Antibiotic Therapy for Rheumatoid Arthritis

An Important Therapeutic Alternative





"At age 11 I noticed a bump on my elbow, and my disease was confirmed at a university medical center as rheumatoid arthritis. Soon my knees became involved, with big knots and swelling, my elbows got bigger, and it affected my neck, shoulders, and all my other joints. The pain was severe, and I lost more than 25 pounds. The doctors tried all different kinds of treatments, but nothing seemed to work.

"By age 20 I had been to three or four major hospitals, and had been treated with gold, hydroxychloroquine, penicillamine, and cortisone. The cortisone got me through high school, but I was never made aware of the potential side effects.

"When I began college, the side effects of cortisone just started getting worse and worse—they were actually worse than the arthritis itself! The breakdown in skin tissue caused skin ulcers all over my body. This was compounded by a very low white blood cell count, so my body had no defenses to fight the constant infections. I spent a lot of time in isolation to control the infection, and once my fever became so high that I went into convulsions. Feeling sick just became a part of my life—I couldn't really tell when I was sick and when I wasn't. No one gave me any hope of getting over the disease. One doctor said he'd be perfectly honest—there was nothing else that he could trust to give me.

"After two years of college I flunked out because I lost the ability to concentrate. By this time I had a large leg ulcer down as deep as the muscle, and others in various places. The penicillamine had caused aplastic anemia—my white blood cell count was so low it was at the fatal level. I was critically ill, and so extraordinarily discouraged that my family became fearful for my life."

Myra Age 28 Rheumatoid arthritis patient

Introduction

The costs of RA are enormous – not only are there great emotional and physical costs of living with a chronic disease, there are the great economic costs of medical care and disability payments for those unable to earn a living.

Myra's story, related on the opposite page, is typical of many young patients with rheumatoid arthritis (RA). Not only is the disease painful and debilitating; therapeutic failure is so rampant that the patient's loss of hope can become as great a problem as the disease itself.

Today, RA is a major health problem. The classic form of RA is known to affect as many as 7 million people in the U.S.A., or about 3% of the adult population; when other forms of this disease are included the numbers are even greater. The costs of RA are enormous—not only are there great emotional and physical costs of living with a chronic disease, there are the enormous economic costs of medical care and disability payments for those unable to earn a living. It is estimated that by the year 2000 the costs of all forms of arthritis in the U.S.A. will approach \$100 billion per year.

RA is an enigmatic disease. It is not the form of arthritis that results from aging; RA affects patients as young as one year and as old as 90. There is no single test or set of clinical findings by which to make the diagnosis; therefore, diagnosis is accomplished by eliminating similar rheumatic diseases. The exact cause of RA also remains elusive, and no one form of therapy has been proven effective for every patient with RA; treatment of the disease must proceed by a trial-and-error method. Many different drugs have been shown to modify the progression of the disease, but their efficacy varies, and most are associated with debilitating and often dangerous side effects.

Antibiotic therapy for RA, an apparently safe and effective treatment, was reported to have some value as early as 1949. Anecdotal evidence and case reports on more than 10,000 patients treated by the staff of the Arthritis Institute of the National Hospital for Orthopaedics and Rehabilitation strongly suggest that antibiotic therapy is of value for patients with RA (see "Prospective Studies" on p. 16 for further details). However, this treatment has not been tested in carefully designed, controlled, prospective studies with adequate numbers of patients. The Institute is now planning to conduct such studies, and has compiled the information in this booklet in order to encourage funding for further appropriate research. It is hoped that this research will help to clarify the role of antibiotic therapy for RA, and document further the efficacy and safety of antibiotics in managing this crippling disease. This should result in F.D.A. recognition of antibiotic therapy as a highly efficacious alternative, leading to its widespread use by clinicians.



Dr. Thomas McPherson Brown with an RA patient

Historic Overview

Early Evidence of RA

Treatment in the 19th Century

Treatment in the 20th Century

Nonsteroidal Antiinflammatory Drugs (NSAIDs)

More often than not, these drugs (NSAIDs) are insufficient to control progressive RA. Side effects of NSAID therapy are fairly common...

