

2006 marked the 40th year of publication for *The Annals*. Throughout its history, *The Annals* has provided important contributions to the development of clinical pharmacy. In 2007, we are continuing to publish articles reflecting on the history of clinical pharmacy through the eyes of practitioners, including those pioneering clinical pharmacy, as well as those who have more recently entered the profession and a well-established specialty. In addition, we are presenting articles and editorials from the early history of *The Annals* that have given direction and shape to the practice of clinical pharmacy (see page 1712).

Evolution of Clinical Pharmacy in the Practice of Rheumatology

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Pharmacists are valuable members of multidisciplinary teams caring for patients with rheumatic diseases, serving as clinicians, educators, and researchers. As pharmacotherapy specialists, pharmacists are essential in providing evidence-based clinical care and drug information and serving as patient care advocates to ensure safe and cost-effective drug therapy.

The need for clinical pharmacy services in the practice of rheumatology has expanded over the past 40 years and continues to evolve as new therapeutic targets are identified and novel technologies and pharmacologic approaches become available. Prior to this time, nonsteroidal antiinflammatory drugs (NSAIDs), colchicine, antimalarial drugs, corticosteroids, penicillamine, and sulfasalazine were available for clinical use.¹⁻³ In 1971, Nobel Prize winner John R Vane demonstrated that the mechanism of acetylsalicylic acid effects was inhibition of cyclooxygenase (COX)-mediated production of prostaglandins and thromboxanes. This research subsequently led to the development of additional NSAIDs, including selective COX-2 inhibitors,⁴ with wide variability in therapeutic⁵ and toxic⁶ responses associated with these agents. However, since NSAIDs provided only symptomatic relief, there

was a need for the use of disease-modifying antirheumatic drugs (DMARDs) that could affect the progression of disabling diseases such as rheumatoid arthritis.

By 1987, the effectiveness of methotrexate in the management of rheumatoid arthritis was so impressive that the Health and Public Policy Committee of the American College of Physicians developed guidelines for its use prior to Food and Drug Administration (FDA) approval for this indication.⁷ Oral gold, azathioprine, cyclosporine, cyclophosphamide, leflunomide, mycophenolate, and biological response modifiers (tumor necrosis factor [TNF] blockers, and interleukin-1 [IL-1] receptor antagonists) were also being used to manage an array of rheumatologic conditions during the 1980s into the 21st century.^{1,8} During that time, it was recognized that combination therapy with several of those DMARDs achieved an additive or synergistic response,⁹ and that early and aggressive intervention in patients with newly diagnosed rheumatoid arthritis could slow radiographic progression of joint damage, limit disability, increase the likelihood of remission, and decrease mortality.¹⁰⁻¹² Most recently, a recombinant form of urate oxidase (rasburicase)^{13,14} and agents that inhibit T-cell activation (abatacept)¹¹ or deplete B lymphocytes (rituximab)¹² are being used in rheumatology.

As we look toward the future, new biologic therapies that deplete or inhibit the activation of other inflammatory cells, proinflammatory/regulatory cytokines, chemokine-induced migration of inflammatory cells into the synovi-

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um, and osteoclast differentiation associated with erosions and/or osteoporosis are entering into clinical development.¹² Antigenic materials are being administered to patients in an attempt to tolerize (turn off) antigen-specific immune responses for prevention or treatment of immune-mediated diseases. Examples include vaccines composed of specific proteins from lymphocytes and antigen-presenting cells, oral dnaJPI (an epitope-specific peptide that induces proinflammatory T-cell response), and oral and injectable collagen. Bone marrow transplant and gene therapy with cytokine regulators, such as IL-1 receptor antagonists and TNF receptors, are additional research initiatives but are not yet practical options for clinical use.

Although the pharmacologic advances in the management of rheumatic conditions have occurred over centuries, the history of clinical pharmacy practice in this field is recent, limited, and evolving. With this rapid and innovative progress in drug development and research, pharmacists need to expand beyond their role in product distribution to become unique and vital members of the rheumatology team, with diverse clinical functions and expertise. Today's clinical pharmacists must continue to focus their efforts on the total healthcare model that includes clinical practice, research, policy-making, training, and education.

