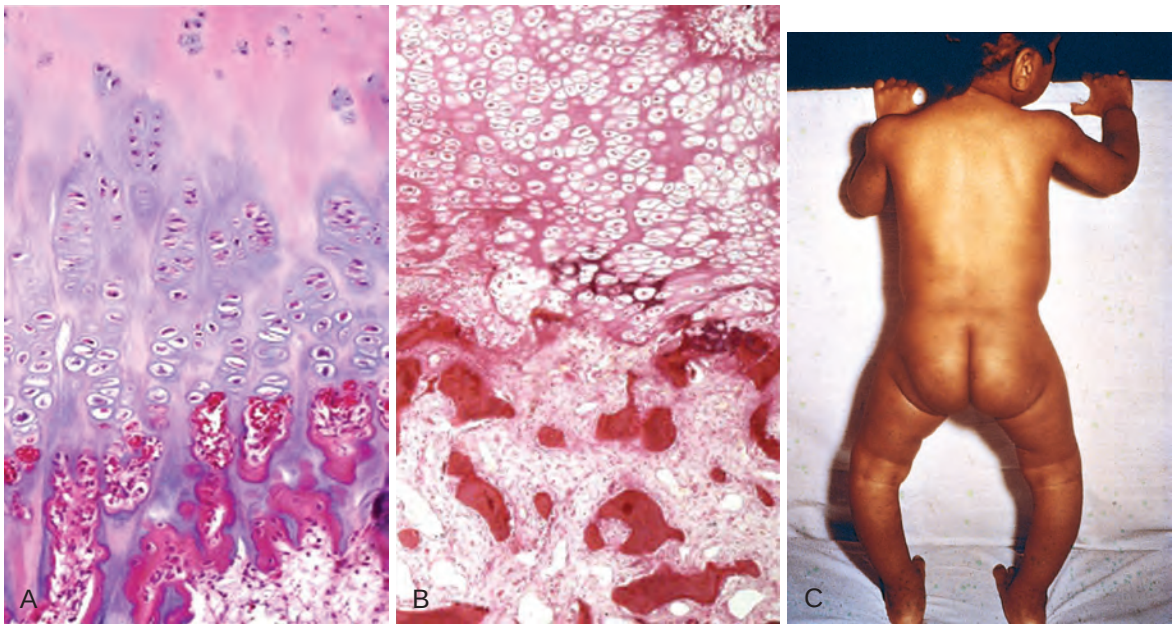

Figure 9-27 Rickets. **A,** Normal costochondral junction of a young child illustrating formation of cartilage palisades and orderly transition from cartilage to new bone. **B,** Detail of a rachitic costochondral junction in which the palisades of cartilage is lost. Darker trabeculae are well-formed bone; paler trabeculae consist of uncalcified osteoid. **C,** Rickets: note bowing of legs due to formation of poorly mineralized bones. (**B,** Courtesy Dr. Andrew E. Rosenberg, Massachusetts General Hospital, Boston, Mass.)

receptor and the formation of a complex with RXR. The complex binds to vitamin D response elements and activates the transcription of TRPV6 (a member of the transient receptor potential vanilloid family), which encodes a critical calcium transport channel.

- *Stimulation of calcium reabsorption in the kidney.* 1,25-dihydroxyvitamin D increases calcium influx in distal tubules of the kidney through the increased expression of TRPV5, another member of the transient receptor potential vanilloid family. TRPV5 expression is also regulated by PTH in response to hypocalcemia.
- *Interaction with PTH in the regulation of blood calcium.* Vitamin D maintains calcium and phosphorus at supersaturated levels in the plasma. The parathyroid glands have a key role in the regulation of extracellular calcium concentrations. These glands have a calcium receptor that senses even small changes in blood calcium concentrations. In addition to their effects on calcium absorption in the intestine and kidneys already described, both 1,25-dihydroxyvitamin D and PTH enhance the expression of RANKL (receptor activator of NF-κB ligand) on osteoblasts. RANKL binds to its receptor (RANK) located in preosteoclasts, thereby inducing the differentiation of these cells into mature osteoclasts (Chapter 26). Through the secretion of hydrochloric acid and activation of proteases such as cathepsin K, osteoclasts dissolve bone and release calcium and phosphorus into the circulation.
- *Mineralization of bone.* Vitamin D contributes to the mineralization of osteoid matrix and epiphyseal cartilage in both flat and long bones. It stimulates osteoblasts to synthesize the calcium-binding protein osteocalcin, involved in the deposition of calcium during bone development. Flat bones develop by intramembranous bone formation, in which mesenchymal cells differentiate directly into osteoblasts, which synthesize the collagenous osteoid matrix on which calcium is deposited. Long bones develop by endochondral ossification, through which growing cartilage at the epiphyseal plates is provisionally mineralized and then progressively resorbed and replaced by osteoid matrix that is mineralized to create bone (Fig. 9-27*A*).

When *hypocalcemia* occurs due to vitamin D deficiency (Fig. 9-28), PTH production is elevated, causing: (1) activation of renal 1α-hydroxylase, increasing the amount of active vitamin D and calcium absorption; (2) increased resorption of calcium from bone by osteoclasts; (3) decreased renal calcium excretion; and (4) increased renal excretion of phosphate. The latter is explained by increased synthesis in bone of fibroblast growth factor 23 (FGF-23), one of a group of agents known as *phosphatonins* that block phosphate absorption in the intestine and phosphate reabsorption in the kidney. Although a normal serum level of calcium may be restored, hypophosphatemia persists, impairing the mineralization of bone. Increased production of FGF-23 may be responsible for tumor-induced osteomalacia and some forms of hypophosphatemic rickets.

Deficiency States. The normal reference range for circulating 25-(OH)-D is 20 to 100 ng/mL; concentrations of less than 20 ng/mL constitute vitamin D deficiency.

Rickets in growing children and osteomalacia in adults are skeletal diseases with worldwide distributions. They may result from diets deficient in calcium and vitamin D, but an equally important cause of vitamin D deficiency is limited exposure to sunlight. This most often affects inhabitants of northern latitudes, but can even be a problem in tropical countries, in heavily veiled women, and in children born to mothers who have frequent pregnancies