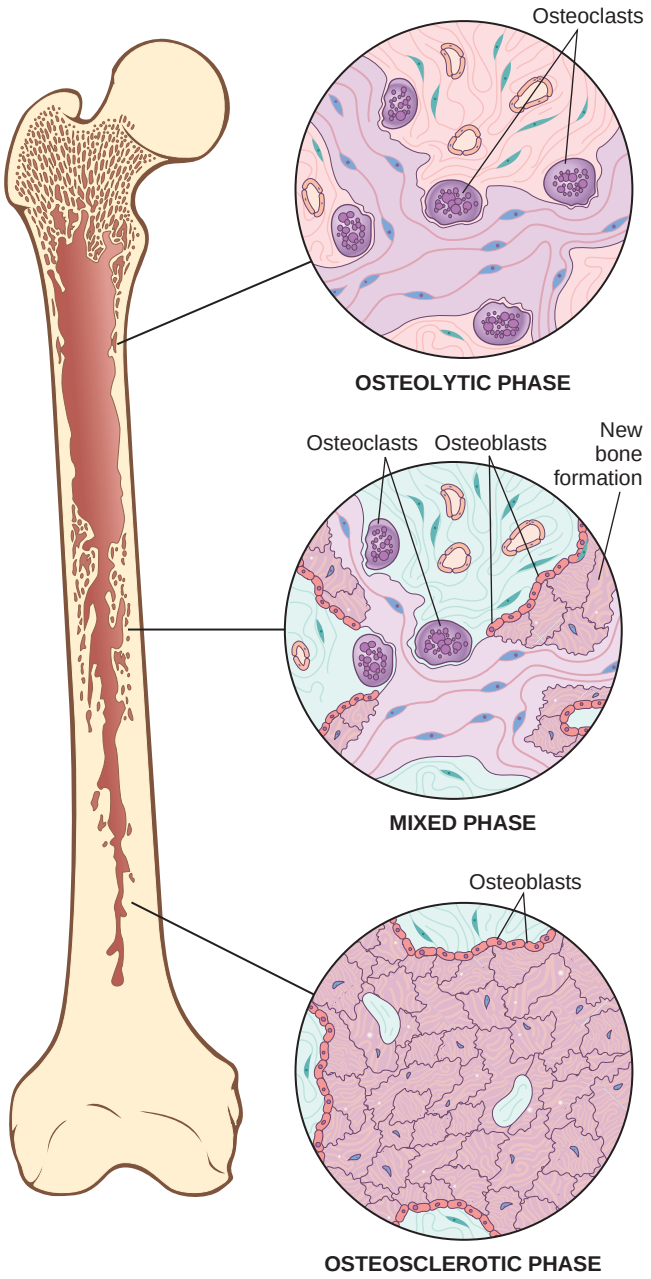

Figure 26-12 Diagrammatic representation of Paget disease of bone demonstrating the three phases in the evolution of the disease.

Pathogenesis. The cause of Paget disease remains uncertain, and current evidence suggests both genetic and environmental factors contribute. Forty percent to 50% of cases of familial Paget disease, and 5% to 10% of sporadic cases, harbor mutations in the *SQSTM1* gene. The net effect of these mutations is to increase the activity of NF-κB, which as already discussed increases osteoclast activity. Activating mutations in *RANK* and inactivating mutations in *OPG* account for some cases of juvenile Paget disease. Cell culture studies have show modulation of vitamin D sensitivity and IL-6 secretion by virally infected osteoclasts. These results suggest that chronic infection of osteoclast precursors by measles or other RNA viruses may play a role in the disease. The geographic distribution is also consistent with some environmental influence.

MORPHOLOGY

Paget disease shows remarkable histologic variation over time and from site to site. **The hallmark is a mosaic pattern of lamellar bone, seen in the sclerotic phase**. This jigsaw puzzle-like appearance is produced by unusually **prominent cement lines**, which join haphazardly oriented units of lamellar bone (Fig. 26-13). The findings during the other phases are less specific. In the initial lytic phase there are waves of osteoclastic activity and numerous resorption pits. The osteoclasts are abnormally large and have many more than the normal 10 to 12 nuclei; sometimes 100 nuclei are present. Osteoclasts persist in the mixed phase, but now many of the bone surfaces are lined by prominent osteoblasts. The marrow adjacent to the bone-forming surface is replaced by loose connective tissue that contains osteoprogenitor cells and numerous blood vessels. The newly formed bone may be woven or lamellar, but eventually all of it is remodeled into lamellar bone. As the mosaic pattern unfolds and the cell activity decreases, the periosseous fibrovascular tissue recedes and is replaced by normal marrow. In the end, the bone is composed of coarsely thickened trabeculae and cortices that are soft and porous and lack structural stability. These aspects make the bone vulnerable to deformation under stress; consequently, it fractures easily.

Clinical Course. Clinical findings are extremely variable and depend on the extent and site of the disease. Most cases are asymptomatic and are discovered as an incidental radiographic finding. Paget disease is *monostotic* in about 15% of cases and *polyostotic* in the remainder. The axial skeleton or proximal femur is involved in up to 80% of cases. Pain localized to the affected bone is common. It is caused by microfractures or by bone overgrowth that compresses spinal and cranial nerve roots. Enlargement of the craniofacial skeleton may produce *leontiasis ossea* (lion face) and a cranium so heavy that is difficult for the person to hold the head erect. The weakened Pagetic bone may lead to invagination of the skull base *(platybasia)* and compression of the posterior fossa. Weight bearing causes anterior bowing of the femurs and tibiae and distorts the femoral

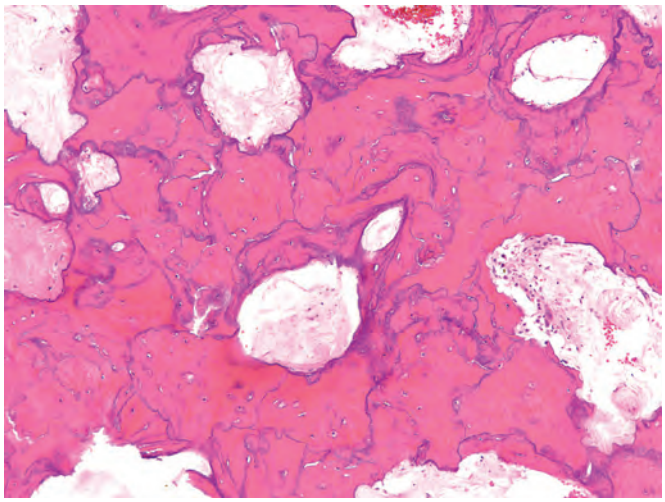

Figure 26-13 Mosaic pattern of lamellar bone pathognomonic of Paget disease.