Handbook of

DRUG THERAPY IN RHEUMATOLOGY

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Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required. The authors and the publisher of this work have made every effort to ensure that the treatment and drug dosage schedules herein are accurate and in accord with the standards accepted at the time of publication. Readers are advised, however, to check the product information sheet included in the package of each drug they plan to administer to be certain that changes have not been made in the recommended dose or in the indications and contraindications for administration. This recommendation is of particular importance in regard to new or infrequently used drugs.

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FOREWORD

Despite the advent of many new drugs for the treatment of rheumatic diseases, it would seem that the subject of rheumatologic pharmacology and therapeutics is in greater disarray than ever before. The average practitioner is confused and uncertain of his directions.

The multiple, and seemingly contradictory, claims of the various pharmaceutical companies, especially as they relate to the nonsteroidal antiinflammatory drugs, have not eased the problem any. In contrast to 20 years ago when the number of drugs available could be counted on one hand, there is now a vast selection to choose from, mainly in rheumatoid arthritis, but also in a number of the other rheumatic diseases. It is not difficult to understand how a practitioner would be perplexed at trying to select naproxen in preference to ibuprofen, or tolmetin in preference to indomethacin, or sulindac in preference to any of the others. Furthermore, are these just aspirin substitutes or do they have remittive qualities and capabilities as has been suggested in more recent reports?

In addition, we are confounded with whether remittive drugs truly have the capacity for inducing remission and we are now not in full agreement as to which of these remittive agents should be the first to be used. Immunosuppressives would seem to be the next in order for treatment but there is some question whether these truly suppress immune function, and even if they do, is this the modus operandi in bringing about a remission (if and when they do).

Sanford Roth and his colleagues have set out to bring order out of this chaos, to enlighten and clarify in an orderly manner the application of drug therapy in rheumatic disease. They saw the great need and determined to answer it. They have performed this job handsomely!

Norman O. Rothermich, MD
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INTRODUCTION

This text has been developed to provide a structured, organized guide to the use of drugs for the treatment of rheumatic diseases. This is no small challenge. In recent years, a very eclectic and almost never-ending assortment of antirheumatic agents has evolved to represent the most rapidly expanding field in the pharmacotherapy of any segment of medicine to date. In the face of the many choices and the continuing research and development of antiinflammatory and disease-modifying agents, a clear need now exists. The clinical therapist must better understand and identify the properties, efficacy, toxicity, and appropriate use of these agents. In addition, a practical decision-making schema is necessary for choice and proper application. That is the charge of this textbook.

Internationally recognized experts have contributed their guidance to such an approach. The opening chapter begins with a discussion of specific factors that the therapist must consider when choosing a drug. It proceeds to the logical extension of measuring the response to that choice in placing, modifying, and altering treatment as the central concern of long-term management of rheumatic disease. Its concern is directed toward the difficult factors involved in treating a chronic and sometimes lifetime disease process in which symptoms wax or wane, but basic disease may progress. Yet, a basic regimen must have long-range goals balanced by appropriate intervention therapy, and occasionally a total revision of therapy. A rational schema to guide the therapist through these continuing choices is eloquently established.

The pharmacological considerations of rheumatic disease therapy begin with understanding what the drug does to the patient. It goes on to look at how the patient responds and reacts to the drug. It must ultimately answer how we can interpret clinical outcome, efficacy determinations, toxicity, and intolerance. In one of the most lucid presentations of a technically engaging subject, Chapter 2 introduces the reader to such necessary understandings. It proceeds from competent pharmacotherapy of the most common antiinflammatory choices to the most promising, but dangerous, immunoregulatory alternatives.

Ultimately, selecting and prescribing individual antirheumatic drugs requires a practical pattern. Chapter 3 presents the gamut of agents now available or soon to be available. They are placed in a pragmatic perspective of existing clinical experience. A workable pattern for choices and effective implementation is effectively structured.

From general concepts to specific examples and drug applications, the chapter dealing with the particular variants in the rheumatoid spectrum provides practical illustrations of the use of these drugs. It is based upon proper understanding of the range of inflammatory disease expression. Thus, the necessary emphasis upon proper diagnosis and understanding of the patient, his or her problems, co-morbidity and co-therapy factors, are placed in the perspective of experienced understanding of present antirheumatic applications.

