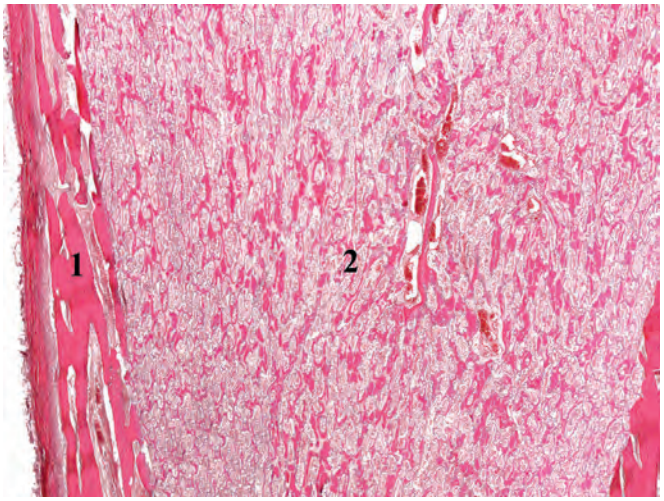

Figure 26-8 Section of proximal tibial diaphysis from a fetus with osteopetrosis. The cortex (1) is present, but the medullary cavity (2) is filled with primary spongiosa, which replaces the hematopoietic elements.

Clinical Features. Severe infantile osteopetrosis is autosomal recessive and usually becomes evident in utero or soon after birth. Fracture, anemia, and hydrocephaly are often seen, resulting in postpartum mortality. Affected individuals who survive into their infancy have cranial nerve defects (optic atrophy, deafness, and facial paralysis) and repeated—often fatal—infections because of leukopenia, despite extensive extramedullary hematopoiesis that can lead to prominent hepatosplenomegaly. The mild autosomal dominant form may not be detected until adolescence or adulthood, when it is discovered on x-ray studies performed because of repeated fractures. These individuals may also have mild cranial nerve deficits and anemia.

Osteopetrosis was the first genetic disease treated with hematopoietic stem cell transplantation, which is effective because osteoclasts are derived from hematopoietic precursors. The normal osteoclasts produced from donor stem cells reverse many of the skeletal abnormalities.

Diseases Associated with Defects in Degradation of Macromolecules

Mucopolysaccharidoses

The mucopolysaccharidoses, discussed in Chapter 5, are a group of lysosomal storage diseases that are caused by deficiencies in the enzymes that degrade dermatan sulfate, heparan sulfate, and keratan sulfate. The affected enzymes are mainly acid hydrolases. Mesenchymal cells, especially chondrocytes, normally degrade extracellular matrix mucopolysaccharides. In these diseases, mucopolysaccharides accumulate inside the chondrocytes, causing apoptotic death of the cells, and also in the extracellular space, resulting in structural defects in articular cartilage. Consequently, many of the skeletal manifestations of the mucopolysaccharidoses result from abnormalities in hyaline cartilage, including the cartilage anlage, growth plates, costal cartilages, and articular surfaces. Affected individuals are frequently of short stature and have chest wall abnormalities, and malformed bones.

KEY CONCEPTS

Developmental Disorders of Bone and Cartilage

Abnormalities in a single bone or a localized group of bones are called **dysostoses** and arise from defects in the migration and condensation of mesenchyme. They manifest as absent, supernumerary or abnormally fused bones. Global disorganization of bone and/or cartilage is called a **dysplasia**. Developmental abnormalities can be categorized by the associated genetic defect.

- Transcription factors: Homeobox genes, such as *HOXD13*, are frequently mutated in some cases of brachydactyly syndromes.
- Hormones and signal transduction molecules: *FGFR3* mutations are responsible for achondroplasia and thanatophoric dysplasia, both of which manifest as dwarfism.
- Structural proteins: Mutations in the genes for type I collagen underlie most types of osteogenesis imperfecta (brittle bone disease), characterized by defective bone formation and skeletal fragility.
- Metabolic enzymes and transporters: Mutations in *CA2* result in osteopetrosis (marble bone disease, in which bones are hard but brittle) and renal tubular acidosis.

Acquired Disorders of Bone and Cartilage

Osteopenia and Osteoporosis

The term osteopenia refers to decreased bone mass, and osteoporosis is defined as osteopenia that is severe enough to significantly increase the risk of fracture. Radiographically, osteoporosis is considered bone mass at least 2.5 standard deviations below mean peak bone mass in young adults and osteopenia as 1 to 2.5 standard deviations below the mean. Alternatively, the presence of an atraumatic or vertebral compression fracture signifies osteoporosis. The disorder may be localized to a certain bone or region, as in disuse osteoporosis of a limb, or may involve the entire skeleton, as a manifestation of a metabolic bone disease. Generalized osteoporosis, in turn, may be primary or secondary to a large variety of conditions (Table 26-4).

The most common forms of osteoporosis are the senile and postmenopausal types. An estimated one million Americans experience a fracture related to osteoporosis each year, at a cost of more than 14 billion dollars. Effective treatment and prevention are imperative. The following discussion relates largely to these dominant forms of osteoporosis.

Pathogenesis. Peak bone mass is achieved during young adulthood. Its magnitude is determined largely by hereditary factors, especially polymorphisms in the genes that influence bone metabolism (discussed later). Physical activity, muscle strength, diet, and hormonal state also make important contributions. Once maximal skeletal mass is attained, a small deficit in bone formation accrues with every resorption and formation cycle of each bone