Drugs for Rheumatic Disease

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This book is dedicated to the memory of Carl M. Pearson, M.D. and to the high standards of scientific investigation, medical practice, and human relationships that he espoused.

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Foreword

For many years, the drug therapy of rheumatic diseases has been largely empirical. Drugs of plant origin, such as aspirin and colchicine, were the mainstay of therapy long before their mechanism of action became reasonably well established. Corticosteroids added a new dimension to the therapy of rheumatic diseases, although use of this class of compounds is limited by serious adverse effects. Next, the medicinal chemist, armed with the knowledge that aspirin inhibited the cyclooxygenase step in prostaglandin synthesis, was able to provide a large number of nonsteroidal antiinflammatory drugs. Unfortunately, these compounds do not significantly alter the destructive sequelae of these diseases, and most do not differ markedly from each other in their therapeutic and risk profiles.

We currently have a reasonable understanding of the immune system and the factors mediating inflammation. As more is learned about the disturbed control mechanisms of these systems in rheumatic diseases, a basis will be provided for discovering new types of drugs that may alter the course of the disease, not just control the symptoms. Levamisole, penicillamine, antimetabolites, and cyclosporins are available as prototypes. With the help of advances in biotechnology, a variety of peptides with immunomodulatory activity will become available for careful clinical evaluation of their therapeutic potential. Similarly, compounds that inhibit tissue-destroying enzymes (e.g., collagenase and elastase) are being developed by pharmaceutical companies and may complement therapy with enzymes such as superoxide dismutase.

The latest information about the agents to treat rheumatic diseases will be found in this book by Harold Paulus and his colleagues. Based on the clinical literature and their own clinical skills and experience, the authors provide not only detailed scientific information about each compound but also a rational approach to the selection and use of what at times may seem a bewildering array of drugs for rheumatic diseases.

Daniel L. Azarnoff, M.D., F.A.C.P.

Preface

Drugs have assumed an important role in the treatment of rheumatic diseases. Although gout is the only rheumatic disease for which drug therapy is almost always successful, both the quality and the length of life have improved for patients with systemic lupus erythematosus, vasculitis, rheumatoid arthritis, and other autoimmune rheumatic conditions, to a considerable extent due to increased skill in the use of drugs. The pharmaceutical industry has recognized this change and responded with a multitude of improved nonsteroidal antiinflammatory compounds. Increased knowledge of the molecular biology of inflammatory and immune responses, coupled with the ability of pharmaceutical chemists to synthesize almost any desired compound, points toward increasing precision in our ability to modify immune and inflammatory responses in the not-too-distant future.

Drugs for Rheumatic Disease is intended to provide a coherent review of drugs used to treat rheumatic diseases, emphasizing clinically important aspects of their pharmacology, toxicity, and efficacy. The first two chapters introduce some concepts and constraints in the treatment of chronic inflammatory diseases, and define the pharmacokinetic principles and terminology used throughout the book. Subsequent chapters discuss important drugs and drug groupings. Drugs for Rheumatic Disease can be read or scanned as a comprehensive overview of the field, or used as a reference to obtain specific information about a particular drug. Extensive literature citations provide leads to pertinent scientific publications.

The latest information about the agents to treat rheumatic diseases will be found in this Hard. M.D. John Hard E. Paulus, M.D. John Hard E. Paulus, M.D. John Hard E. Paulus and their own

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Concepts and Targets for Drug Treatment of Chronic Rheumatic Diseases

Harold E. Paulus

The rheumatic diseases are characterized by chronicity and by misdirected and inadequately controlled inflammation that causes tissue destruction and loss of function. Examples include rheumatoid arthritis, in which disability results from loss of joint function, systemic lupus erythematosus with nephritis, in which misdirected inflammation may lead to loss of renal function, progressive systemic sclerosis, in which chronic progressive fibrosis may produce disability due to loss of pulmonary function, and polymyositis, in which inflammation of muscle fibers causes progressive weakness.

Amplification of normal inflammation by products

of injured tissue

Because of the prominence of the manifestations of inflammation in most of these diseases, we tend to focus on the inflammatory process and its consequences to the exclusion of other considerations. Vast diagrams and tables attempt to codify and define the complex interrelationships of the various structural, cellular, and biochemical constituents of the inflammatory response. It is comfortable to deal with a specific segment of the inflammatory response and to become expert about it, e.g., kinins, prostaglandins, leukotrienes, granulocytes,

platelets, etc. However, since the interaction of the disease with the patient is not limited by the boundaries of our knowledge, it is not surprising that we are usually unsuccessful when we attempt to treat only a kinin, a prostaglandin, a histamine, or a complement component.

