composed of water (70%), type II collagen (10%), proteoglycans (8%), and chondrocytes. The collagen fibers enable the cartilage to resist tensile stresses and transmit vertical loads. The water and proteoglycans give hyaline cartilage its resistance to compression and have an important role in limiting friction. The chondrocytes synthesize the matrix as well as enzymatically digest it, with the half-life of the different components ranging from weeks (proteoglycans) to years (type II collagen). Chondrocytes secrete degradative enzymes in inactive forms and enrich the matrix with enzyme inhibitors. Diseases that destroy articular cartilage do so by activating the catabolic enzymes and decreasing the production of inhibitors, thereby accelerating the rate of matrix breakdown. Cytokines such as IL-1 and TNF trigger the degradative process; their sources include chondrocytes, synoviocytes, fibroblasts, and inflammatory cells. Destruction of articular cartilage by indigenous cells is an important mechanism in many joint diseases.

Osteoarthritis

Osteoarthritis, also called degenerative joint disease, is characterized by degeneration of cartilage that results in structural and functional failure of synovial joints. It is the most common type of joint disease. Annual costs from lost productivity and treatment of osteoarthritis in the United States are estimated to be more than 65 billion dollars. Although the term osteoarthritis implies an inflammatory disease, it is considered to be an intrinsic disease of cartilage in which chondrocytes respond to biochemical and mechanical stresses resulting in breakdown of the matrix.

In most instances osteoarthritis appears insidiously, without apparent initiating cause, as an aging phenomenon *(idiopathic* or *primary osteoarthritis)*. In these cases the disease is usually oligoarticular (affects few joints) but may be generalized. In about 5% of cases, osteoarthritis appears in younger individuals with some predisposing condition, such as joint deformity, a previous joint injury, or an underlying systemic disease such as diabetes, ochronosis, hemochromatosis, or marked obesity that places joints at risk. In these settings the disease is called *secondary osteoarthritis*. Gender has some influence on distribution. The knees and hands are more commonly affected in women and the hips in men.

Pathogenesis. **The lesions of osteoarthritis (OA) stem from degeneration of the articular cartilage and its disordered repair.** The articular cartilage contributes to the virtually frictionless movement of the joint while providing resistance to tension and compression, from type II collagen and proteoglycans, respectively, both synthesized by chondrocytes. Although historically OA was considered an inevitable process of wear and tear, this is an oversimplification, as the disease actually involves complex pathologic changes in chondrocytes and matrix.

The changes to chondrocytes can be divided into three phases: (1) chondrocyte injury, related to genetic and biochemical factors; (2) early OA, in which chondrocytes proliferate and secrete inflammatory mediators, collagens, proteoglycans, and proteases, which act together to remodel the cartilaginous matrix and initiate secondary inflammatory changes in the synovium and subchondral bone; and (3) late OA, in which repetitive injury and chronic inflammation lead to chondrocyte drop out, marked loss of cartilage, and extensive subchondral bone changes.

Virtually every extracellular component of articular cartilage is affected in OA. Collagen type II is degraded by matrix metalloproteinases. Although chondrocytes continuously synthesize and secrete proteoglycans during disease progression, degradation ultimately exceeds synthesis, and the composition of proteoglycans changes. Inflammatory cells are sparse, but cytokines and diffusible factors associated with other inflammatory conditions, particularly TGF-β (which induces matrix metalloproteinases), TNF, prostaglandins and nitric oxide, have been implicated in osteoarthritis.

Environmental and genetic influences contribute to the pathogenesis of OA. The major environmental factors relate to aging and biomechanical stress. The association with aging is strong; the prevalence of OA increases exponentially beyond the age of 50, and about 40% of people older than 70 are affected. Studies of families and twins have suggested that the risk of OA is the sum of multiple genes, each with a small effect. Candidate gene studies and genome-wide association studies show that OA is genetically heterogeneous.

MORPHOLOGY

In the early stages of osteoarthritis, the chondrocytes proliferate, forming clusters (so-called cloning). Concurrently, the water content of the matrix increases and the concentration of proteoglycans decreases. The normally horizontally arranged collagen type II fibers in the superficial zone are cleaved, yielding fissures and clefts at the articular surface (Fig. 26-39*A*). This manifests as a granular soft articular surface. Eventually, chondrocytes die and full-thickness portions of the cartilage are sloughed. The dislodged pieces of cartilage and subchondral bone tumble into the joint, forming loose bodies (joint mice). The exposed subchondral bone plate becomes the new articular surface, and friction with the opposing surface smooths and burnishes the exposed bone, giving it the appearance of polished ivory (bone eburnation) (Fig. 26-39*B*). There is rebuttressing and sclerosis of the underlying cancellous bone. Small fractures through the articulating bone are common, and the fracture gaps allow synovial fluid to be forced into the subchondral regions in a one-way, ball valve-like mechanism. The loculated fluid collection increases in size, forming fibrous-walled cysts. Mushroom-shaped osteophytes (bony outgrowths) develop at the margins of the articular surface and are capped by fibrocartilage and hyaline cartilage that gradually ossify. The synovium is usually only mildly congested and fibrotic, and may have scattered chronic inflammatory cells.

Clinical Course. Osteoarthritis is an insidious disease. Patients with primary disease are usually asymptomatic until they are in their 50s. If a young person has significant manifestations of osteoarthritis, a search for some underlying cause should be made. Characteristic symptoms include deep, achy pain that worsens with use, morning stiffness, crepitus, and limitation of range of movement. Impingement on spinal foramina by osteophytes results in cervical and lumbar nerve root compression and radicular pain, muscle