Nonsteroidal anti-inflammatory drugs (NSAIDs) are often the initial treatment for rheumatoid arthritis. NSAID-induced inhibition of cyclooxygenase-2 (COX2) and cyclooxygenase-1 appears to correlate with clinical efficacy and toxicity, respectively. Newer NSAIDs with greater COX2 selectivity offer the promise of less toxic therapy.

Rheumatoid arthritis (RA) is a systemic autoimmune disorder that affects approximately 1% of the world’s population. Its peak incidence is found between the ages of 30 and 40 years, and its prevalence increases significantly with age, approaching 7% in the population over the age of 65 years. Rheumatoid arthritis is associated with an increased mortality rate principally due to an increase in deaths secondary to infection, gastrointestinal disease, respiratory conditions and renal failure. The clinical hallmark of RA is persistent inflammation, which principally affects synovial joints, resulting in a progressive, deforming polyarthritis in the majority of those affected. Symmetrical involvement of the small joints of the hands and feet is the most typical initial presentation, but any synovial joint of the appendicular and axial skeleton may become involved in patients with long-standing disease.

The course of RA is variable and may be quite mild in some cases, but most patients will experience some degree of deformity and disability. Although the prognosis of any individual patient cannot be predicted with certainty, the appearance of extra-articular features, an insidious onset to the disease, and an elevated rheumatoid factor often portend a poorer outcome.

No precise pathogenesis has been determined but the persistent inflammatory activity appears to be induced initially by T lymphocytes and then propagated by macrophages. The precipitating events resulting in T-lymphocyte activation are not known but once activated these cells secrete cytokines, which stimulate synovial plasma cells and macrophages. Activated macrophages within synovial tissue and fluid contribute to the further release of cytokines, accounting for the markedly elevated levels of interleukin 1, interleukin 6, and tumor necrosis factor alpha, which are found in the synovial fluid of patients with RA. The action of these proinflammatory cytokines on fibroblasts and chon-
Thus, the T lymphocyte appears critical to the destruction. An additional action of the proinflammatory cytokines is the induction of prostaglandin synthesis within the synovium, which further augments the intensity of the inflammatory response. Thus, the T lymphocyte appears critical to the induction of the inflammatory process through stimulation of humoral and cellular elements, whereas the macrophage and fibroblast appear to play a larger role in the perpetuation of inflammatory activity through persistent cytokine release.

As no cure exists for RA, the goals of current therapy are to decrease pain, minimize inflammation, and preserve joint function. Present therapeutic interventions are usually categorized as being either first-line or second-line therapy. The mainstay of first-line therapy continues to be nonsteroidal anti-inflammatory agents (NSAIDs). These agents provide symptomatic relief but do not appear to influence disease progression or attenuate cartilage destruction. Second-line agents, often referred to as disease-modifying agents, are usually employed when NSAIDs are insufficient to control symptoms and/or when evidence of joint destruction becomes evident. Treatment patterns over the past decade have favored the earlier institution and more aggressive use of second-line therapy; however, there is presently no consensus among rheumatologists as to when to initiate these agents. Given the considerable toxicity of existing second-line agents and the significant expense associated with novel therapies, the early and accurate identification of patients destined to have progressive disease is increasingly important. In addition to appropriately instituting and monitoring pharmacologic interventions, the clinician must give ongoing attention to patient education, continually emphasize the importance of range of motion exercises, and coordinate the important efforts of physical and occupational therapists.

In selecting a first-line agent, there are currently more than 20 NSAIDs, including aspirin, which are available to the clinician, some of which are listed in Table 1. These drugs were first shown to be of benefit in RA in 1965, when Fremont-Smith and Bayles demonstrated aspirin to be efficacious. Since that time, the use of aspirin has steadily declined as better tolerated and more convenient NSAIDs have become available. However, aspirin still represents the efficacy standard against which all other NSAIDs have been compared. Presently available NSAIDs should be considered of equivalent efficacy in the treatment of RA, because comparative clinical trials have failed to demonstrate any compelling differences. In an analysis of 61 controlled clinical trials, Heller et al. could find no significant difference in the efficacy of any particular NSAID that was not better explained by a variation in the study design and/or the dosing regimen. There is, however, a great deal of variability in the response of an individual patient to a specific NSAID. The choice of both initial and subsequent NSAID therapy remains entirely empiric at present, and a therapeutic trial should not be considered adequate unless the NSAID has been given in full doses for a period of not less than 2 to 4 weeks, depending on the half-life of the particular agent.

All NSAIDs have antipyretic, analgesic, and anti-inflammatory properties. They are highly protein-bound organic acids, which allows them to achieve high concentrations in inflamed, acidic tissues. Both their clinical efficacy and toxicity appear to be explained by their ability to block prostaglandin synthesis through inhibition of the enzyme cyclooxygenase (COX), which is also known as prostaglandin endoperoxide synthase. The prostaglandin pathway originates with the conversion of phospholipids to arachidonic acid by the enzyme phospholipase A2, a step that can be suppressed by the administration of glucocorticoids (Figure 1). Arachidonic acid is converted to the cyclic endoperoxides through the action of COX or, alternatively, it is converted to leukotrienes through the action of 5'-lipoxygenase. The cyclic endoperoxides are subsequently metabolized to eventually form thromboxane A2, the prostacyclins, and the proinflammatory prostaglandins, PGE1 and PGE2. Thus, the observed efficacy of NSAIDs appears to be the result of the impaired synthesis of proinflammatory prostaglandins. Present NSAIDs appear to have no direct effect on the action of 5'-lipoxygenase or on the synthesis of leukotrienes. A theoretical consequence of COX blockade is an enhanced synthesis of leukotrienes due to increased availability of arachidonic acid for the 5'-lipoxygenase pathway; however, the clinical impact of this phenomenon in most patients appears to be negligible.

**CYCLOOXYGENASE ISOFORMS**

Recently, 2 cyclooxygenase isoforms, cyclooxygenase-1 (COX1) and cyclooxygenase-2 (COX2), have been identified and appear to have distinct func-