In this chapter, we will present general concepts regarding the inflammatory process and chronic inflammatory disease, categorize drugs for rheumatic diseases according to their potential effects on the inflammatory process, and identify target areas toward which we may profitably direct our future efforts.

INFLAMMATION AND INFLAMMATORY DISEASES

Inflammation is the complex, multifaceted reaction of the living organism to tissue injury by which the causative factor is isolated or eliminated, the injured tissue is repaired, and normal function is restored. It is the normal protective response to any noxious stimulus that threatens the well-

Table 1-1. Sequence of Events in Normal Inflammation

Prime cause (etiology)
Mediators of initial tissue injury
Initial tissue injury
Normal protective inflammatory response
Eradication of prime cause
Healing of injured tissue (restoration of function)

being of the host. Because of its critical importance in the perpetual need to maintain the integrity of the individual against the insults and attacks of the environment, multiple levels and pathways of inflammatory response have developed. Many of these levels and pathways have been identified and studied, but it is likely that many others have not yet been discovered.

The events in normal inflammation can be considered as a sequence of interrelated steps (Table 1-1). The process is initiated by an etiologic factor or "prime cause." In some cases the prime cause may produce tissue injury directly, whereas in other cases intermediary events are initiated by the apparently innocuous prime cause, and these events produce the initial tissue injury. When tissue injury has occurred, the normal protective inflammatory response ensues. This response may involve only a few pathways of the inflammatory cascade or may involve many pathways. In any event, the inflammatory response progresses toward elimination or isolation of the cause of tissue injury and culminates in repair and restoration of function to injured tissue. When the healing process has been completed, the inflammatory response terminates spontaneously and awaits another challenge.

When tissue injury is caused by a single nonrecurring event, such as mechanical trauma, the inflammatory and reparative processes progress smoothly from the injury to the healed state. In this situation, the inflammatory process is truly beneficial and provides an example of complex homeostatic mechanism restoring the affected tissue to its former healthy state. However,

Table 1-2. Sequence of Events in Chronic Inflammatory Disease

Prime cause (etiology)
Mediators of initial tissue injury
Initial tissue injury
Normal protective inflammatory response
Persistence of prime cause
Amplification of normal inflammation by products
of injured tissue
Chronic inflammation
Progressive tissue injury
Manifestions of disease (loss of function)

if tissue injury is caused by a self-replicating parasite, the ensuing inflammatory response is more complex because some form of tissue injury will continue to occur until the agent itself is eliminated. Clearly, although more prolonged and complex, the inflammation produced in response to a bacterial infection leads to rapid healing and restoration of normal function as soon as the causative bacteria are destroyed, whether by the normal immune response or by antibiotic therapy.

If the prime cause cannot be destroyed or readily eliminated, the host may attempt to isolate it from the rest of the body by forming a granuloma, as is seen in pulmonary tuberculosis and in silicosis, or a gumma, as in syphilis. For example, the calcified Ghon's complex may contain viable but encapsulated tubercle bacilli, functionally isolated from the host.

In a situation in which the prime cause cannot be eradicated or isolated, tissue injury continues to occur, both as a result of the direct action of the prime cause or its mediators of initial tissue injury and due to injurious products of the inflammatory response itself (Table 1-2). In this situation, inflammation cycles back on itself, continually producing more tissue injury, and becomes self-perpetuating. The chronic inflammation that develops is responsible for the manifestations of disease and ultimately for loss of function. The specific manifestations may depend on the organ or organ system in which the inflammation is loand to become expert about it, e.g., batch prostaglandins, leitkotrienes, granulocyte

