with genetic and environmental factors (e.g., smoking, periodontal disease), are involved in the development of RA.

RA pathogenesis occurs in stages. In the induction phase, the joint's environment enables recruitment of inflammatory cells. Cigarette smoke, bacterial products, viral components, and other environmental stimuli may amplify this process. A genetic propensity for autoreactivity may initiate an irreversible pathway to RA.

The destructive phase, which can be antigen dependent or independent, involves mesenchymal elements such as fibroblasts and synoviocytes. Bone erosions result from local differentiation and activation of osteoclasts, whereas cartilage damage appears to be caused by proteolytic enzymes produced by synoviocytes, macrophages, and synovial fluid neutrophils. Counter-regulatory mechanisms (e.g., soluble TNF-α receptors, suppressive cytokines, protease inhibitors, natural cytokine antagonists) are not produced in high enough levels, leading to a loss of tolerance.

Cytokines, which are hormone-like proteins that regulate many immune cell functions, have been implicated in synovial inflammation. The inflammatory milieu of the joint is dominated by proinflammatory factors produced by macrophages and fibroblasts, especially in the synovial intimal lining. IL-1, IL-6, TNF-α, and many other cytokines and chemokines have been identified at the protein and mRNA levels in the synovium.

Joint damage in RA results from proliferation of the synovial intimal layer that forms a pannus that overgrows, invades, and destroys adjacent cartilage and bone (Fig. 77-1). Fibroblast-like synoviocytes and macrophages are the predominant cellular components of the invading pannus of the synovium. Extracellular matrix damage resulting from synovial expansion is caused by several families of enzymes, including serine proteases, cathepsins, and matrix metalloproteinases.

For a deeper discussion of these topics, please see Chapter 264, "Rheumatoid Arthritis," in Goldman-Cecil Medicine, *25th Edition.*

CLINICAL PRESENTATION

Articular Manifestations

RA manifests with a symmetrical polyarthritis that typically starts with the small joints of the hands, wrists, and feet and progresses to the synovium of the shoulders, elbows, hips, knees, and ankles. Patients have an insidious onset of inflammatory pain, which is pain and stiffness that is worse with inactivity and is improved with movement. Prolonged morning stiffness, usually lasting more than 1 hour, is a classic feature of RA (Table 77-1). Any diarthrodial (synovial) joint may be involved, including the apophyseal (spinal), temporomandibular, and cricoarytenoid joints. Involved joints are swollen, warm, and tender, and they may have effusions. The synovium, which is normally a few cell layers thick, becomes palpable on examination (i.e., synovitis).

Without treatment, RA progresses in some patients to joint destruction and deformity. Erosive lesions of bone and cartilage

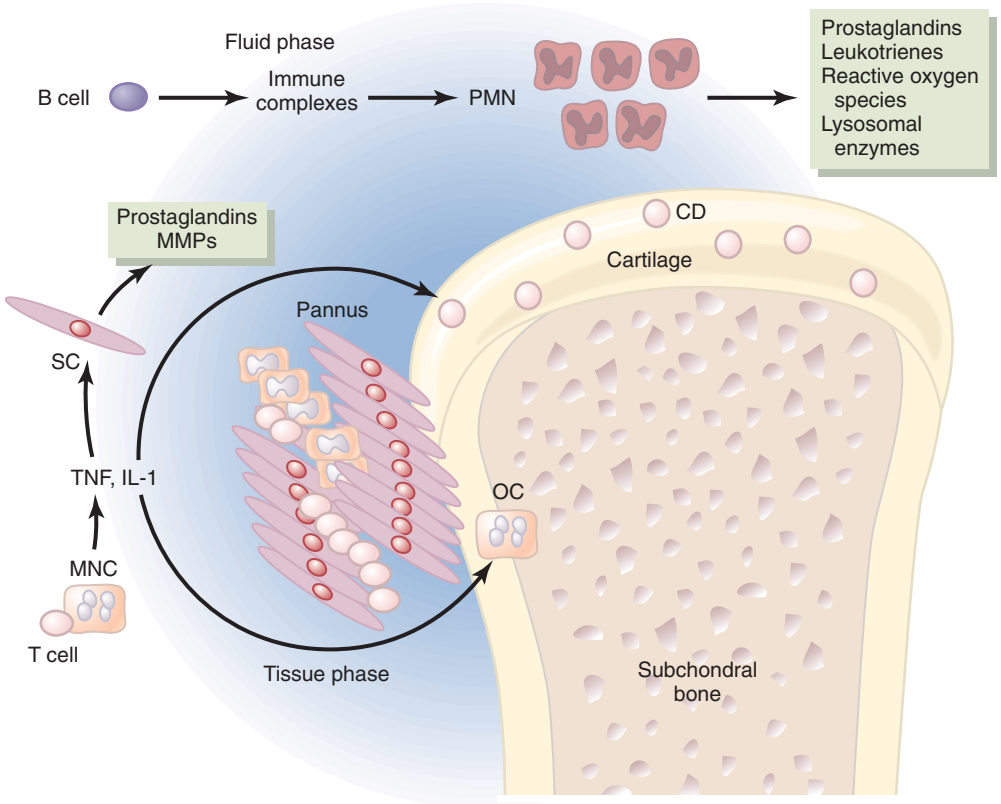

FIGURE 77-1 Pathogenetic events in rheumatoid arthritis. The proliferative synovial pannus invades at the bone-cartilage interface. Interleukin-1 (IL-1) and tumor necrosis factor-α (TNF) activate synovial cells (SC) to produce prostaglandins and matrix metalloproteinases (MMPs). In the synovial fluid, polymorphonuclear leukocytes (PMN), activated by immune complexes and complement, produce mediators of inflammation and destruction. CD, Chondrocytes; MNC, mononuclear cell; OC, osteoclast.