Corticosteroids

Although many of the arthritic disorders prevalent today were described as early as the time of ancient Greece and Rome, until the 1700s there was no historic evidence of any disease exhibiting the deformities characteristic of RA. The term "rheumatoid arthritis" became associated with the disease in 1859, when Garrod published his classic description.

During the 19th century, the various methods of treating RA included bleeding, surgical removal of areas of inflammation, various forms of homeopathy, and vaccination.

The beginning of the 20th century saw little advancement in the therapy of RA. It was not until the late 1940s that great advances in treatment were achieved, and research into the possible causes and management of rheumatic and connective tissue disorders has flourished since then. Clinical diagnosis has become more sophisticated, with increasingly more accurate laboratory analyses. New arthritic disease entities have been recognized, and definition of all rheumatic disorders has become more precise. There has been a proliferation of medical journals, special reports, conferences, workshops, symposia, monographs, special reviews, textbooks, and handbooks. Despite this preponderance of research, the etiology and best methods for treating RA remain elusive.

It is hoped that by the end of the 20th century the growing complexity and wealth of knowledge in the field will have led to the discovery of the causes of rheumatic diseases, and eventually to the cures. Until then, physicians must depend on the therapies currently used to treat RA. These drugs offer either symptomatic relief with a relatively favorable safety profile, or disease-modifying activity with an increased risk of toxic side effects. In many patients they become less effective over time. The following is a brief overview of these current therapies.

Acetylsalicylate, or aspirin, was first used in the U.S.A. in 1899, and soon gained widespread acceptance for its analgesic and antiinflammatory effects on the painful joints of RA. It has remained the drug of first choice for chronic inflammatory joint disease. Since the early 1960s, newer NSAIDs have been introduced and are frequently used in place of salicylates. Despite many hypotheses, the exact mode of action of NSAIDs remains unknown. Different formulations of NSAIDs have been shown equally effective in reducing the pain and swelling of RA, but efficacy varies among patients. More often than not, these drugs are insufficient to control progressive RA. Side effects of NSAID therapy are fairly common, and are most likely to involve the gastrointestinal and nervous systems. Toxic effects on the kidney are less common, but remain a serious concern when NSAIDs are used in elderly patients.

Corticosteroid therapy for RA was considered revolutionary and so beneficial at the time of its introduction in 1949 that its discoverers were awarded the Nobel Prize in Medicine the next year. The potent antiinflammatory properties of corticosteroids produced dramatic improvements in patients with RA, but the results proved to be short-lived. Serious side effects occur frequently in patients on long-term

corticosteroid therapy, and affect every system of the body. Among the more common side effects are Cushing's syndrome (increased fat deposition on the face, neck, and trunk; osteoporosis and outward curvature of the spine; hypertension; amenorrhea in women and impotence in men; purplish striation of the skin; muscle wasting and weakness), diabetes, ulcer, cataracts, and suppression of the immune system. Because of these undesirable side effects, low-dose corticosteroid therapy for RA now is used cautiously, and only after careful assessment of the risks and benefits for a particular patient. Although corticosteroids can provide symptomatic relief, they do not halt the progression of RA.

Slow-Acting Antirheumatic Drugs (SAARDs) Several different classes of drugs belong in the category of SAARDs, which may effect modulation of disease in patients with RA and may even result in disease remission. These classes of drugs include antimalarials like hydroxychloroquine, gold compounds, penicillamine, and sulfasalazine. Interestingly, none of these SAARDs was originally developed to treat RA; all were used initially to treat other diseases. Their usage in the treatment of RA was based on anecdotal reports of successful results; it was years before their efficacy was documented in clinical trials. None of these SAARDs works well in all patients with RA, and all are associated with toxic side effects.

Hydroxychloroquine is probably the safest of the currently used SAARDs, but is associated with recurrence of disease after an initial period of remission. In addition, retinal toxicity remains a serious concern.