Although we are used to dealing with chronic inflammatory diseases of unknown etiology, it is easier to understand the concepts expressed above if we use an historical example. Fifty years ago, syphilis was viewed as a chronic inflammatory disease of uncertain etiology. It had a variable course, many possible manifestations, and multiple organ system involvement. Spontaneous remissions occurred, sometimes accompanied by permanent cure and sometimes terminated by a recurrence of further manifestations of the disease. A characteristic tissue lesion was sometimes produced, and a typical but nonspecific antibody response could be detected in the serum of patients with the disease. Thus, syphilis appeared to be a chronic inflammatory disease in which aberrant immune responses probably played a major role. In an attempt to treat this devastating disease, a variety of nonspecific therapies were applied with variable success. The isolation of Treponema organisms from some of the lesions of syphilis suggested an etiology, but other lesions that appeared to be connected to the disease did not contain the organism. The true relationship of the secondary and tertiary manifestations of syphilis to the Treponema organism was not fully appreciated until the widespread application of penicillin therapy cured the patients. With this evidence in hand, syphilis was no longer considered to be a chronic inflammatory disease, and the evidence for immunological meditation was quickly forgotten. Surprisingly, even in the most chronic tertiary stages of the disease, with the strongest suggestion of autoimmune mechanisms, elimination of the prime cause by penicillin therapy frequently produced dramatic reversal of disease manifestations. Similarly, the chronic inflammatory diseases of unknown etiology with which we deal today may become historical curiosities in the future if specific methods can be found to eraticate their causes.

There are suggestions that systemic lupus

erythematosus is associated with an intracellular infectious agent that leaves its calling card in electron micrographs, but Koch's postulates have not yet been satisfied. Autoantibodies and other autoimmune phenomena are clearly involved in the pathogenesis of systemic lupus erythematosus and trigger a destructive chronic inflammatory response. Reports of parvovirus association with rheumatoid arthritis, and infections with retrovirus acquired immunodeficiency syndrome (AIDS) similarly suggest a relationship between occult infections and autoimmune phenomena.

In some diseases, a genetic predisposition may be directly responsible for the disease or may indirectly permit the disease to develop by making the host susceptible to an environmental prime cause. It is possible that some chronic inflammatory diseases may be due to disorders in the regulation of the inflammatory response. Although regulatory mechanisms have not as yet been completely defined, their existence is indicated by the purposeful progression of the various stages of inflammation, which must be delicately controlled by some natural mechanisms. If this is so, we might expect to find some diseases due to disorders of these control mechanisms that in some cases might be treated by exogenous replacement of insufficient or defective regulatory "hormones."

TARGETS FOR ANTIRHEUMATIC THERAPY

The above explanation of the role of inflammation in chronic inflammatory disease provides at least four potential target areas for pharmacological intervention (Table 1-3). The methods of evaluation, efficacy, and inherent toxicity of drugs for each of these areas differ. A clear understanding of the differences between the target areas is necessary if one hopes to improve the treatment of rheumatic diseases. A drug de-

Table 1-3. Potential Targets for Antirheumatic

Eradicate prime cause Prevent initial tissue injury Moderate normal inflammatory response Enhance tissue repair

signed for one target area cannot be expected to be effective against another target. For example, a drug intended to antagonize one mediator of inflammation, e.g., an antiprostaglandin E2 cannot be expected to eradicate the cause of the disease, no matter how efficiently it may block the function of prostaglandin E2. Potential targets for drug therapy include: (1) the prime cause (etiology), (2) mediators of initial tissue injury released by, or produced in response to, the prime cause, (3) the nonspecific inflammatory response evoked by this initial tissue injury, and (4) the processes attempting to repair the injury and restore normal function.2

Eradicate the Prime Cause

If the prime cause can be removed, eliminated, or isolated from the host, initial tissue injury should stop and the inflammatory process should progress in the normal fashion to produce healing with either complete restoration of function or perhaps with some permanent residual disability due to scar formation or structural damage. There are many examples of favorable termination of inflammatory conditions following the elimination of an infectious agent, but the elimination of a noninfectious prime cause (such as the antigen in serum sickness or the toxic agent in heavy metal poisoning) also "cures" the disease. Often the manifestations of a "disease" are determined by the host's reaction to the injured tissue rather than by the specific etiologic agent; thus a particular "disease" may be caused by any one of several etiologic agents, each causing similar manifestations. If an antietiologic drug is effective against only one of these agents, then it will appear to cure a subgroup of patients with the disease, but will be ineffective for others with the same disease. Thus effective treatment of the prime cause may require as many appropriate drugs as there are etiologic agents for a particular disease, as in the treatment of the disease "pneumonia."

