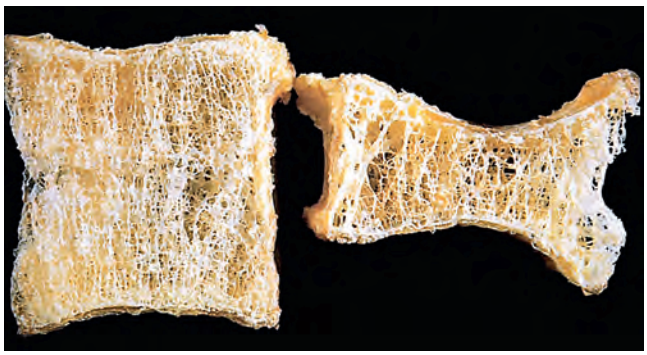

Figure 26-10 Osteoporotic vertebral body *(right)* shortened by compression fractures compared with a normal vertebral body *(left)*. Note that the osteoporotic vertebra has a characteristic loss of horizontal trabeculae and thickened vertical trabeculae.

osteoporosis. Decreased estrogen levels after menopause actually increase *both* bone resorption and formation but the latter does not keep up with the former, leading to **high-turnover** osteoporosis. The decreased estrogen appears to increase secretion of inflammatory cytokines by blood monocytes and bone marrow cells. These cytokines stimulate osteoclast recruitment and activity by increasing the levels of RANKL, diminishing the expression of OPG, decreasing osteoclast proliferation and preventing osteoclast apoptosis. Cytokines such as IL-6, TNF-α, and IL-1 have also been implicated in postmenopausal osteoporosis, either independently or as downstream mediators of estrogen signaling.

MORPHOLOGY

The hallmark of osteoporosis is histologically normal bone that is decreased in quantity. The entire skeleton is affected in postmenopausal and senile osteoporosis (Fig. 26-10), but certain bones tend to be more severely impacted. In postmenopausal osteoporosis the increase in osteoclast activity affects mainly bones or portions of bones that have increased surface area, such as the cancellous compartment of vertebral bodies. The trabecular plates become perforated, thinned, and lose their interconnections (Fig. 26-11), leading to progressive microfractures and eventual vertebral collapse. In senile osteoporosis the cortex is thinned by subperiosteal and endosteal resorption and the Haversian systems are widened. In severe cases the Haversian systems are so enlarged that the cortex mimics cancellous bone.

Clinical Course. The clinical manifestations of osteoporosis depend on which bones are involved. Vertebral fractures that frequently occur in the thoracic and lumbar regions are painful, and, when multiple, can cause significant loss of height and various deformities, including lumbar lordosis and kyphoscoliosis. Complications of fractures of the femoral neck, pelvis, or spine, such as pulmonary embolism and pneumonia, are frequent and result in 40,000 to 50,000 deaths per year.

Osteoporosis cannot be reliably detected in plain radiographs until 30% to 40% of the bone mass is lost, and measurement of blood levels of calcium, phosphorus, and alkaline phosphatase are not diagnostic. Osteoporosis is thus a difficult condition to screen for in asymptomatic people. The best estimates of bone loss, aside from biopsy (which is rarely performed), are specialized radiographic imaging techniques, such as dual-energy x-ray absorptiometry and quantitative computed tomography, both of which measure bone density.

The prevention and treatment of senile and postmenopausal osteoporosis includes exercise, appropriate calcium and vitamin D intake, and pharmacologic agents, most commonly bisphosphonates, which reduce osteoclast activity and induce apoptosis. Although menopausal hormone therapy has been used to prevent fracture, complications, particularly deep venous thrombosis and stroke, have prompted search for more selective estrogen receptor modulators. Denosumab, an anti-RANKL antibody, has shown promise in treating some forms of postmenopausal osteoporosis. Other novel investigational therapeutic approaches include anti-sclerostin antibodies and cathepsin K inhibitors.

Paget Disease (Osteitis Deformans)

Paget disease is a disorder of increased, but disordered and structurally unsound, bone mass. This unique skeletal disease can be divided into three sequential phases: (1) an initial osteolytic stage, (2) a mixed osteoclastic-osteoblastic stage, which ends with a predominance of osteoblastic activity and evolves ultimately into (3) a final burned-out quiescent osteosclerotic stage (Fig. 26-12).

Paget disease usually begins in late adulthood (average age at diagnosis, 70 years) and becomes progressively more common thereafter. An intriguing aspect is the striking geographic variation in its prevalence. Paget disease is relatively common in whites in England, France, Austria, regions of Germany, Australia, New Zealand, and the United States. In contrast, the disease is rare in the native populations of Scandinavia, China, Japan, and Africa. The exact incidence is hard to determine because many affected individuals are asymptomatic; it is estimated that 1% of the US population older than age 40 is affected and the prevalence in England is 2.5% for men and 1.6% for women 55 years or older. Recent surveys show that there has been a decrease in new cases in some countries over the past 25 to 30 years.

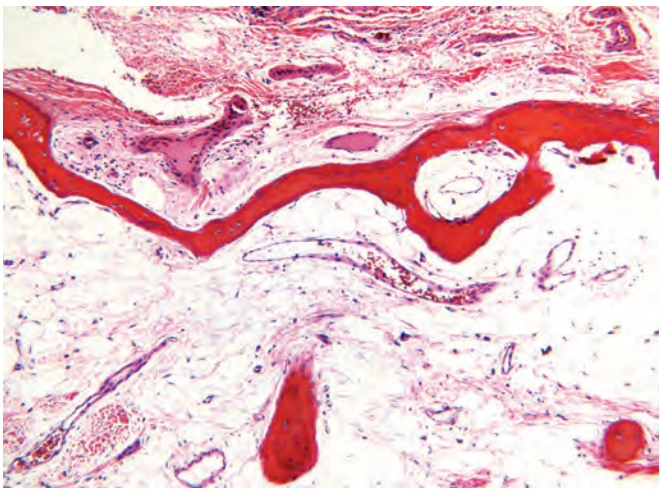

Figure 26-11 In advanced osteoporosis, both the trabecular bone of the medulla (*bottom*) and the cortical bone (*top*) are markedly thinned.