peripheral joints and, to a lesser degree, peripheral small joints. Pain ranges from moderate to incapacitating. The involved joints can be warm, erythematous, swollen, and tender. Arthritis usually has a sudden onset, lasts from a few days to 2 weeks, and does not cause joint damage. Episodes may suggest acute gout attacks. Several attacks occur per year. Synovial fluid from involved joints is not inflammatory and contains few white cells and no crystals. Joint involvement may actually represent inflammatory periarthritis or peritendinitis and not true arthritis. The recurrent, transient nature of the arthritis may suggest rheumatic fever, especially because patients with hyperlipoproteinemia may have an elevated erythrocyte sedimentation rate and elevated antistreptolysin O titers (the latter being quite common). Attacks of tendinitis, including the large Achilles and patellar tendons, may come on gradually and last only a few days or may be acute as described above. Patients may be asymptomatic between attacks. Achilles tendinitis and other joint manifestations often precede the appearance of xanthomas and may be the first clinical indication of hyperlipoproteinemia. Attacks of tendinitis may follow treatment with a lipid-lowering drug. Over time, patients may develop tendinous xanthomas in the Achilles, patellar, and extensor tendons of the hands and feet. Xanthomas have also been reported in the peroneal tendon, the plantar aponeurosis, and the periosteum overlying the distal tibia. These xanthomas are located within tendon fibers. Tuberous xanthomas are soft subcutaneous masses located over the extensor surfaces of the elbows, knees, and hands as well as on the buttocks. They appear during childhood in homozygous patients and after the age of 30 in heterozygous patients. Patients with elevated plasma levels of very-low-density lipoprotein (VLDL) and triglycerides (previously referred to as *type IV hyperlipoproteinemia*) may also have a mild inflammatory arthritis affecting large and small peripheral joints, usually in an asymmetric pattern, with only a few joints involved at a time. The onset of arthritis usually comes in middle age. Arthritis may be persistent or recurrent, with episodes lasting a few days or weeks. Some patients may experience severe joint pain or morning stiffness. Joint tenderness and periarticular hyperesthesia may also be present, as may synovial thickening. Joint fluid is usually noninflammatory and without crystals but may have increased white blood cell counts with predominantly mononuclear cells. Radiographs may show juxtaarticular osteopenia and cystic lesions. Large bone cysts have been noted in a few patients. Xanthoma and bone cysts are also observed in other lipoprotein disorders. The pathogenesis of arthritis in patients with familial hypercholesterolemia or with elevated levels of VLDL and triglycerides is not well understood. NSAIDs or analgesics usually provide adequate relief of symptoms when used on an as-needed basis.

Patients may improve clinically as they are treated with lipid-lowering agents; however, patients treated with an HMG-CoA reductase inhibitor may experience myalgias, and a few patients develop myopathy, myositis, or even rhabdomyolysis. Patients who develop myositis during statin therapy may be susceptible to this adverse effect because of an underlying muscle disorder and should be reevaluated after discontinuation of the drug. Myositis has also been reported with the use of niacin (Chap. 388) but is less common than myalgias.

Musculoskeletal syndromes have not clearly been associated with the more common mixed hyperlipidemias seen in general practice.

OTHER ARTHRITIDES

NEUROPATHIC JOINT DISEASE

Neuropathic joint disease (Charcot joint) is a progressive destructive arthritis associated with loss of pain sensation, proprioception, or both. Normal muscular reflexes that modulate joint movement are impaired. Without these protective mechanisms, joints are subjected to repeated trauma, resulting in progressive cartilage and bone damage. Today, diabetes mellitus is the most frequent cause of neuropathic joint disease (Fig. 397-1). A variety of other disorders are associated with neuropathic arthritis, including tabes dorsalis, leprosy, yaws, syringomyelia, meningomyelocele, congenital indifference to pain, peroneal muscular atrophy (Charcot-Marie-Tooth disease), and amyloidosis. An arthritis resembling neuropathic joint disease has been reported in

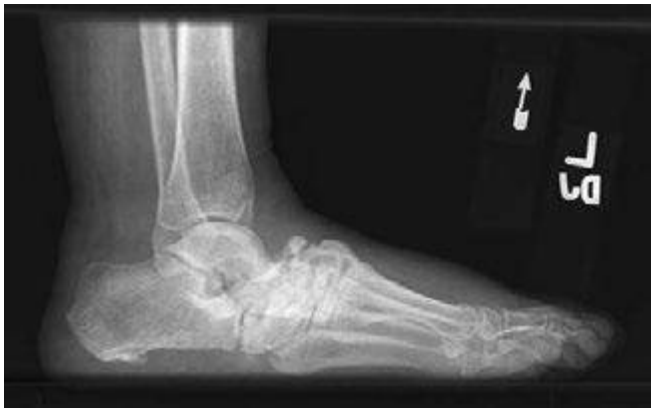

FIGURE 397-1 Charcot arthropathy associated with diabetes mellitus. Lateral foot radiograph demonstrating complete loss of the arch due to bony fragmentation and dislocation in the midfoot. *(Courtesy of Andrew Neckers, MD, and Jean Schils, MD; with permission.)*

patients who have received intraarticular glucocorticoid injections, but this is a rare complication and was not observed in one series of patients with knee osteoarthritis who received intraarticular glucocorticoid injections every 3 months for 2 years. The distribution of joint involvement depends on the underlying neurologic disorder (Table 397-2). In tabes dorsalis, the knees, hips, and ankles are most commonly affected; in syringomyelia, the glenohumeral joint, elbow, and wrist; and in diabetes mellitus, the tarsal and tarsometatarsal joints.

PATHOLOGY AND PATHOPHYSIOLOGY

The pathologic changes in the neuropathic joint are similar to those found in the severe osteoarthritic joint. There is fragmentation and eventual loss of articular cartilage with eburnation of the underlying bone. Osteophytes are found at the joint margins. With more advanced disease, erosions are present on the joint surface. Fractures, devitalized bone, intraarticular loose bodies, and microscopic fragments of cartilage and bone may be present.

At least two underlying mechanisms are believed to be involved in the pathogenesis of neuropathic arthritis. An abnormal autonomic nervous system is thought to be responsible for the dysregulated blood flow to the joint with subsequent resorption of bone. Loss of bone, particularly in the diabetic foot, may be the initial finding. With the loss of deep pain, proprioception, and protective neuromuscular reflexes, the joint is subjected to repeated microtrauma, resulting in ligamental tears and bone fractures. The injury that follows frequent intraarticular glucocorticoid injections is thought to be due to the analgesic effect of glucocorticoids, leading to overuse of an already damaged joint; the result is accelerated cartilage damage, although steroid-induced cartilage damage be more common in some other animal species than in humans. It is not understood why only a few patients with neuropathy develop clinically evident neuropathic arthritis.

CLINICAL MANIFESTATIONS

Neuropathic joint disease usually begins in a single joint and then becomes apparent in other joints, depending on the underlying neurologic disorder. The involved joint becomes progressively enlarged as a result of bony overgrowth and synovial effusion. Loose bodies may be palpated in the joint cavity. Joint instability, subluxation, and crepitus occur as the disease progresses. Neuropathic joints may develop rapidly, and a totally disorganized joint with multiple bony fragments may evolve within weeks or months. The amount of pain experienced

TABLE 397-2 DISORDERS ASSOCIATED WITH NEUROPATHIC JOINT DISEASE

Diabetes mellitus	Amyloidosis
Tabes dorsalis	Leprosy
Meningomyelocele	Congenital indifference to pain
Syringomyelia	Peroneal muscular atrophy