Clinical pharmacists have often participated in the management of various rheumatic conditions as part of routine care for internal medicine, ambulatory care, pediatric, and geriatric patients. Chronic musculoskeletal and autoimmune conditions, such as osteoarthritis, osteoporosis, gout, rheumatoid arthritis, systemic lupus erythematosus, and vasculitis are common in these practices, and clinical pharmacists provide valuable insight into medication-related issues. Among hospitalized patients cared for by internal medicine and rheumatology services, pharmacist-conducted patient interviews identified more drug-related problems (4.4 vs 2.4 per patient; $p < 0.01$) than were found through usual care procedures. Sixty-three percent of the pharmacist-identified problems were assessed to be of major clinical importance.¹⁵ In a long-term care facility, results from a small pilot trial of patients with osteoarthritis suggest that drug regimen review and interventions by pharmacists may also be associated with a reduction in costs, morbidity, and mortality.¹⁶

Pharmacovigilance in rheumatology is another essential role for clinical pharmacists. The need for pharmacotherapy specialists who understand research principles and post-marketing surveillance was evident in the late 1990s with the controversy surrounding selective COX-2 inhibitors that resulted in the removal of 2 members of this class, rofecoxib and valdecoxib, from the US market. Retrospective and prospective trials comparing selective COX-2 inhibitors with nonselective NSAIDs have reported conflicting results regarding the cardiovascular risks associated with these agents.¹⁷ Additionally, few prospective, random-

ized, controlled trials were of long enough duration or powered adequately to determine cardiovascular outcomes. Interpretation of results from retrospective, case-control and observational studies, and meta-analysis reports are limited in their applicability. Pharmacists with skills in research design who are capable of applying controversial research findings to the patient care setting are needed to safeguard the public. This becomes especially important with the relatively recent approval of several new classes of rheumatologic drugs that have limited long-term safety data.

Community and primary care pharmacists are also a valuable, yet often underutilized, resource. In addition to their ability to identify and resolve drug-related problems in ambulatory patients with musculoskeletal disorders,^{18,19} pharmacists also have the potential to play a greater role in the diagnosis and management of rheumatologic diseases, thereby filling existing gaps in current healthcare practices. This was evident in the results of a pilot study that used a simple screening questionnaire to identify individuals with knee osteoarthritis.²⁰ Community pharmacists were able to accurately identify undiagnosed osteoarthritis in more than 70% of individuals with knee pain. In a separate study that involved older adults with knee pain, enhanced pharmacy review and pharmacologic management by an experienced community pharmacist resulted in short-term improvements in physical function and pain, reduced use of NSAIDs, and greater patient satisfaction compared with the standard of care provided by general practitioners.²¹

Pharmacist involvement in clinical research of rheumatic diseases has been limited. Since 1992, only 6 grant applications were submitted to the Arthritis Foundation by pharmacists with a PharmD degree, none of which received funding. Although the funding of approximately 36% ($n = 64$) of grant applications from PharmD investigators by the National Institutes of Arthritis and Musculoskeletal and Skin Diseases is encouraging, this only accounted for 0.4% of all applications for 2006.

Pharmacy is still largely underrepresented in national rheumatology policy-making organizations. Currently, there are no pharmacists on the FDA Arthritis Drug Advisory Committee, and only one pharmacist serves on the United States Pharmacopeia's Rheumatology Expert Committee. Further, although in 2006, the number of pharmacists in the Association of Rheumatology Health Professionals increased more than that of other healthcare workers, pharmacists make up only 5% of the membership of this national organization of allied health professionals that fosters excellence in the care of people with rheumatic and musculoskeletal diseases.

The National Institutes of Health offers a pharmacy fellowship that includes training in rheumatology clinical practice and research. However, the American Pharmaceutical Association, the American Society of Health-System

Pharmacists, and the American College of Clinical Pharmacy were unaware of rheumatology specialty residencies, fellowships, board certifications, or clinical training opportunities for pharmacists. As the evolution of clinical pharmacy in the practice of rheumatology continues, greater efforts should be made to expand education, postgraduate training, and research opportunities to enhance pharmacy's presence in this field. With these efforts, pharmacists will have greater influence and impact on the care of patients with rheumatic diseases.

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