dehydration of cartilage that occurs with aging. The tidemark zone, separating the calcified cartilage from the radial zone, is invaded by capillaries. Chondrocytes initially are metabolically active and release a variety of cytokines and metalloproteinases, contributing to matrix degradation. In the later stages, this results in the penetration of fissures to the subchondral bone and the release of fibrillated cartilage into the joint space.

An imbalance between tissue inhibitors of metalloproteinases and the production of metalloproteinases may be operative in osteoarthritis. Subchondral bone remodels and increases in density. Cystlike bone cavities containing myxoid, fibrous, or cartilaginous tissue may form. Osteophytes or bony proliferations at the margin of joints at the site of the bone-cartilage interface may form at capsule insertions. Osteophytes contribute to joint motion restriction and are thought to be the result of new bone formation in response to the degeneration of articular cartilage, but the precise mechanism for their production remains unknown.

Several crystals have been identified in synovial fluid and other tissues from osteoarthritic joints, most notably calcium pyrophosphate dehydrate and hydroxyapatite. Although these crystals have potent inflammatory potential, their role in the pathogenesis of osteoarthritis remains unclear. Frequently, the crystals are asymptomatic and do not correlate with extent or severity of disease.

The diversity of risk factors predisposing to osteoarthritis suggests that many insults to the joints, including biomechanical trauma, chronic articular inflammation, and genetic and metabolic errors, can contribute to or trigger the cascade of events that results in the characteristic pathologic features described earlier. At some point, the cartilage degradative process becomes irreversible. With progressive changes in articular cartilage, joint mechanics become altered, perpetuating the degradative process.

CLINICAL PRESENTATION

Pain is the characteristic feature of osteoarthritis and the most common presenting symptom. Pain is usually worse with activity or weight bearing and better with rest. In later stages, pain may also occur at rest. Early in the disease course, pain tends to be transient, intermittent, and unpredictable. The pain may be characterized as severe, and its unpredictable nature is an extremely bothersome feature that limits activity and affects quality of life. With disease progression, pain tends to become constant but is reported to be less severe and have an aching quality. Other prominent symptoms, such as stiffness, gelling, fatigue, and sleep disturbance, often lead to functional limitation and disability.

Pain tends to localized to the specific joint involved, but it may be referred to a more distant site. The cause of pain is unclear but is likely to be heterogeneous. Pain may result from interactions among structural pathology; the motor, sensory, and autonomic innervation of the joint; and pain signal processing at the spinal and cortical levels. Specific individual and environmental factors also may be important. A subset of patients may have neuropathic pain.

Patient-specific factors may modify pain reception and pain reporting. Patients' affective status, such as depression, anxiety, and anger, may influence the level of pain reported. Their cognitive status, including pain beliefs, expectations, and memories of past pain, and their communication skills may determine how pain is perceived and reported. Studies have shown that demographic factors such as age, sex, socioeconomic status, race or ethnicity, and cultural background may affect pain reporting.

Patients may have stiffness, particularly after prolonged inactivity, but it is not a major feature of osteoarthritis and usually lasts for less than 30 minutes. Patients do not report systemic features such as fever.

Examination of an involved joint may reveal tenderness and bony enlargement. Joint effusion and soft tissue swelling may occur with knee involvement, but they tend to be intermittent. Persistent inflammation with joint warmth, erythema, effusion, and soft tissue swelling is usually not seen. Crepitus with movement, limitation of joint motion, and joint deformity, malalignment, and joint laxity or instability may be detected on evaluation. Joint deformity as manifested by lateral subluxation is fixed and not reducible. Muscle weakness and gait abnormalities may be seen.

Several subtypes of osteoarthritis have been identified. The nodal form involves the distal interphalangeal joints (DIPs), also known as Heberden's nodes, and the proximal interphalangeal joints (PIPs), also known as Bouchard's nodes. It is most common in middle-aged women, typically those with a strong family history among first-degree relatives. Erosive, inflammatory osteoarthritis is associated with prominent destructive changes, especially in the finger joints, and it is often quite symptomatic. Generalized osteoarthritis is characterized by involvement of the DIP, PIP, and first carpal-metacarpal joints, as well as the knees, feet, and hips.

For a deeper discussion of these topics, please see Chapter 256, "Approach to the Patient with Rheumatic Disease," and Chapter 262, "Osteoarthritis," in Goldman-Cecil Medicine, *25th Edition.*

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of osteoarthritis is based on the signs and symptoms previously outlined. Although there are characteristic radiographic features, they are not necessary to make the clinical diagnosis. Imaging may be used to confirm the diagnosis and exclude other diseases, but radiographs are insensitive and may not show findings early in the disease course. Despite radiographic findings of osteoarthritis, pain may have other sources, such as bursitis, tendonitis, or referred pain. For example, hip disease may manifest as knee pain.

Osteoarthritis must be distinguished from inflammatory joint diseases such as rheumatoid arthritis and the spondyloarthropathies. This is accomplished by identifying the characteristic pattern of joint involvement and the nature of the individual joint deformity. Joints commonly involved in osteoarthritis include the DIPs, PIPs, first carpal-metacarpal, cervical and lumbar spine facet joints, hips, knees, and first metatarsophalangeal joints. Involvement of the metacarpal phalangeal joints (MCPs), wrist, elbows, shoulders, and ankles is uncommon, except in the case of trauma, congenital disease, or coexisting endocrine or metabolic disease.