These chapters are assimilated in a final chapter emphasizing organized steps that can lead the clinical therapist to effective use of an ever-broadening armamentarium in the face of difficult-to-treat, uncurable, potentially disabling rheumatic diseases. Emphasis is placed upon the patient–physician relationship and compliance. The difficulties of long-term drug use, abuse, and inherent toxicities are balanced. This equation must ultimately include suffering, pain, and disability as the inescapable consequences of untreated progressive, uncontrolled arthritis versus effective, involved intervention, which is the direction of this text.

Though the text is concise, the answers sought for the effective pharmacotherapy of the major rheumatic diseases will not be found quickly and simply. Rather, the material presented will require the reader's forethought, involvement, and commitment. A better understanding of the pharmacology of choices for the differential range of rheumatic diseases will result in effective and ultimately successful management. If this text inspires the reader toward attempts to better treat these difficult disorders, then it will have achieved the goals of its authors.

Sanford H. Roth, MD

ACKNOWLEDGMENTS

This book represents the work of five authors who have collaborated closely and each presented a unique insight into their own experience and expertise. So, it is to John Calabro, George Ehrlich, Ted Huskisson, and Hal Paulus that I express my deepest gratitude for their unique contributions.

I am indebted for the support and encouragement of my colleagues Dr. Arthur L. Scherbel and Dr. Ralph E. Bennett and to my entire staff at the Arthritis Center. A special thanks to my outstanding executive secretary, Linette Cooke, and to our chief librarian at St. Luke's Hospital, Kay Wellik, for her dedicated efforts and assistance.

And finally, an understanding, supporting and knowing wife, my Marcia, deserves special acknowledgment.

S.H.R.

CONTENTS

CHAPTER 1

FACTORS AFFECTING THE CHOICE OF DRUG AND THE RESPONSE TO TREATMENT

GEORGE E. EHRLICH

Drugs are only one of the elements of proper treatment of chronic diseases such as rheumatoid arthritis. Until the basic mechanisms of rheumatic diseases are better understood and means of prevention or cure are found, medical treatment requires augmentation by physical, surgical, and psychosocial approaches. To know when to use a single medication and when to organize an entire team to treat the patient is the art of managing chronic disease. It is no wonder that the problems of definition and treatment of arthritis have engendered a specialty devoted to this subject.

Neurology, David Hawkins said, deals with the diagnosis of untreatable disease, but rheumatology deals with the treatment of untreatable disease. Can there be a more telling definition of frustration? One need not wonder why rheumatologists envy the techniques of crisis intervention used by surgeons, or the satisfaction that interns derive from saving a life threatened by a major medical catastrophe. Treating an arthritic condition is often like watching a child grow; we know there is progress because the intermittent observer can detect it and because the chart reflects it, but close observation obscures it. Yet progress in rheumatology is obviously not an exercise in futility: it makes a fundamental difference for patients afflicted with rheumatic diseases. The proper approach reduces crippling disability in rheumatoid arthritis from an estimated 25% to 5%, and in ankylosing spondylitis from 15% to 1%.[1] The difference in outcome is not a result of secret remedies available at one institution which are not available at others, but derives from an approach to disease that recognizes the futility of emphasis on the disease itself, on the laboratory reflections of that disease, or on a particular treatment, and instead, substitutes a more global approach in which the patient is seen for what he is: a person seeking medical help. The afflicted person plays many roles; the role of patient is but one.[2] To treat the disease without understanding its host, to treat the patient without understanding his or her role in family, employment, and community, and to

insist upon the divine right of diagnostic terms to the exclusion of an understanding of the dynamics of what is going on, may resemble science in its preciseness of language, but lacks both science and humanity. Rheumatologists are not frustrated, therefore, because their humanity permits them to share the quiet triumphs of their patients. Rheumatologists have become, in effect, psychiatrists of the body, helping their patients achieve their share of a satisfactory life. The disservice to rheumatology of the incorrect emphasis has already been pointed out by others.[3,4] Clinical data often feature short-term controlled trials that measure behavior and laboratory aspects that are quantifiable. This is pseudoscience, in a sense, as one learns to compare two measures, two drugs, two approaches, but chiefly in their effect upon aspects that do not really measure whether patients can continue to function, can alter the prognosis favorably, or can even gain some satisfaction from the treatment.

