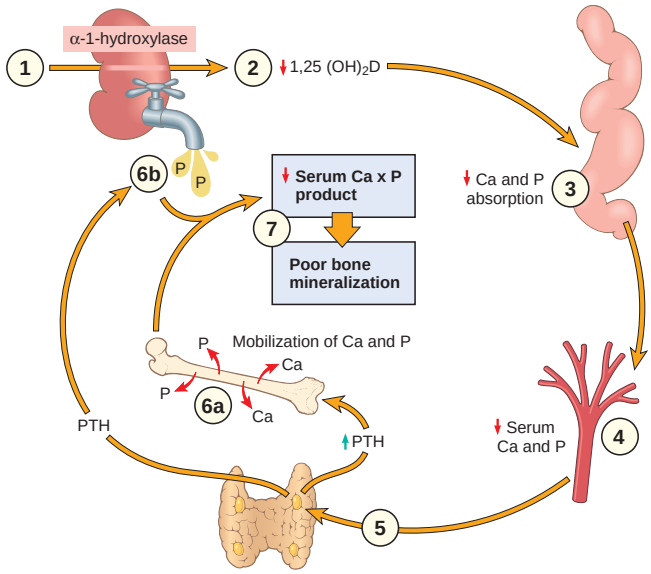

Figure 9-28 Vitamin D deficiency. There is inadequate substrate for the renal 1α-hydroxylase (1), yielding a deficiency of $1,25(OH)_2D$ (2), and deficient absorption of calcium and phosphorus from the gut (3), with consequently depressed serum levels of both (4). The hypocalcemia activates the parathyroid glands (5), causing mobilization of calcium and phosphorus from bone (6a). Simultaneously, the parathyroid hormone (PTH) induces wasting of phosphate in the urine (6b) and calcium retention. As a result, the serum levels of calcium are normal or nearly normal, but phosphate levels are low; hence, mineralization is impaired (7).

followed by lactation. In all of these situations, vitamin D deficiency can be prevented by a diet high in fish oils. Other, less common causes of rickets and osteomalacia include renal disorders causing decreased synthesis of 1,25-dihydroxyvitamin D, phosphate depletion, malabsorption disorders, and some rare inherited disorders. Although rickets and osteomalacia rarely occur outside high-risk groups, milder forms of vitamin D deficiency (also called *vitamin D insufficiency*), leading to an increased risk of bone loss and hip fractures, are quite common in older adults in the United States and Europe. Some genetically determined variants of the vitamin D receptors are also associated with an accelerated loss of bone minerals with aging and certain familial forms of osteoporosis (Chapter 26).

MORPHOLOGY

Vitamin D deficiency in both rickets and osteomalacia results in an **excess of unmineralized matrix**. The following sequence ensues in rickets:

- Overgrowth of epiphyseal cartilage due to inadequate provisional calcification and failure of the cartilage cells to mature and disintegrate
- Persistence of distorted, irregular masses of cartilage, which project into the marrow cavity
- Deposition of osteoid matrix on inadequately mineralized cartilaginous remnants
- Disruption of the orderly replacement of cartilage by osteoid matrix, with enlargement and lateral expansion of the osteochondral junction (Fig. 9-27*B*)
- Abnormal overgrowth of capillaries and fibroblasts in the disorganized zone resulting from microfractures and stresses on the inadequately mineralized, weak, poorly formed bone
- Deformation of the skeleton due to the loss of structural rigidity of the developing bones

The gross skeletal changes in rickets depend on the severity and duration of the process and, in particular, the stresses to which individual bones are subjected. During the nonambulatory stage of infancy, the head and chest sustain the greatest stresses. The softened occipital bones may become flattened, and the parietal bones can be buckled inward by pressure; with the release of the pressure, elastic recoil snaps the bones back into their original positions **(craniotabes)**. An excess of osteoid produces **frontal bossing** and a **squared appearance to the head**. Deformation of the chest results from overgrowth of cartilage or osteoid tissue at the costochondral junction, producing the **"rachitic rosary."** The weakened metaphyseal areas of the ribs are subject to the pull of the respiratory muscles and thus bend inward, creating anterior protrusion of the sternum **(pigeon breast deformity)**. When an ambulating child develops rickets, deformities are likely to affect the spine, pelvis, and tibia, causing **lumbar lordosis** and **bowing of the legs** (Fig. 9-27*C*).

In adults with **osteomalacia**, the lack of vitamin D deranges the normal bone remodeling that occurs throughout life. The newly formed osteoid matrix laid down by osteoblasts is inadequately mineralized, thus producing the excess of persistent osteoid that is characteristic of osteomalacia. Although the contours of the bone are not affected, the bone is weak and vulnerable to gross fractures or microfractures, which are most likely to affect vertebral bodies and femoral necks. The unmineralized osteoid appears as a thickened layer of matrix (which stains pink in hematoxylin and eosin preparations) arranged about the more basophilic, normally mineralized trabeculae.

Nonskeletal Effects of Vitamin D. As mentioned earlier, the vitamin D receptor is present in various cells and tissues that do not participate in calcium and phosphorus homeostasis. In addition, macrophages, keratinocytes, and tissues such as breast, prostate, and colon can produce 1,25-dihydroxyvitamin D. Within macrophages, synthesis of 1,25-dihydroxyvitamin D occurs through the activity of CYP27B located in the mitochondria. It appears that pathogen-induced activation of Toll-like receptors in macrophages causes increased expression of vitamin D receptor and CYP27B, leading to local synthesis of 1,25-dihydroxyvitamin D and activation of vitamin-D-dependent gene expression in macrophages and other neighboring immune cells. The net effect of this altered gene expression on the immune response remains to be determined. One recent clinical trial in patients with tuberculosis showed that vitamin D supplements increased lymphocyte counts, altered circulating levels of multiple cytokines and chemokines, and enhanced clearance of *Mycobacterium tuberculosis* from sputum, suggesting the vitamin D has complex effects that may, on the whole, be beneficial in this setting. Other regulatory effects of vitamin D in the innate and adaptive immune system have been reported, but the data are often contradictory. It has also been reported that low levels of 1,25-dihydroxyvitamin D (<20 ng/mL) are associated with a 30% to 50% increase in