunction, serum PTH is inappropriately elevated, whereas serum PTH is low to undetectable in those with hypercalcemia caused by nonparathyroid diseases, including malignancy. Other laboratory alterations referable to PTH excess include hypophosphatemia and increased urinary excretion of both calcium and phosphate.

Primary hyperparathyroidism traditionally has been associated with a constellation of symptoms that include *painful bones, renal stones, abdominal groans, and psychic moans*. Pain, secondary to fractures of bones weakened by osteoporosis or osteitis fibrosa cystica and resulting from renal stones, with obstructive uropathy, was at one time a prominent manifestation of primary hyperparathyroidism. Because serum calcium is now routinely assessed in most patients who need blood tests for unrelated conditions, hyperparathyroidism is usually detected early in its course. Hence, many of the classic clinical manifestations, particularly those referable to bone and renal disease, are seen much less frequently. Additional signs and symptoms that may be encountered in some cases include the following:

- *Gastrointestinal disturbances,* including constipation, nausea, peptic ulcers, pancreatitis, and gallstones
- *Central nervous system alterations,* including depression, lethargy, and seizures
- *Neuromuscular abnormalities,* including weakness and hypotonia
- *Polyuria* and secondary polydipsia

Although some of these alterations (e.g., polyuria and muscle weakness) are clearly related to hypercalcemia, the pathophysiology of many of the other manifestations of the disorder remains poorly understood.

Secondary Hyperparathyroidism

Secondary hyperparathyroidism is caused by chronic depression of serum calcium levels, most often as a result of renal failure, leading to compensatory overactivity of the parathyroids. The mechanisms by which chronic renal failure induces secondary hyperparathyroidism are complex and not fully understood. Chronic renal insufficiency is associated with decreased phosphate excretion, which in turn results in hyperphosphatemia. The elevated serum phosphate levels directly depress serum calcium levels. In addition, loss of renal α_1-hydroxylase activity, which is required for the synthesis of the active form of vitamin D, reduces the intestinal absorption of calcium (Chapter 8). These alterations cause chronic hypocalcemia, which stimulates the activity of the parathyroid glands.

MORPHOLOGY

The parathyroid glands in secondary hyperparathyroidism are hyperplastic. As in primary hyperplasia, the degree of glandular enlargement is not necessarily symmetric. On microscopic examination, the hyperplastic glands contain an increased number of chief cells, or cells with more abundant, clear cytoplasm **(water-clear cells),** in a diffuse or multinodular distribution. Fat cells are decreased in number. **Bone changes** similar to those seen in primary hyperparathyroidism also may be present. **Metastatic calcification** may be seen in many tissues.

Clinical Features

The clinical manifestations of secondary hyperparathyroidism usually are dominated by those related to chronic renal failure. Bone abnormalities *(renal osteodystrophy)* and other changes associated with PTH excess are, in general, less severe than those seen in primary hyperparathyroidism. Serum calcium remains near normal because the compensatory increase in PTH levels sustains serum calcium. The metastatic calcification of blood vessels (secondary to hyperphosphatemia) occasionally may result in significant ischemic damage to skin and other organs—a process referred to as *calciphylaxis*. In a minority of patients, parathyroid activity may become autonomous and excessive, with resultant hypercalcemia—a process sometimes termed *tertiary hyperparathyroidism.* Parathyroidectomy may be necessary to control the hyperparathyroidism in such patients.

SUMMARY

HYPERPARATHYROIDISM

- Primary hyperparathyroidism is the most common cause of asymptomatic hypercalcemia.
- In a majority of cases, primary hyperparathyroidism is caused by a sporadic parathyroid adenoma and, less commonly, by parathyroid hyperplasia.
- Parathyroid adenomas are solitary, while hyperplasia typically is a multiglandular process.
- Skeletal manifestations of hyperparathyroidism include bone resorption, *osteitis fibrosa cystica,* and *brown tumors*. Renal changes include nephrolithiasis (stones) and nephrocalcinosis.
- Most cases of hyperparathyroidism are clinically silent because of early detection of hypercalcemia during routine blood testing.
- Secondary hyperparathyroidism is caused by hypercalcemia most often secondary to renal failure, and the parathyroid glands are hyperplastic.
- Malignancies are the most important cause of symptomatic hypercalcemia, which results from osteolytic metastases or release of PTH-related protein from nonparathyroid tumors.

HYPOPARATHYROIDISM

Hypoparathyroidism is far less common than hyperparathyroidism. The major causes of hypoparathyroidism include the following:

- *Surgical ablation*: The most common cause is inadvertent removal of parathyroids during thyroidectomy or other surgical neck dissections.