Injectable gold, while effective in many patients, has an unacceptably high risk of complications, including rash, mouth ulcers, blood disorders, and kidney toxicity.

Auranofin, an oral form of gold, has been shown to be safer than injectable gold and nearly as effective. However, it has been associated with thrombocytopenia (a blood disorder) and proteinuria (an excess of protein in the urine).

The large doses of penicillamine required for efficacy result in a high risk of toxic side effects. These include the development of other rheumatologic disorders such as lupus erythematosus and Sjögren's syndrome, and the same kidney and blood disorders associated with gold therapy.

Sulfasalazine is as effective as gold, but can have serious toxic effects on the blood, liver, and kidneys.

With all of these SAARDs, there is a very high dropout rate after 3-5 years of therapy, because of side effects or lack of continued efficacy. Therefore, they are not considered optimal for long-term therapy.

Immunosuppressive Therapy

The proliferation of immunologic research over the past 15 years has led to the theory that RA is a disorder of the body's immune system. For this reason immunosuppressive drugs, including azathioprine, cyclophosphamide, and methotrexate, have been used experimentally for patients with persistent, progressive RA. Although these treatment methodologies have been successful in limited cases, they are recom-

mended for use only by highly qualified experts and for severe intractable RA, in order to avoid the serious consequences of their potent immunosuppressive activities.

Other Forms of Therapy

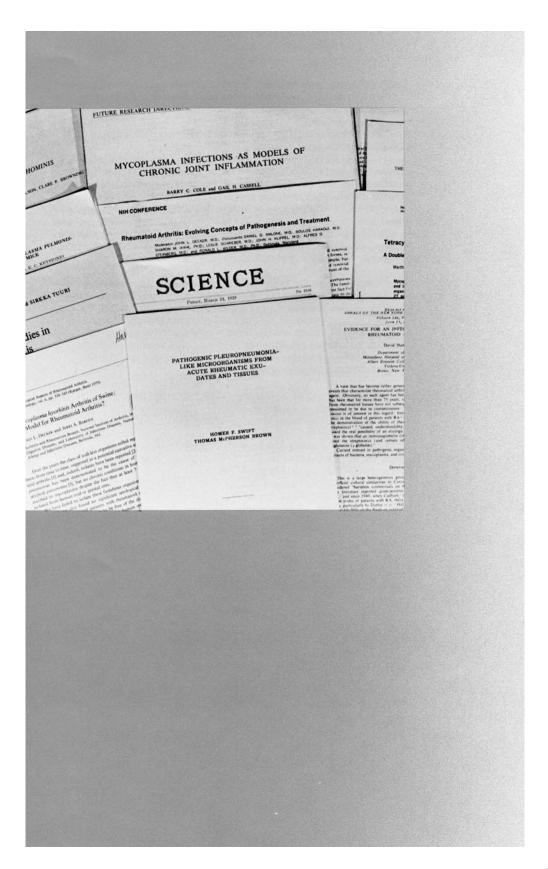
Several other forms of therapy for RA have been tried; all have limited usefulness.

Lymph node irradiation varies in efficacy and has a high risk of complications. Plasmapheresis, a method of "washing" the patient's blood to remove certain elements, has produced only transient improvement in symptoms. Levamisole is associated with a high risk of toxicity.

The Future of Therapy for RA It has been more than 125 years since RA was identified as a disease entity, and during that time many methods of treatment have been employed. None is considered universally effective or safe.

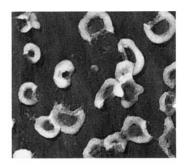
... well-designed prospective studies on antibiotic therapy are warranted. The anticipated results should demonstrate that antibiotic treatment is a safe, effective alternative for the management of RA.

Antibiotic therapy for RA has been shown to be highly effective in clinical practice, but has not been tested in adequately controlled scientific studies. Because of the excellent results obtained with this form of therapy, and because there are many problems associated with currently accepted treatment regimens, well-designed prospective studies on antibiotic therapy are warranted. The anticipated results should demonstrate that antibiotic treatment is a safe, effective alternative for the management of RA.