The much vilified patient response to the question "How do you feel?" may be anecdotal, as claimed, but definitely gives the most accurate information about the importance of treatment, although not necessarily about the impact on underlying mechanisms. These mechanisms remain elusive, and even when we can show that inflammation has been curbed, we cannot prove that the course of the disease has in any measure been altered. Therefore, the void that remains is the translation of effects upon known mechanisms to the functional prognosis of the individual who harbors the disease. Here definitions are lacking, partially because, as Medawar[5] has pointed out, there has been a commitment to questions that seem to be soluble, or as De Blecourt and his colleagues[3] state, this has obscured the much more difficult but also "more fundamentally relevant problem – that with a chronic disease, it is the outcome over the long haul that is of the greatest importance."

The problems to be discussed in this chapter, then, include the patient in context, the importance of disease classification, the pitfalls of this classification, the assessment of response to drug treatment, and factors that may account for variations in response. The natural history of the various rheumatic inflammations and the constellation in which they are placed obviously influence the choices for treatment of their various manifestations in the assessment of what is happening. These questions cannot be addressed exclusively in the abstract; thus, standard terminology will be employed with the understanding that it is descriptive of syndromic presentations rather than defining distinctly separate entities.

THE PATIENTS

Recent investigations have focused on the individual who contracts a rheumatic disease and, in some instances, identified genetic factors that provide markers to the individual at greatest risk. Most of these investi-

gations have concentrated on the histocompatibility antigens found on the sixth chromosome. While the relationship between certain manifestations and alloantigens currently remains a statistical one, it may also shed light on the pathogenesis of these disorders. Thus, a specific or nonspecific, even ubiquitous irritant may be the trigger of the disease in a predisposed individual, who will then develop one or another rheumatic disease, whereas a different person faced with the same provocation may respond in another manner. We have recently seen, for example, the greater likelihood of spondyloarthropathy in HLA-B27 positive individuals, regardless of a subdiagnosis, be it ankylosing spondylitis, Reiter's syndrome, other reactive spondyloarthropathies, psoriatic spondyloarthropathy, or spondyloarthropathy associated with granulomatous bowel disease.[6] At the same time, individuals who have psoriasis, granulomatous bowel disease, various forms of dysentery, or nonspecific venereal diseases often develop arthritic syndromes, but the preponderance of HLA-B27 positive individuals will be found among those who also develop spondyloarthropathy, while among those who fail to develop spinal involvement, HLA-B27 seems to be hardly more common than in the population at large. Thus, a subgroup of the population appears to be at greater risk of developing a specific rheumatic syndrome, and we have a marker to help us identify this group. Whether this genetic factor plays an etiologic role remains to be seen, but it certainly identifies patients and potential patients as well as other, more superficial genetic markers. For example, Nordic-descended, light-skinned, light-haired individuals clearly are more likely to develop sunburn upon concentrated exposure than darker-skinned people.

Many recent studies concentrate upon such associations. In Behçet's syndrome, for example, HLA-B5 is more common among patients than in the population at large, and the specific subtype B51, in particular, predominates among those who have ocular involvement,[7] while B12 is seen frequently with the skin lesions.[8] HLA-DR5 and 7 and MT2 likewise cluster among Behçet's syndrome patients,[7,8] while DR4 is more prevalent among those who have rheumatoid arthritis,[9] DR3, Sjögren's syndrome, and DR2, systemic lupus erythematosus.[10] HLA-B8 clusters in groups of patients who have a variety of rheumatic and nonrheumatic conditions, such as Sjögren's syndrome, dermatitis herpetiformis, chronic active hepatitis, and Graves' disease.

These genetic markers, then, not only seem to identify susceptible subgroups, they may also provide some information about drug metabolism in these individuals. Again, HLA-DR3 is found far more frequently in individuals who develop nephrotoxicity to gold and perhaps to penicillamine as well than in others,[11] and may even, in time, provide a valid marker for avoiding giving these compounds to such patients. Another genetic mechanism, acetylation rates, may also play an important role in

disease pathogenesis and treatment; slow acetylators predominate among those suffering a secondary form of lupus, seemingly induced by prior drug intake, chiefly hydralazine, diphenylhydantoin, certain antibiotics, and other cardiac drugs.[12] Slow acetylators may also be more likely to have primary systemic lupus erythematosus, suggesting the possibility of induction by some common environmental chemical as yet unidentified, and even among those who have rheumatoid arthritis. However, those who have rheumatoid arthritis of such severity that it is mutilating and rapidly progressive appear to be fast acetylators, suggesting that drugs that could retard rheumatoid arthritis may be metabolized too quickly to exert their desired actions and that the individuals in question may have one or more related mechanisms for so doing or for making the drugs unavailable where they are most needed.[13]

