the parathyroid *calcium-sensing receptor gene* (*CASR*), which results in decreased sensitivity to extracellular calcium.

MORPHOLOGY

The morphologic changes seen in primary hyperparathyroidism include those in the parathyroid glands as well as those in other organs affected by elevated levels of PTH and calcium. Parathyroid **adenomas** are almost always solitary and, similar to the normal parathyroid glands, may lie in close proximity to the thyroid gland or in an ectopic site (e.g., the mediastinum). The typical parathyroid adenoma averages 0.5 to 5 gm and consists of a well-circumscribed, soft, tan to reddish-brown nodule invested by a delicate capsule. In contrast to primary hyperplasia, the glands outside the adenoma are usually normal in size or somewhat shrunken because of feedback inhibition by elevated levels of serum calcium. Microscopically, parathyroid adenomas are mostly composed of uniform, polygonal chief cells with small, centrally placed nuclei (Fig. 24-25). At least a few nests of larger oxyphil cells are present as well; uncommonly, adenomas are composed entirely of this cell type **(oxyphil adenomas)**. These may resemble Hürthle cell tumors in the thyroid. A rim of compressed, nonneoplastic parathyroid tissue, generally separated by a fibrous capsule, is often visible at the edge of the adenoma. Mitotic figures are rare, but it is not uncommon to find bizarre and pleomorphic nuclei even within adenomas (so-called **endocrine atypia**); this is not a criterion for malignancy. In contrast to the normal parathyroid parenchyma, adipose tissue is inconspicuous.

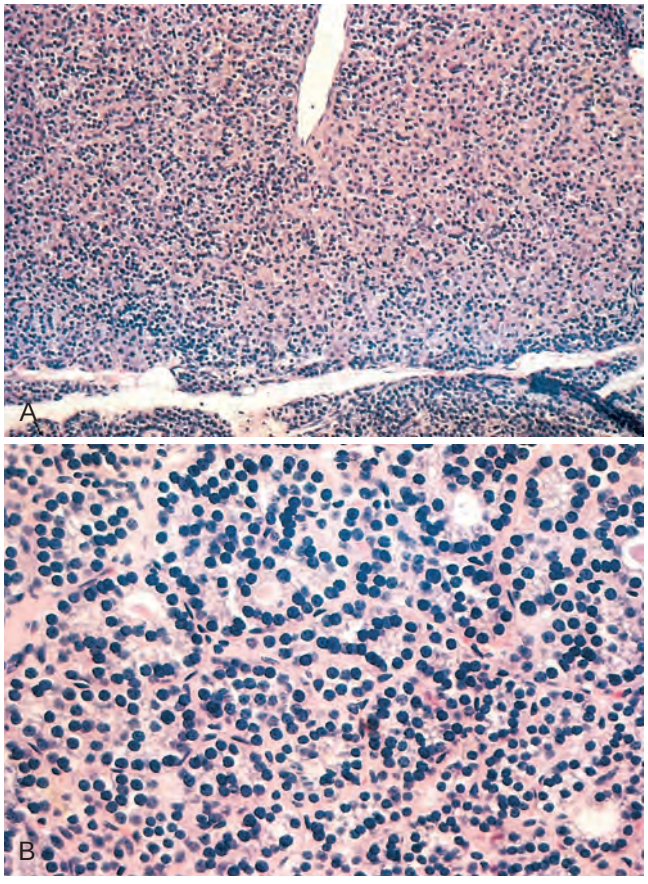

Figure 24-25 Parathyroid adenoma. **A,** Solitary chief cell parathyroid adenoma (low-power photomicrograph) revealing clear delineation from the residual gland below. **B,** High-power detail of a chief cell parathyroid adenoma. There is some slight variation in nuclear size but no anaplasia and some slight tendency to follicular formation.

Primary hyperplasia may occur sporadically or as a component of MEN syndrome. Although classically all four glands are involved, there is frequently asymmetry with apparent sparing of one or two glands, making the distinction between hyperplasia and adenoma difficult. The combined weight of all glands rarely exceeds 1 gm and is often less. 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 water-clear cells ("water-clear cell hyperplasia"). In many instances there are islands of oxyphils, and poorly developed, delicate fibrous strands may envelop the nodules. As in the case of adenomas, stromal fat is inconspicuous within hyperplastic glands.

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 gm in weight. The cells are usually uniform and resemble normal parathyroid cells, and are arrayed in nodular or trabecular patterns. The mass is usually enclosed by a dense, fibrous capsule. **Diagnosis of carcinoma based on cytologic detail is unreliable, and invasion of surrounding tissues and metastasis are the only reliable criteria.** Local recurrence occurs in one third of cases, and more distant dissemination occurs in another third.

Morphologic changes of hyperparathyroidism in the skeletal system (Chapter 26) and the urinary tract deserve special mention. Symptomatic, untreated primary hyperparathyroidism manifests with three interrelated skeletal abnormalities: osteoporosis, brown tumors and osteitis fibrosa cystica. The osteoporosis results in decreased bone mass, with preferential involvement of the phalanges, vertebrae and proximal femur. For unknown reasons, the increased osteoclast activity in hyperparathyroidism affects cortical bone (subperiosteal and endosteal surfaces) more severely than medullary bone. In medullary bone, osteoclasts tunnel into and dissect centrally along the length of the trabeculae, creating the appearance of railroad tracks and producing what is known as dissecting osteitis (Fig. 24-26). The marrow spaces around the affected surfaces are replaced by fibrovascular tissue. The correlative radiographic finding is a decrease in bone density or osteoporosis.

The bone loss predisposes to microfractures and secondary hemorrhages that elicit an influx of macrophages and an ingrowth of reparative fibrous tissue, creating a mass of reactive tissue, known as a **brown tumor** (Fig. 26-16, Chapter 26). The brown color is the result of the vascularity, hemorrhage, and hemosiderin deposition, and it is not uncommon for the lesions to undergo cystic degeneration. The combination of increased osteoclast activity, peritrabecular fibrosis, and cystic brown tumors is the hallmark of severe hyperparathyroidism and is known as **generalized osteitis fibrosa cystica (von Recklinghausen disease of bone**). Osteitis fibrosa cystica is now rarely encountered because hyperparathyroidism is usually diagnosed on routine blood tests and treated at an early, asymptomatic stage (see later).

PTH-induced hypercalcemia favors formation of **urinary tract stones** (nephrolithiasis) as well as calcification of the renal interstitium and tubules (nephrocalcinosis). Metastatic