Rationale for Antibiotic Therapy

Pioneering Work by Thomas McPherson Brown, M.D.



... corticosteroids... reduced immunity, did nothing to balt disease progress, and resulted in a variety of serious adverse effects.



The idea that RA might be caused by an unusual group of infectious agents called pleuropneumonia-like organisms (PPLO) was first proposed by H. F. Swift and Thomas McPherson Brown (now Chairman of the Arthritis Institute), who published their original findings in *Science* in 1939. Since then, Dr. Brown has continued his work in arthritis research.

Dr. Brown had observed a phenomenon known as the Jarisch-Herxheimer (JH) reaction in an arthritic patient treated with gold. In this reaction, originally found to occur in syphilitic patients, there is a flareup of disease after administration of an antimicrobial agent. This flareup is believed to be caused by a migration into the bloodstream of microorganisms and their products released from body tissues after antibiotic therapy. Working with patients in whom the JH reaction had occurred, Dr. Brown isolated PPLO from joint fluids and body tissues. These PPLO were later classified as mycoplasmas and bacterial L-forms, microscopic organisms whose properties fall between those of viruses and bacteria.

Intrigued by these early results, which suggested a relationship between RA and mycoplasmas or bacterial L-forms, Dr. Brown and others continued research on forms of therapy presumed to be effective against such organisms. Gold salts, which were known to be effective against RA, also controlled the mycoplasma-induced arthritis in mice and rats. With the introduction of the tetracyclines and closely related compounds, including clindamycin, lincomycin, and doxycycline, therapy focused on the use of these drugs because of their known efficacy against mycoplasmas and bacterial L-forms. In addition, they proved more tolerable than gold for large numbers of patients, and were not associated with a buildup of resistance to the drug by bacteria.

The theory of an infectious cause of RA received attention for some time, but was abandoned by most researchers abruptly in 1949 with the discovery and popularization of the "cortisone effect." The dramatic action of the corticosteroid drugs seemed to indicate that arthritis was a metabolic or endocrinologic (hormonal) disorder. Unfortunately, it was several years before it became known that the dramatic initial symptomatic relief afforded by corticosteroids provided false security that they were effective, while actually they reduced immunity, did nothing to halt disease progress, and resulted in a variety of serious adverse effects.

Further support for Dr. Brown's theory of an infectious cause of RA came later, as newer SAARDs were prescribed for RA. These drugs, notably antimalarial agents, gold, and penicillamine, also produced flares similar to the JH reaction. Antimicrobial agents that did not produce this flare reaction did not seem to be effective in sustained control of RA. Moreover, a common denominator between these drugs and antibiotics was their similar ability to suppress mycoplasma organisms.

The inability to isolate any microbial organisms with consistency frustrated many researchers, dissuading them from further efforts. However, Dr. Brown's overwhelmingly favorable results convinced him to continue antibiotic treatment of patients. As time and funds permitted, he also continued his research, investigating the infectious etiology of arthritis in various animal species, including gorillas

Reasons for General Lack of Interest in Antibiotic Therapy for RA

The Skinner study is often cited as proof that antibiotics are ineffective in treating RA. However, careful analysis reveals flaws in the research design that cast doubts on the conclusions made.

and elephants. Although the scientific bases for these findings and conclusions in animal models were indisputable, many physicians were reluctant to believe that there could be a relatively simple solution to the cause of RA in humans.

Surprisingly, much of the lack of enthusiasm among the medical community for pursuing further research on antibiotic therapy for RA has been based on results of a single study by Skinner et al., published in *Artbritis and Rheumatism* in 1971. Briefly, these researchers proposed to test whether tetracycline is beneficial in the treatment of rheumatoid arthritis by conducting a double-blind study in which patients received one capsule per day of tetracycline or placebo for one year.