Beside the genetic makeup, the individual also brings a social constellation into the equation. Responses to adversity vary widely. Some people, plunged into grief or despair, contract acute illnesses, such as the common cold, or other diseases, and we say that their resistance is down. Not everyone contracts even the most virulent diseases, as was learned during the Middle Ages when epidemics and pandemics swept across Europe, felling many but sparing others similarly exposed. It may be premature to look upon rheumatic diseases as viral-induced or otherwise infective, but the conjunction of onset of exacerbations or first manifestations shortly after some notable adverse event, such as an accident or a major loss, has been noted, at least in law, and may well point to other host factors yet to be discerned.

In addition, our joints are what we have done with them. The use to which joints are put, and particularly their repetitive use, abuse, disuse, or overuse, may play a role in promoting later changes in these joints.[14] The integrity and development of our muscles and other soft tissues play a role at least in influencing severity of symptoms, and the many unanalyzed physical treatments offered to patients seem to make a difference in the way they function and feel. Supportive family, friends, coworkers, and employers have an enormous impact upon function, and governmental and social programs help determine how someone who has arthritis fares.

DISEASE CLASSIFICATION

The classic approach to rheumatic diseases has been to list them either under presumed causations or under areas of involvement. In the former category, there are 13 headings, adopted in 1963 by the American Rheumatism Association. They include:

I. Polyarthritis of unknown etiology
II. Connective tissue disorders (acquired)

III. Rheumatic fever
IV. Degenerative joint disease (osteoarthritis, osteoarthrosis)
V. Nonarticular rheumatism
VI. Diseases with which arthritis is frequently associated
VII. Associated with known infectious agents
VIII. Traumatic and/or neurogenic disorders
IX. Associated with known or strongly suspected biochemical or endocrine abnormalities
X. Neoplasms
XI. Allergy and drug reactions
XII. Inherited and congenital disorders
XIII. Miscellaneous disorders

It is clear from a study of the above that the majority of disorders fall under three headings: polyarthritis of unknown etiology, which would include rheumatoid arthritis; degenerative joint disease, which would include all progressive changes that are noted more commonly by the radiologist than by the clinician; and nonarticular rheumatism, which would adumbrate psychogenic rheumatism, fibrositis, polymyalgia rheumatica, and the myriad forms of bursitis and peritendinitis. There is considerable overlap, of course, in that the second category also includes some aspects of category I, and all categories ultimately include the fourth category in their natural history. For that reason, a second taxonomy groups the various disorders in a schema emphasizing clinical presentation, thus separating monoarticular from polyarticular disease and subdividing polyarticular disease into inflammatory, degenerative, and metabolic processes. Inflammatory disorders are further subdivided into those that appear to be reflected in serological abnormalities (rheumatoid arthritis, systemic lupus erythematosus, progressive systemic sclerosis, dermatomyositis, and transient viral disorders and sarcoidosis) and those generally seronegative for the various antibodies of interest to the rheumatologist, which tend to present asymmetrical and centripetal distribution and include ankylosing spondylitis and variant disorders in which spondylitis is at least part of the presentation.

These working diagnoses help us to a shorthand mode of expression, in which the name of the disease encompasses the manifestations that are meant to be brought to mind (the obverse also being true, the listing of all the manifestations bringing the name of the disease to mind). In this respect, the classification is both time saving and useful for communication. A classification that is based on localization also serves a time-saving purpose, but tends to be less useful to an understanding of the disorder because of its simplistic descriptiveness. Classifications can expand, as they have been doing in recent years, or contract, as they did in the classic monograph, *Rheumatoid Arthritis*, by Short, Bauer, and Reynolds,[15] in which the term rheumatoid arthritis included not only

what we today consider rheumatoid arthritis but also ankylosing spondylitis, Reiter's syndrome, juvenile rheumatoid arthritis in all its manifestations, psoriatic arthritis, and a host of variants. The flaws of such an inclusive classification are obvious: they obscure the differences that we are seeking to help us define subsets and therefore to develop more specific treatment.

For example, if uveitis occurs in a large proportion of patients who have ankylosing spondylitis but not in patients who have rheumatoid arthritis, and if the two are grouped together, then the overall incidence of uveitis in what is now called rheumatoid arthritis is higher than expected (and considerably lower than in ankylosing spondylitis alone). The result is a belief that uveitis complicates rheumatoid arthritis and may be associated with it, when there really is no evidence for this if the two syndromes are segregated. Again, the segregation does not necessarily imply that they have different causation, but it at least defines subgroups in such a fashion that needed information can be gleaned from the classification itself.

