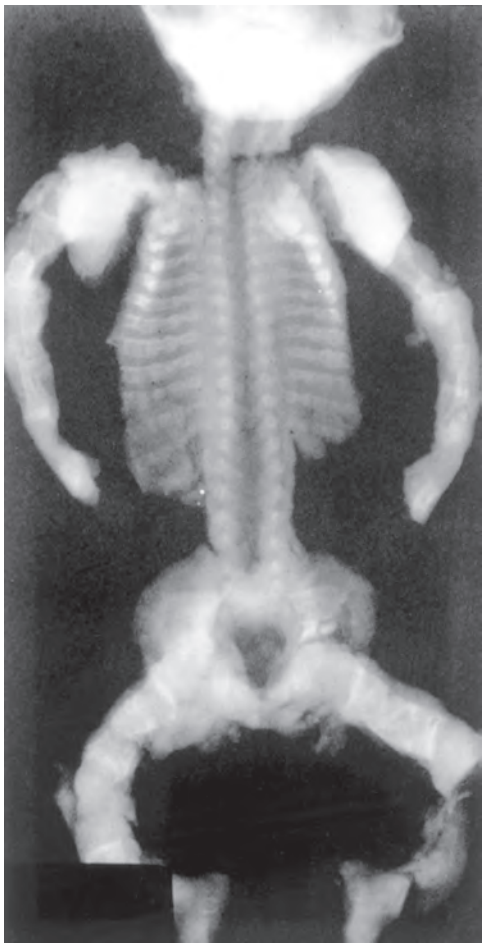

Figure 26-6 Skeletal radiograph of a fetus with lethal type 2 osteogenesis imperfecta. Note the numerous fractures of virtually all bones, resulting in accordion-like shortening of the limbs.

array of disorders of varying severity (Table 26-2). In the severe disorders, the type II collagen molecules are not secreted by the chondrocytes, and insufficient bone formation occurs. In the milder disorders there is reduced synthesis of normal type II collagen.

Defects in Metabolic Pathways (Enzymes, Ion Channels, and Transporters)

Osteopetrosis

Osteopetrosis, also known as *marble bone disease* and *Albers-Schönberg disease*, refers to a group of rare genetic diseases that are characterized by reduced bone resorption and diffuse symmetric skeletal sclerosis due to impaired formation or function of osteoclasts. The term *osteopetrosis* reflects the stone-like quality of the bones. However, the bones are abnormally brittle and fracture easily, like a piece of chalk. Osteopetrosis is classified into variants based on both the mode of inheritance and the severity of clinical findings.

Pathogenesis. Most of the mutations underlying osteopetrosis interfere with the process of acidification of the osteoclast resorption pit, which is required for the dissolution of the calcium hydroxyapatite within the matrix. Examples include autosomal recessive defects in the gene for the enzyme carbonic anhydrase 2 (*CA2*). CA2 is required by osteoclasts and renal tubular cells to generate protons from carbon dioxide and water. The absence of CA2 prevents osteoclasts from acidifying the resorption pit and solubilizing hydroxyapatite, and also blocks the acidification of urine by the renal tubular cells. Other forms of the disease are caused by mutations in *CLCN7*, which encodes a proton pump located on the surface of osteoclasts.

MORPHOLOGY

Due to deficient osteoclast activity, bones involved by osteopetrosis lack a medullary canal, and the ends of long bones are bulbous (Erlenmeyer flask deformity) and misshapen (Fig. 26-7). The neural foramina are small and compress exiting nerves. The primary spongiosa, which is normally removed during growth, persists and fills the medullary cavity, leaving no room for the hematopoietic marrow and preventing the formation of mature trabeculae (Fig. 26-8). Deposited bone is not remodeled and tends to be woven in architecture. Depending on the underlying genetic defect, the number of osteoclasts may be normal, increased, or decreased.

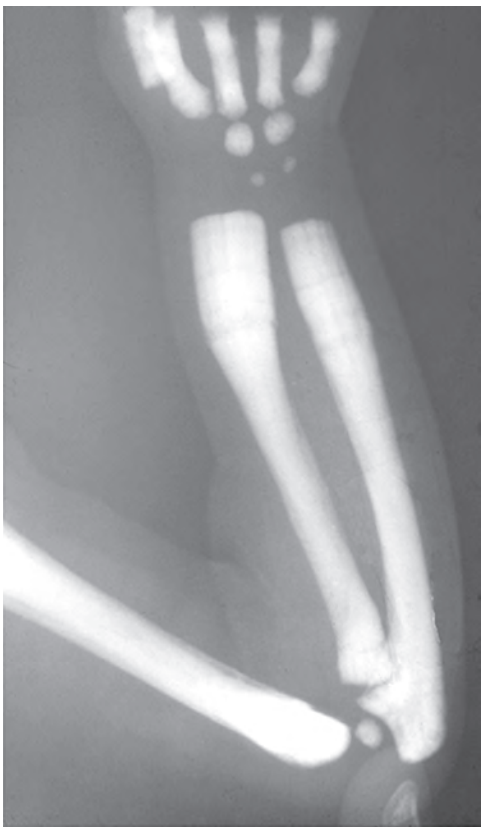

Figure 26-7 Radiograph of the upper extremity in an individual with osteopetrosis. The bones are diffusely sclerotic, and the distal metaphyses of the ulna and radius are poorly formed.