The Skinner study is often cited as proof that antibiotics are ineffective in treating RA. However, careful analysis reveals flaws in the research design that cast doubts on the conclusions made. For example:

- There were only 13 patients in the tetracycline group and 14
 in the placebo group, and the groups differed with respect to
 sex, duration of disease, presence of nodules, and presence
 of anemia. In addition, three patients received corticosteroid
 therapy throughout the study. Most scientists would agree
 that this number of patients is too small to make any definitive scientific claims about the method of therapy (Type II
 statistical error).
- The medication had been administered orally rather than in the injectable form, which appeared to be more effective in both humans and animals.
- 3. There was no evidence that the medication had been taken as directed. Patients were given capsules to be taken orally. They were re-examined two weeks after beginning therapy, and then at intervals ranging from six to 12 weeks. In any study of this type it is logical to assume that at least some of the patients will fail to take the medication as prescribed. However, the research protocol did not call for blood studies to monitor serum levels of antibiotic. Serum and synovial fluid levels of antibiotic were measured only in three patients who had knee joint aspirations. In one of these patients, antibiotic levels were inadequate to kill bacteria.

Unfortunately, the conclusions of the study were supported by an accompanying editorial: "Clearly, the answer is that [tetracycline therapy] is not of demonstrable benefit for [rheumatoid arthritis] patients." Most biostatisticians would argue that the answer was not clear. The proper conclusion should have been that the study findings were inadequate to either confirm or deny the value of antibiotic therapy for patients with RA, and that further research would be indicated.

Renewed Interest in the Role of Microbial Agents in Arthritis Over the past decade, there has been renewed interest in the theory that infectious microorganisms are the etiologic agents responsible for RA. Research in this area was summarized during a Combined Clinical Staff Conference, sponsored by the National Institutes of Health, which covered evolving concepts of the pathogenesis and treatment of RA.

An edited transcript of the NIH Conference was published in the December 1984 *Annals of Internal Medicine*. In this article, Ronald L. Wilder, M.D., Ph.D., of the Arthritis and Rheumatism Branch, National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, listed the current hypotheses of the etiology of the inflammatory response in patients with RA (Table 1), and discussed the reasons for proposing each hypothesis.

Table 1



Current Hypotheses of the Etiology of Inflammation in Patients with Rheumatoid Arthritis

- Deposits of immune complexes and rheumatoid factors in joints
- Presence of mycoplasmas or parts of mycoplasmas in joints
- Presence of viruses (rubella, Epstein-Barr, parvovirus, or others) in joints
- Deposits of bacterial cell walls or other microbial debris in joints
- 5. Antibodies against type II collagen in joints
- An innate irregularity in the immune system, causing overstimulation of cells in joints

In Hypothesis 1, a persistent unknown causative stimulus results in the deposition of rheumatoid factors and other immune complexes in joint tissues, inducing inflammation. These immune complexes are known to be associated with many types of persistent infection in animals and humans, and may be a normal reaction to infection. This hypothesis also states that although immune complexes contribute to the disease process, they are not the primary cause of RA.

According to Dr. Wilder, all of the remaining hypotheses belong in a single category: RA is a response to a definite stimulus, whether that stimulus is endogenous [originating within the body] or exogenous [originating outside the body]. Possible exogenous stimuli include mycoplasma infection or virus infection (Hypotheses 2 and 3). As Dr. Wilder stated: "infectious agents must still be considered as possible exogenous agents that can induce the inflammatory process in rheumatoid arthritis."

... infectious agents must still be considered as possible exogenous agents that can induce the inflammatory process in rheumatoid arthritis. Particular types of bacteria, including group A streptococci and several strains of *Lactobacillus* [major components of normal human intestinal bacteria] have been associated with the development of arthritis (Hypothesis 4). The cell walls of these bacteria contain peptoglycan, a potent stimulator of inflammation.

In animal studies, administration of type II collagen [a substance necessary for binding of connective tissue] also has resulted in arthritis (Hypothesis 5).