Another instance is uveitis and juvenile rheumatoid arthritis. It is said that uveitis occurs more commonly in juvenile rheumatoid arthritis than when the disease is not present. Juvenile rheumatoid arthritis, however, can probably be subdivided into several subsets that may or may not be related.[16] These include a polyarticular disease that looks like adult rheumatoid arthritis and progresses into adult life, with which uveitis is rarely associated, or, one should say, not more commonly than with the absence of juvenile rheumatoid arthritis. In other words, no specific relationship exists. The second category, characterized by an acute febrile onset, (generally named Still's disease in the United States) also is not associated with any notable increase in incidence of uveitis. Three subsets of pauciarticular arthritis have been identified. One, which may go on after some time to be polyarticular, also is not associated with uveitis. Another variety, in which the genetic haplotype HLA-B27 is usually found, may be a juvenile variant of ankylosing spondylitis.[17] In this subset, acute uveitis occurs, as it does in adult ankylosing spondylitis, in a large proportion of individuals. This uveitis is painful, associated with circumlimbal redness, and generally easily detected because it is symptomatic. The most important category is the last pauciarticular variety, more common in young girls than in young boys, in which HLA-B27 is not present, and in which the ultimate development of antinuclear antibodies usually takes place.[18] This group of children is at risk of developing an indolent and chronic uveitis that may remain asymptomatic for some time, is not associated with severe pain or redness of the eye, goes undetected if unsuspected, and may therefore progress to blindness. It is precisely this chronic uveitis that one should be most on the alert for, and if the most appropriate subset can be identified, then measures can be

taken to monitor the illness and keep the eye under surveillance so that treatment can be started early enough to attempt to avoid progressive keratopathy and other consequences. But a classification that lumps all joint diseases of children together under one term, juvenile rheumatoid arthritis, will show an increase of uveitis in general and fail to identify the subgroup that most needs attention. Specific surveillance of those not needing it is not only a waste of resources but can ultimately lull the clinician into carelessness when the expected rate of incidence of uveitis fails to eventuate. Taking all these cases and including them under rheumatoid arthritis in general, as was done in the monograph, will then also serve seemingly to increase the occurrence of uveitis in the group as a whole. Confusing data can only lead to confusing results, and meaningless statistics lead to bad science and demonstrably erroneous conclusions.

On the other hand, too much subclassification leads to a different type of confusion. If the subclassification identifies too many different disorders, the attempt to diagnose may supersede the need to identify the dynamics of the disorder in order to calculate the best therapeutic intervention. Then, research efforts are directed at fitting the syndromes into groupings circumscribed by serologic resemblances, marveling over the appearance of a serologic hallmark of one in the context of another, and producing, ultimately, a procrustean bed that requires purity of diagnosis while obscuring the simple fact that in most instances we still do not know the cause or causes. There is the possibility that the mode of presentation of the rheumatic diseases we have identified owes more to a genetic predisposition and to other host factors than to any specific incitement. Viruses, trauma, crystals, and other provokers may well initiate the process, but they probably need to find fertile soil, prepared to respond now and not earlier, to initiate a process that becomes self-perpetuating. Disease is the consequence.

Disease leads to disability, the functional consequence. Disability leads to handicap, the social consequence, and the totality leads to disablement.[19]

Disability represents an interference with daily routine, real or potential. The magnitude of disability will be discussed later, but the consequence, handicap, is provided by social and environmental factors. Clumsiness of the fingers because of large Heberden's nodes should not interfere with the ability to sweep a floor, to run a vacuum cleaner, or to drive a car, but may make it impossible to split a diamond properly. Therefore, even minor changes in the finger joints can be a disaster for a jeweler while even major changes may be at most a cosmetic annoyance for others. Conversely, severe osteoarthritic changes in the hip joint which preclude most motion and produce considerable pain on effort nevertheless permit the jeweler to continue working as long as the finger joints are whole, while preventing manual labor and, in the case of

women, interfering with sexual intercourse, so raising a host of vocational and social problems in addition. Obviously, then, it is handicap that often motivates consultation with a physician, yet remains outside the realm of the natural history of the disease and motivates the individuality of treatment so necessary for chronic disease management. The physician who wishes to manage rheumatic disorders must keep the escalation of impairment to disability to handicap to disablement in mind.

