77

# Rheumatoid Arthritis

Rayford R. June and Larry W. Moreland

## DEFINITION AND EPIDEMIOLOGY

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory disorder of unknown cause that is characterized by symmetrical, polyarticular pain and swelling, morning stiffness, and fatigue. RA has a variable course, often with periods of exacerbations and, less frequently, true remissions. Outcomes range from rarely seen remitting disease to severe disease that produces disability and, for some patients, premature death.

Without treatment, most patients have progressive joint damage and significant disability within a few years. Since the introduction of tumor necrosis factor-α (TNF-α) inhibitors in the 1990s, there has been a change in the treatment paradigm, and many conventional and biologic therapies are now available to treat this previously debilitating chronic disease.

RA is a worldwide problem, with a prevalence of 0.5% to 1% of the adult population and an annual incidence of 0.03%. RA is three times more common among woman than men, and the disease affects individuals at any age, including infants and the elderly. However, it occurs most commonly in women between the ages of 40 and 50 years. RA is uncommon among men younger than 45 years of age, but the incidence rises steeply with increasing age. Among women, the incidence rises until age 45, plateaus until age 75, and then declines. Numerous studies have demonstrated increased mortality rates for patients with RA compared with the general population. The increased mortality rate is attributed to infectious and cardiovascular complications.

The underlying cause of RA (i.e., triggers in the susceptible host) is unknown. RA may consist of multiple diseases now defined by common clinical manifestations, and there may not be a single predominant mechanism of initiation or perpetuation. As for most autoimmune diseases, RA is thought to result from a complex interaction of genetic and environmental factors. Smoking, obesity, silica exposure, mineral oil, and organic solvents have been associated with the development of RA. Smoking has the most impact, particularly on anti–cyclic citrullinated peptide (CCP) antibody–positive disease.

An individual's genetic profile also plays a critical role in the susceptibility to and severity of RA. Supporting a genetic component, studies have revealed a 15% concordance in monozygotic twins that is approximately four times greater than the rate in dizygotic twins. The genes with the greatest impact lie in the class II major histocompatibility (MHC) locus, which accounts for one third of the genetic risk for RA. A specific sequence on the HLA-DR haplotype involved in antigen recognition is called the *shared epitope* because it is strongly associated with more severe RA and extra-articular manifestations. Although important, the shared epitope does not fully explain RA because it occurs in only 25% to 35% of the white population. The chance of developing RA in carriers is only 1 in 25.

The interplay between environmental and genetic factors is most clearly seen with the increased risk of RA associated with smoking and the MHC class II loci. The exact association between the two is unclear, but research has shown that the bacteria in periodontal disease, which are increased with smoking, can promote citrullination. Anti-CCP antibodies are associated with a more aggressive disease.

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

## PATHOLOGY AND PATHOGENESIS

RA is a heterogeneous disease with a complex pathogenesis. RA is a clinical diagnosis and a single phenotype, but the underlying genotype may not be unique. Instead, several signaling pathways may lead to the same clinical presentation.

Synovial inflammation characterizes RA, along with loss of tolerance, autoantibody production, bone destruction, and systemic inflammation. Many advances have been made in understanding the cell-cell interactions and cytokine signaling, but little is known about the loss of tolerance. Many of the insights into the pathogenesis of RA have resulted from analyzing the responses to cytokine inhibition (i.e., interleukin-1 [IL-1], TNF-α, and interleukin6 [IL-6]) and to specific T- and B-cell–directed therapies.

The process of synovial inflammation and proliferation may be initiated by an interaction between antigen-presenting cells (APCs) and $CD4^+$ T cells. APCs display complexes of class II MHC molecules and peptide antigens that bind to specific receptors on the T cells. Clonal expansion of T-cell subsets occurs with an appropriate second signal or costimulation delivered by the APC to the T cell. Activated $T_H1$ and $T_H17$ cell subsets appear to predominate in synovial tissues. These cell types stimulate synovial macrophages to secrete proinflammatory cytokines such as IL-1, TNF-α, and IL-6 to activate many inflammatory pathways.

The humoral immune system is also involved in the pathogenesis of RA. The autoantibodies found most frequently in patients with RA are immunoglobulin M (IgM) rheumatoid factor (RF) and anti-CCP. RF and anti-CCP are associated with aggressive, erosive RA (see Diagnosis and Differential Diagnosis) and are found in serum before the development of clinical RA. Although a causal link has not been confirmed, CCP antibodies, combined