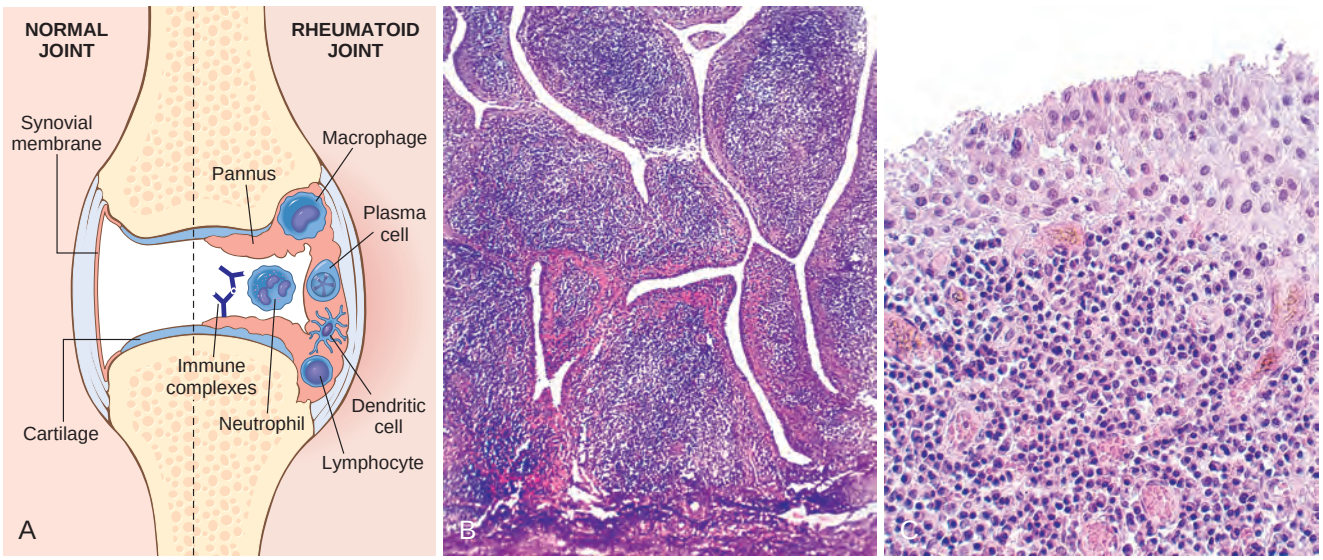

Figure 26-43 Rheumatoid arthritis. **A,** Schematic view of the joint lesion. **B,** Low magnification reveals marked synovial hypertrophy with formation of villi. **C,** At higher magnification, subsynovial tissue containing a dense lymphoid aggregate. (**A,** Modified from Feldmann M: Development of anti-TNF therapy for rheumatoid arthritis. Nat Rev Immunol 2:364, 2002.)

MORPHOLOGY

Joints. RA typically manifests as a symmetric arthritis principally affecting the small joints of the hand and feet. The synovium becomes grossly edematous, thickened, and hyperplastic, transforming its smooth contour to one covered by delicate and bulbous villi (Fig. 26-43*A, B*). The characteristic histologic features include (1) **synovial cell hyperplasia** and proliferation; (2) **dense inflammatory infiltrates** (frequently forming lymphoid follicles) of CD4+ helper T cells, B cells, plasma cells, dendritic cells, and macrophages (Fig. 26-43*C*); (3) increased vascularity due to angiogenesis; (4) fibrinopurulent exudate on the synovial and joint surfaces; (5) osteoclastic activity in underlying bone, allowing the synovium to penetrate into the bone and cause periarticular erosions and subchondral cysts. Together, the above changes produce a **pannus:** a mass of edematous synovium, inflammatory cells, granulation tissue, and fibroblasts that grows over the articular cartilage and causes its erosion. In time, after the cartilage has been destroyed, the pannus bridges the apposing bones to form a **fibrous ankylosis**, which eventually ossifies and results in fusion of the bones, called **bony ankylosis** (Fig. 26-41).

Skin. **Rheumatoid subcutaneous nodules** are the most common cutaneous lesions. They occur in approximately 25% of affected individuals, usually those with severe disease, and arise in regions of the skin that are subjected to pressure, including the ulnar aspect of the forearm, elbows, occiput, and lumbosacral area. Less commonly they form in the lungs, spleen, pericardium, myocardium, heart valves, aorta, and other viscera. Rheumatoid nodules are firm, nontender, and round to oval, and in the skin arise in the subcutaneous tissue. Microscopically they resemble necrotizing granulomas with a central zone of fibrinoid necrosis surrounded by a prominent rim activated macrophages and numerous lymphocytes and plasma cells (Fig. 26-44).

Blood Vessels. Affected individuals with severe erosive disease, rheumatoid nodules, and high titers of rheumatoid factor are at risk of developing **vasculitis** (Chapter 11). The acute necrotizing vasculitis involves small and large arteries. It may involve the pleura, pericardium or lung evolving into chronic fibrosing processes. Frequently, segments of small arteries such as vasa nervorum and the digital arteries are obstructed by an obliterating endarteritis resulting in peripheral neuropathy, ulcers, and gangrene. Leukocytoclastic vasculitis produces purpura, cutaneous ulcers, and nail bed infarction. Ocular changes such as uveitis and keratoconjunctivitis (similar to Sjögren syndrome, Chapter 6) may be prominent.

Clinical Course. In about half of patients, RA may begin slowly and insidiously with malaise, fatigue, and generalized musculoskeletal pain, likely mediated by IL-1 and TNF. After several weeks to months the joints become involved. The pattern of joint involvement varies, but it is generally symmetrical and the small joints are affected before the larger ones. Symptoms usually develop in the hands (metacarpophalangeal and proximal interphalangeal joints) and feet, followed by the wrists, ankles, elbows,

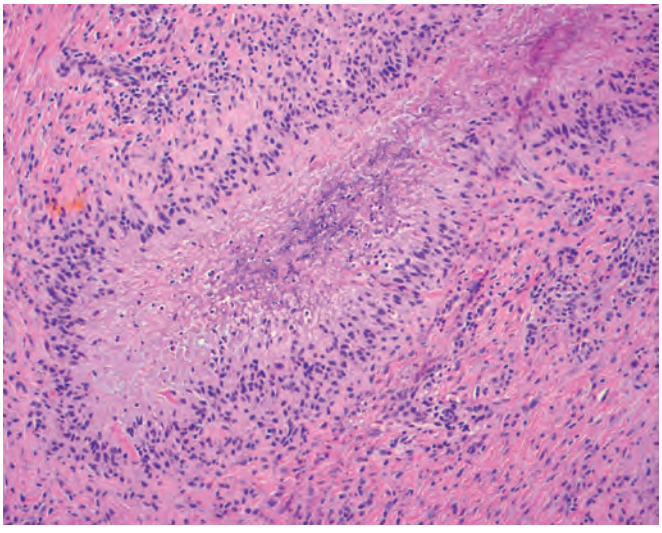

Figure 26-44 Rheumatoid nodule composed of central necrosis rimmed by palisaded histiocytes.