The initial presentation of rheumatoid arthritis already can be recognized as chronic (as distinct from acute) inflammation. Acute inflammation still produces the Galenic quintet: heat, redness, swelling, pain, and loss of function. One look at a gouty toe confirms the validity of this observation of acute inflammation. Red and swollen, the toe is exquisitely tender, movement is almost completely inhibited, the function of the foot is temporarily interfered with, and the heat emanating from the area can readily be ascertained through the slightest touch. But in early rheumatoid arthritis, rarely is the joint so severely involved; most commonly, there is modest heat and redness over the joint, but there is swelling and tenderness. Pain may not be very severe, but its chronicity ultimately makes it intolerable. Function is not lost, but there is already enough interference with function so that impairment of function can be identified. With progression, heat and redness become even less pronounced. Tenderness may become rather minimal (for example, the common swelling of the extensor tendon sheath over the wrist in rheumatoid arthritis rarely is particularly tender, yet it is characteristic and almost pathognomonic of the disorder). The swelling itself now has many components; it is no longer occasioned by edema of the tissues alone, but is marked by proliferating tissue, effusion, and even, after a time, osteophytic response. Function continues, if diminished, and can be enhanced by local measures, such as appropriate splinting or intra-lesional injections of a corticosteroid compound. The vaunted morning stiffness is qualitatively not too dissimilar from the stiffness that attends any joint disease, but quantitatively differs, in that its duration is longer and lengthening, its degree is major, difficult to counteract, and its distribution global rather than regional, afflicting the entire body rather than a specific joint. Fatigue creeps forward slowly to approach the ever-lengthening morning stiffness, and aching attends both. The diagrammatic presentation would resemble a spreading puddle closing in on the middle of the day from both ends. The nights are uncomfortable, and rest does not necessarily bring relief. In fact, rest aggravates the stiffness and provokes the aching. In that respect, these most explicit symptoms of rheumatoid arthritis, beside the joint swelling, resemble fibrositis, and can, in fact, be thought of as fibrositis in the context of rheumatoid arthritis.

Fibrositis

Fibrositis is a vague concept, not helped by the fact that the English include under it what we call both fibrositis and psychogenic rheumatism, whereas in the United States these two are segregated somewhat artificially.[20] In both, there are pains around the body, described by patients often as "everything hurts." In fibrositis, these have an orderly distribution, often being exaggerations of tenderness in areas that are more sensitive to begin with; these include the back of the occiput, the lowest cervical vertebra, the trapezius about a third of the way between the neck and the shoulder in the suprascapular area, the supratrochanteric bursae lateral to the hips, the medial aspects of the knees over the fat pad and anserine bursae, the dimples over the sacroiliac joints above the buttocks, the second rib anteriorly below the clavicles, and the epicondyles of the elbows.[21] In many of these places, there are structures that can be inflamed, and often are inflamed as a result of some activities. It would be an unusual activity indeed, to cause inflammation simultaneously in all of them. Yet patients who have fibrositis generally complain of pain or at least report tenderness on examination of almost all of these spots at the same time. The tenderness causes the patient to shrink away from the examining finger. The symptoms are worse in the mornings upon arising and after any period of rest, thus reproducing morning stiffness and gelling, as seen in rheumatoid arthritis, although the duration tends to be less prolonged. As in rheumatoid arthritis, the continuation of achey symptoms helps make the patient querulous and irritable, and evokes in the examiner a counterreaction, at least as important as a clinical sign as the symptoms reported by the patient. Simply, the examiner shrinks from the patient, feels uncomfortable in the presence of the patient, feels attacked, and often feels frustrated by not making any advances despite intelligently conceived therapeutic measures. A pattern of mutual hostility often marks the encounter between patient and physician, although the patient remains rather tenacious in staying with the unhappy physician.

Examination also reveals that the muscles feel tight, the patient does not move loosely, and there may be little tender spots, called fibrositic nodules, in some of the large muscles, especially those of the back. Fibrositis is also known as myofascial pain syndrome, and is perhaps a more common cause of back pain than mechanical derangements and inflammatory disease of the spine. Some recent studies have been able to reproduce the syndrome in volunteers through deprivation of deep non-REM sleep, as monitored by electroencephalography.[21] Enough deprivation, depending upon the physical state of the individual, reproduces the fibrositic symptoms within the expected individual variation.