hyperparathyroidism in that bone volume, turnover, and mineralization can vary independently.

- **Decreased production of secreted factors.** The kidney converts vitamin D to its active form (1,25-OH_2-vitamin D_3) and secretes the proteins BMP-7 and Klotho. Decreased vitamin D_3 results in hypocalcemia and contributes to secondary hyperparathyroidism. A hormonal feedback loop between kidney and bone that regulates calcium and phosphate homeostasis involves secreted BMP-7 and FGF-23 and the membrane protein Klotho. BMP-7, produced by renal renal tubular cells, induces osteoblast differentiation and proliferation, whereas FGF-23, made by osteocytes, acts on the kidney to regulate phosphate homeostasis and vitamin D production, which are dependent on production of membrane-bound Klotho in the kidney. The mechanism of action of Klotho is not understood. The levels of these signals change in chronic renal failure, interrupting the steady state and resulting in osteopenia and osteomalacia.

Other factors, such as aluminum from dialysis, oral phosphate binders, iron deposition, and diabetes mellitus may indirectly contribute to bone disease in the setting of renal failure.

KEY CONCEPTS

Acquired Disorders of Bone and Cartilage

- **Osteopenia** and **osteoporosis** represent histologically normal bone that is decreased in quantity, but osteoporosis is sufficiently severe to significantly increase risk of fracture. The disease is very common with marked morbidity and mortality from fractures. Multiple factors including peak bone mass, age, activity, genetics, nutrition and hormonal influences contribute to its pathogenesis.
- **Paget disease** is a disorder of locally increased but disordered bone. Typically asymptomatic, it is usually discovered incidentally. A mosaic pattern of mineralization is the histologic hallmark at the late stage of the disease. Genetic and possibly viral infectious etiologies have been proposed.
- **Osteomalacia** is characterized by bone that is insufficiently mineralized. In the developing skeleton, the manifestations are characterized by a condition known as rickets.
- **Hyperparathyroidism** arises from either autonomous or compensatory hypersecretion of PTH and can lead to **osteoporosis**, **brown tumors,** and **osteitis fibrosa cystica**. However, in developed countries, where early diagnosis is the norm, these manifestations are rarely seen.
- **Renal osteodystrophy** represents the constellation of bone abnormalities (osteopenia, osteomalacia, hyperparathyroidism, and growth retardation) from chronic renal failure. The mechanisms are complex but stem from decreased tubular, glomerular, and hormonal functions of the kidney.

Fractures

A fracture is defined as loss of bone integrity due to mechanical injury and/or diminished bone strength. Fractures are some of the most common pathologic conditions affecting bone. The following qualifiers describe fracture types and affect treatment:

- **Simple:** the overlying skin is intact.
- **Compound:** the bone communicates with the skin surface.
- **Comminuted:** the bone is fragmented.
- **Displaced:** the ends of the bone at the fracture site are not aligned.
- **Stress:** a slowly developing fracture that follows a period of increased physical activity in which the bone is subjected to repetitive loads
- "**Greenstick**": extending only partially through the bone, common in infants when bones are soft
- **Pathologic**: involving bone weakened by an underlying disease process, such as a tumor

Healing of Fractures

Bone has a remarkable capacity for repair. This process involves regulated expression of a multitude of genes and can be separated into overlapping stages with particular molecular, biochemical, histologic, and biomechanical features.

Immediately after fracture, rupture of blood vessels results in a hematoma, which fills the fracture gap and surrounds the area of bone injury. The clotted blood provides a fibrin mesh, sealing off the fracture site and at the same time creates a framework for the influx of inflammatory cells and ingrowth of fibroblasts and new capillaries. Simultaneously, degranulated platelets and migrating inflammatory cells release PDGF, TGF-β, FGF, and other factors, which activate osteoprogenitor cells in the periosteum, medullary cavity, and surrounding soft tissues and stimulate osteoclastic and osteoblastic activity. Thus, by the end of the first week, the major changes are organization of the hematoma, matrix production in adjacent tissues, and remodeling of the fractured ends of the bone. This fusiform and predominantly uncalcified tissue—called *soft tissue callus* or *procallus*—provides some anchorage between the ends of the fractured bones but not structural rigidity for weight bearing.

After approximately 2 weeks, the soft tissue callus is transformed into a *bony callus*. The activated osteoprogenitor cells deposit subperiosteal trabeculae of **woven bone** that are oriented perpendicular to the cortical axis and within the medullary cavity. In some cases, the activated mesenchymal cells in the soft tissues and bone surrounding the fracture line also differentiate into chondrocytes that make fibrocartilage and hyaline cartilage. The bony callus reaches its maximal girth at the end of the second or third week and helps to stabilize the fracture site. The newly formed cartilage along the fracture line undergoes enchondral ossification, forming a contiguous network of bone with newly deposited bone trabeculae in the medulla and beneath the periosteum. In this fashion, the fractured ends are bridged, and as it mineralizes, the stiffness and strength of the callus increases to the point that controlled weight bearing is tolerated (Fig. 26-18).

In the early stages of callus formation, an excess of fibrous tissue, cartilage, and woven bone is produced. As the callus matures and is subjected to weight-bearing