thereby stimulate parathyroid gland activity. In addition, loss of renal substance reduces the availability of α-1-hydroxylase necessary for the synthesis of the active form of vitamin D, which in turn reduces intestinal absorption of calcium (Chapter 9). Because vitamin D has suppressive effects on parathyroid growth and PTH secretion, its relative deficiency compounds the hyperparathyroidism in renal failure.

MORPHOLOGY

The **parathyroid glands in secondary hyperparathyroidism are hyperplastic.** As in primary hyperparathyroidism, the degree of glandular enlargement is not necessarily symmetric. Microscopically, the hyperplastic glands contain an increased number of chief cells, or cells with more abundant, clear cytoplasm (so-called water-clear cells) in a diffuse or multinodular distribution. Fat cells are decreased in number. **Metastatic calcification** may be seen in many tissues, including lungs, heart, stomach, and blood vessels.

Clinical Course. The clinical features of secondary hyperparathyroidism are usually dominated by the inciting chronic renal failure. Secondary hyperparathyroidism *per se* is usually not as severe or as prolonged as primary hyperparathyroidism, hence the skeletal abnormalities (referred to as *renal osteodystrophy)* tend to be milder. Control of the hyperparathyroidism allows the bony changes to regress significantly or disappear completely. The vascular calcification associated with secondary hyperparathyroidism may occasionally result in significant ischemic damage to skin and other organs, a process sometimes referred to as *calciphylaxis*. Patients with secondary hyperparathyroidism often respond to dietary vitamin D supplementation, as well as phosphate binders, which decrease the prevailing hyperphosphatemia.

In a minority of patients, parathyroid activity may become autonomous and excessive, with resultant hypercalcemia, a process that is sometimes termed *tertiary hyperparathyroidism*. Parathyroidectomy may be necessary to control the hyperparathyroidism in such patients.

KEY CONCEPTS

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.
- The clinical manifestations of hyperparathyroidism can be summarized as "painful bones, renal stones, abdominal groans, and psychic moans."
- Secondary hyperparathyroidism most often is caused by renal failure, which lowers serum calcium levels, resulting in reactive hyperplasia of parathyroid glands.
- 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 is hyperparathyroidism. Acquired hypoparathyroidism is almost always an inadvertent consequence of surgery; in addition, there are several genetic causes of hypoparathyroidism.

- *Surgically induced hypoparathyroidism* occurs with inadvertent removal of all the parathyroid glands during thyroidectomy, excision of the parathyroid glands in the mistaken belief that they are lymph nodes during radical neck dissection for some form of malignant disease, or removal of too large a proportion of parathyroid tissue in the treatment of primary hyperparathyroidism.
- *Autoimmune hypoparathyroidism* is often associated with chronic mucocutaneous candidiasis and primary adrenal insufficiency; this syndrome is known as autoimmune polyendocrine syndrome type 1 (APS1) and is caused by mutations in the *autoimmune regulator (AIRE)* gene. The syndrome typically presents in childhood with the onset of candidiasis, followed several years later by hypoparathyroidism and then adrenal insufficiency during adolescence. APS1 is discussed further under "Adrenal Glands."
- *Autosomal-dominant hypoparathyroidism* is caused by gain-of-function mutations in the *calcium-sensing receptor* (*CASR*) gene. Inappropriate CASR activity due to heightened calcium sensing suppresses PTH, resulting in *hypocalcemia* and *hypercalciuria*. Recall that loss-of-function CASR mutations are a rare cause of familial parathyroid adenomas.
- *Familial isolated hypoparathyroidism* (FIH) is a rare condition with either autosomal dominant or autosomal recessive patterns of inheritance. Autosomal-dominant FIH is caused by a mutation in the gene encoding PTH precursor peptide, which impairs its processing to the mature hormone. Autosomal-recessive FIH is caused by loss-of-function mutations in the transcription factor gene *glial cells missing-2* (*GCM2*), which is essential for development of the parathyroid.
- *Congenital absence* of parathyroid glands can occur in conjunction with other malformations, such as thymic aplasia and cardiovascular defects, or as a component of the 22q11 deletion syndrome. As discussed in Chapter 6, when thymic defects are present, the condition is called *DiGeorge syndrome.*

Clinical Features. The major clinical manifestations of hypoparathyroidism are related to the severity and chronicity of the hypocalcemia.

- The hallmark of hypocalcemia is *tetany*, which is characterized by *neuromuscular irritability*, resulting from

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