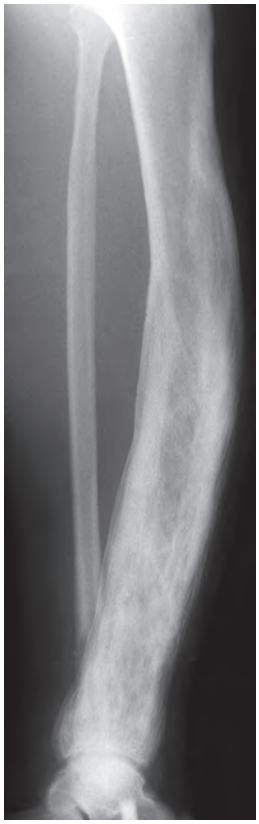

Figure 26-14 Severe Paget disease. The tibia is bowed and the affected portion is enlarged, sclerotic, and exhibits irregular thickening of both the cortical and cancellous bone.

heads, resulting in the development of severe *secondary osteoarthritis*. *Chalk stick-type fractures* are another frequent complication and usually occur in the long bones of the lower extremities. Compression fractures of the spine result in spinal cord injury and the development of kyphosis. The hypervascularity of Pagetic bone warms the overlying skin, and in severe polyostotic disease the increased blood flow acts like an arteriovenous shunt, leading to high-output heart failure or exacerbation of underlying cardiac disease.

A variety of tumor and tumor-like conditions develop in Pagetic bone. The benign lesions include giant cell tumor, giant cell reparative granuloma, and extra-osseous masses of hematopoietic tissue. The most dreaded complication is sarcoma, which occurs in less than 1% of all individuals with Paget disease, and in 5% to 10% of those with severe polyostotic disease. The sarcomas are usually osteosarcoma or fibrosarcoma, and they arise in Paget lesions in the long bones, pelvis, skull, and spine.

The diagnosis can frequently be made from the radiographic findings. Pagetic bone is typically enlarged with thick, coarsened cortices and cancellous bone (Fig. 26-14). Active disease has a wedge-shaped lytic leading edge that may progress along the length of the bone at a rate of 1 cm per year. Many affected individuals have elevated serum alkaline phosphatase levels but normal serum calcium and phosphorus.

In the absence of malignant transformation, Paget disease is usually not a serious or life-threatening disease. Most affected individuals have mild symptoms that are readily suppressed by treatment with calcitonin and bisphosphonates.

Rickets and Osteomalacia

Both rickets and osteomalacia are manifestations of vitamin D deficiency or its abnormal metabolism (and are detailed in Chapter 9). The fundamental defect is an impairment of mineralization and a resultant accumulation of unmineralized matrix. This contrasts with osteoporosis, in which the mineral content of the bone is normal and the total bone mass is decreased. *Rickets* refers to the disorder in children, in whom it interferes with the deposition of bone in the growth plates. *Osteomalacia* is the adult counterpart, in which bone formed during remodeling is undermineralized, resulting in predisposition to fractures.

Hyperparathyroidism

As discussed in Chapter 24, parathyroid hormone (PTH) plays a central role in calcium homeostasis through the following effects:

- Osteoclast activation, increasing bone resorption and calcium mobilization. PTH mediates the effect indirectly by increased RANKL expression on osteoblasts.
- Increased resorption of calcium by the renal tubules
- Increased urinary excretion of phosphates
- Increased synthesis of active vitamin D, 1,25$(OH)_2$-D, by the kidneys, which in turn enhances calcium absorption from the gut and mobilizes bone calcium by inducing RANKL on osteoblasts

The net result of the actions of PTH is an elevation in serum calcium, which, under normal circumstances, inhibits further PTH production. However, excessive or inappropriate levels of PTH can result from autonomous parathyroid secretion *(primary hyperparathyroidism)* or can occur in the setting of underlying renal disease *(secondary hyperparathyroidism)* (see also Chapter 24).

In either setting, **hyperparathyroidism leads to significant skeletal changes related to unabated osteoclast activity**. The entire skeleton is affected, although some sites can be more severely affected than others. PTH is directly responsible for the bone changes seen in primary hyperparathyroidism, but additional alterations contribute to the development of bone disease in secondary hyperparathyroidism. In chronic renal insufficiency there is inadequate 1,25-$(OH)_2$-D synthesis, which ultimately affects gastrointestinal calcium absorption. The hyperphosphatemia of renal failure also suppresses renal α1-hydroxylase, further impairing vitamin D synthesis; additional influences include metabolic acidosis and aluminum deposition in bone. As bone mass decreases, affected patients are increasingly susceptible to fractures, bone deformation, and joint problems. Fortunately, a reduction in PTH levels to normal can completely reverse the bone changes.

MORPHOLOGY

Symptomatic, untreated primary hyperparathyroidism manifests with three interrelated skeletal abnormalities: **osteoporosis, brown tumors** and **osteitis fibrosa cystica.** Osteoporosis is