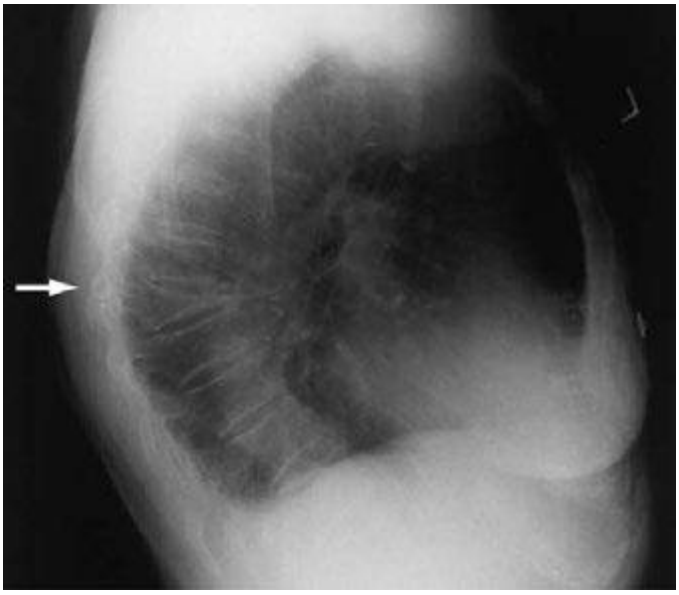

FIGURE 425-2 Lateral spine x-ray showing severe osteopenia and a severe wedge-type deformity (severe anterior compression).

There is also significant morbidity, with about 20–40% of survivors requiring long-term care, and many who are unable to function as they did before the fracture.

There are about 550,000 vertebral crush fractures per year in the United States. Only a fraction (estimated to be one-third) of them are recognized clinically, because many are relatively asymptomatic and are identified incidentally during radiography for other purposes (Fig. 425-2). Vertebral fractures rarely require hospitalization but are associated with long-term morbidity and a slight increase in mortality rates, primarily related to pulmonary disease. Multiple vertebral fractures lead to height loss (often of several inches), kyphosis, and secondary pain and discomfort related to altered biomechanics of the back. Thoracic fractures can be associated with restrictive lung disease, whereas lumbar fractures are associated with abdominal symptoms that include distention, early satiety, and constipation.

Approximately 400,000 wrist fractures and 135,000 pelvic fractures occur in the United States each year. Fractures of the humerus and other bones (estimated to be about 675,000 per year) also occur with osteoporosis; this is not surprising in light of the fact that bone loss is a systemic phenomenon. Although some fractures result from major trauma, the threshold for fracture is reduced for an osteoporotic bone (Fig. 425-3). In addition to bone density, there are a number of risk factors for fracture; the common ones are summarized in Table 425-1 Age, prior fractures (especially recent fractures), a family history of osteoporosis-related fractures, low body weight, smoking, and excessive alcohol use are all independent predictors of fracture. Chronic diseases with inflammatory components that increase skeletal remodeling such as rheumatoid arthritis, increase the risk of osteoporosis, as do

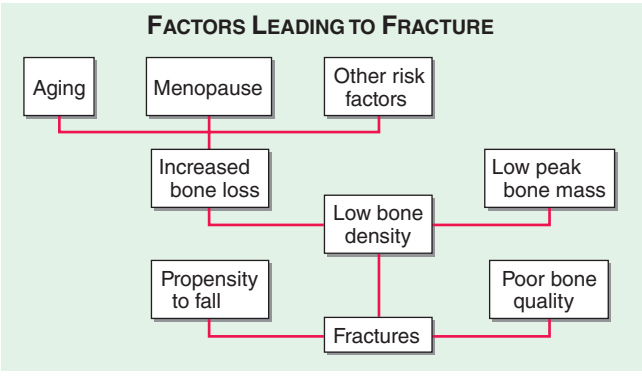

FIGURE 425-3 Factors leading to osteoporotic fractures.

diseases associated with malabsorption. Chronic diseases that increase the risk of falling or frailty, including dementia, Parkinson's disease, and multiple sclerosis, also increase fracture risk.

In the United States and Europe, osteoporosis-related fractures are more common among women than men, presumably due to a lower peak bone mass as well as postmenopausal bone loss in women. However, this sex difference in bone density and age-related increase in hip fractures is not as apparent in some other cultures, possibly due to genetics, physical activity level, or diet.

Fractures are themselves risk factors for future fractures (Table 425-1). Vertebral fractures increase the risk of other vertebral fractures as well as fractures of the peripheral skeleton such as the hip and wrist. Wrist fractures also increase the risk of vertebral and hip fractures. The risk for subsequent fractures is particularly high in the first several years after the first fracture, and the risk wanes considerably thereafter. Consequently, among individuals over age 50, any fracture should be considered as potentially related to osteoporosis regardless of the circumstances of the fracture. Osteoporotic bone is more likely to fracture than normal bone at any level of trauma, and a fracture in a person over 50 should trigger evaluation for osteoporosis. This often does not occur because postfracture care is not always well coordinated.

PATHOPHYSIOLOGY

BONE REMODELING

Osteoporosis results from bone loss due to age-related changes in bone remodeling as well as extrinsic and intrinsic factors that exaggerate this process. These changes may be superimposed on a low peak bone mass. Consequently, understanding the bone remodeling process is fundamental to understanding the pathophysiology of osteoporosis (Chap. 423). During growth, the skeleton increases in size by linear growth and by apposition of new bone tissue on the outer surfaces of the cortex (Fig. 425-4). The latter process is called *modeling*, a process that also allows the long bones to adapt in shape to the stresses placed on them. Increased sex hormone production at puberty is required for skeletal maturation, which reaches maximum mass and density in early adulthood. It is around puberty that the sexual dimorphism in skeletal size becomes obvious, although true bone density remains similar between the sexes. Nutrition and lifestyle also play an important role in growth, although genetic factors primarily determine peak skeletal mass and density. Numerous genes control skeletal growth, peak bone mass, and body size, as well as skeletal structure and density. Heritability estimates of 50–80% for bone density and size have been derived on the basis of twin studies. Although peak bone mass is often lower among individuals with a family history of osteoporosis, association studies of candidate genes (vitamin D receptor; type I collagen, the estrogen receptor [ER], and interleukin 6 [IL-6]; and insulin-like growth factor I [IGF-I]) and bone mass, bone turnover, and fracture prevalence have been inconsistent. Linkage studies suggest that a genetic locus on chromosome 11 is associated with high bone mass. Families with high bone mass and without much apparent age-related bone loss have been shown to have a point mutation in *LRP5*, a low-density lipoprotein receptor–related protein. The role of this gene in the general population is not clear, although a nonfunctional mutation results in osteoporosis-pseudoglioma syndrome, and *LRP5* signaling appears to be important in controlling bone formation. *LRP5* acts through the Wnt signaling pathway. With *LRP5* and Wnt activation, beta-catenin is translocated to the nucleus, allowing stimulation of osteoblast formation, activation, and life span as well as suppression of osteoclast activity, thereby increasing bone formation. The osteocyte product, sclerostin, is a negative inhibitor of Wnt signaling.

Genome-wide scans for low bone mass suggest multiple genes are involved, many of which are also implicated in control of body size.

In adults, bone remodeling, not modeling, is the principal metabolic skeletal process. Bone remodeling has two primary functions: (1) to repair microdamage within the skeleton to maintain skeletal strength and ensure the relative youth of the skeleton and (2) to supply calcium from the skeleton to maintain serum calcium. Remodeling may be