Concepts and Targets for Drug Treatment

In the case of chronic inflammatory diseases, elimination of the prime cause may be expected to cure the disease. This requires a specific attack on a specific etiology. Attacking the specific prime cause has the additional advantage that it does not suppress the beneficial aspects of inflammation and immunity, but cannot benefit those patients in whom the disease is caused by other factors. Among the rheumatic diseases, at the present time only the bacterial joint infections are readily amenable to elimination of the prime cause (Table 1-4).

Prevent Initial Tissue Injury

The goal here is to intercept, interrupt, or turn off mediators of initial tissue injury that are released by the prime cause or produced in response to its presence. Effective drug therapy in this area is inherently less specific than eradication of the prime cause; it cannot cure the disease because the prime cause itself is unaffected by the drug. However, because it prevents initial tissue injury, this type of therapy would be expected to permit the established inflammatory response to run its course and heal the manifestations of disease. Thus, an effective drug in this group may totally suppress the manifestations and the progression of the disease while it is being used. However, because the prime cause is not eliminated by the drug, one would expect a recurrence of the disease process at some time after the drug was discontinued.

It is necessary to differentiate between mediators elicited by the prime cause that Table 1-4. Treatment of Rheumatic Disorders OW 2170 and to alpain able

Target of princip	Agentyd bengamile for 21 921 Examples on 92192118	
Eradicate prime cause Attacked black blacked	Antimicrobial drugs Hypouricemic drugs	Penicillin for gonococcal arthritis Allpurinol or probenecid for gout
Prevent initial tissue injury to the produced based on business and to business of the produced based on the prevent of the pr	Immunosuppressive agents Gold compounds	Cyclophosphamide for Wegener's granulomatosis Gold or penicillamine for rheumatoid arthritis
of the requirements for, and issue repair is minimal, and agents for this area are pres-	d-Penicillamine Antimalarial drugs Corticosteroids (high dose) Levamisole	Prednisone for lupus nephritis
3. Moderate normal inflammatory response	Salicylates	Aspirin for rheumatoid arthritis
excessive formation of non- tissue due to abortive at- r in the presence of ongoing	Nonsteroidal anti-inflammatory drugs Colchicine Corticosteroids (low dose)	Indomethacin for ankylosing spondylitis Colchicine for gout
4. Compensate for destroyed tissue or organs	Arthroplasty	Total joint replacement surgery
probably also in the devel- ophytes in degenerative joint cannot repair scarred or de-	Dialysis Rehabilitation medicine	Dialysis for end-stage lupus nephritis Assistive exercises and devices in rheumatoid arthritis

produce initial tissue injury, and injurious substances released by damaged tissues that amplify the injury. For example, diphtheria bacilli growing in the host cause little direct injury, but diphtheria toxin, released by the bacteria, is responsible for serious tissue injury at distant sites. Treatment with diphtheria antitoxin (or immunization with diphtheria toxoid) can prevent the manifestations of the disease without eliminating the bacterial cause of it. Another example of a mediator of initial tissue injury that is more applicable to rheumatic diseases is the antigen-antibody-complement complex postulated to cause tissue injury in systemic lupus erythematosus and polyarteritis. Prevention of antibody production may inhibit immune complex formation and prevent the activity and progression of the disease without having any effect on the causative agent. Examples of injurious substances released by damaged tissue include histamine, lysosomal constituents, and other factors that participate in the normal inflammatory response. I sold and additional

stroyed tissue or cartilage, but orthopedic surgical procedures, dialysis, and rebabili-

In the present context of the rheumatic

diseases, blocking a mediator of initial tissue injury appears to be a reasonable target for therapy. It is likely that the slowly acting antirheumatic agents are members of this therapeutic group. Drugs such as the gold compounds, penicillamine, the antimetabolites, cytotoxic drugs, and levamisole characteristically do not produce any apparent clinical benefit until they have been given for weeks or months. In some cases, if is possible that it may take that long for the drug to reach therapeutic concentrations in its target tissue. However, it is also possible that the drug is promptly effective against the mediator of initial tissue injury, but the delay in clinical benefit represents time required for the previously initiated inflammatory response to run its course.

The inherent toxicity of a drug that prevented initial tissue injury would be greater than that of a drug that eliminated the prime cause, but would vary with the nature of the process that was affected. For example, if it were necessary to block the entire immunological response to prevent immunologically mediated injury, the unwanted