Finally, Hypothesis 6 postulates that RA may result from abnormal stimulation of various cells in the joints, without exogenous involvement, leading to chronic inflammation.

In summary, Dr. Wilder stated that the current view of RA is that it is a chronic response to either exogenous factors or endogenous factors in the joint tissue.

Subsequent to the publication of this article, the NIH has expressed a strong interest in further research on antibiotic treatment for RA.

Further support of the validity of a microbial etiology for RA was provided by James R. Klinenberg, M.D., in his 1984 Presidential Address to the American Rheumatism Association (ARA). Dr. Klinenberg polled members of the ARA, including practitioners, scientists, and academicians, for their predictions about rheumatology over the next 50 years. The response "was an overwhelming sentiment that there would be additional discoveries of relationships between infections and various forms of inflammatory arthritis," leading to "the elucidation of a specific etiology and pathogenesis for both rheumatoid arthritis and systemic lupus." In addition, the respondents felt that by the year 2034 there would be a vaccine to prevent RA; obviously development of an effective vaccine can occur only if there is a known infectious etiology.

The sanction of an infectious etiology for RA by these two distinguished and respected organizations, the NIH and the ARA, indicates that even further research is required, and that the treatment of RA with antibiotics not only seems increasingly more valid, but may prove ultimately to be the most effective therapy available.

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The Arthritis Institute of the National Hospital for Orthopaedics and Rehabilitation

Institutional Organization



The Arthritis Institute, located in Arlington, Virginia, is part of a medical center that comprises three independent facilities: a hospital, an outpatient clinic, and a research institution. Clinical inpatient care in rheumatology and orthopedics is provided by a 170-bed facility, the National Hospital for Orthopaedics and Rehabilitation; an outpatient facility, the Arthritis Clinic of Northern Virginia, offers consultative care in rheumatology. The Arthritis Institute provides clinical laboratory testing for the Hospital and the Clinic, and conducts research projects on the rheumatic diseases.

The Institute's research staff combines an unsurpassed depth of background knowledge with years of clinical experience. Most members of the research staff have worked together for more than two decades, tracking the treatment and progress of more than 10,000 patients. This kind of continuity of effort is unique, and is particularly important in the research into the causes and cures of rheumatic diseases, which are characteristically chronic.

An independent, nonprofit organization, the Institute is funded from endowments, private contributions, and research grants. These funds provide a sound financial base from which the Institute can efficiently and expeditiously implement research goals.

Medical and Research Staff

Thomas McP. Brown, M.D. Founder and Chairman



A world-renowned leader in arthritis research and treatment, Dr. Brown has served as arthritis consultant to the White House, and has been a member of the National Research Council. Most recently he has been appointed to the Food and Drug Administration's Arthritis Advisory Committee, which reviews and evaluates available data concerning the safety and effectiveness of prescription drugs used in the treatment of arthritis. An example of the esteem in which Dr. Brown is held is this quotation, part of a letter from President Ronald Reagan: "Your accomplishments, both as a practicing physician and as an authority on arthritis, are widely known and valued, and your leadership in clinical practice and research has been responsible for reducing the suffering of arthritis victims throughout the world."

A graduate of Swarthmore College and Johns Hopkins Medical School, Dr. Brown also served as Chief Resident in Medicine at Johns Hopkins and as a resident at the Rockefeller Institute Hospital. He was an Assistant Professor of Medicine at Johns Hopkins before becoming Chief of Medicine and Director of Arthritis Research at the V.A. Hospital in Washington, D.C. Dr. Brown was named Chairman, Department of Medicine, at George Washington University School of Medicine, where he served for 21 years before leaving to establish the Arthritis Institute in 1970.

In 1939 Dr. Brown published the first paper on the isolation of PPLO from rheumatic tissues, and his clinical research efforts since that time have produced more than 80 scientific papers on arthritis, as well as

Harold W. Clark, Ph.D. Research Director



John T. Hicks, M.D. Clinical Director



chapters in medical textbooks. He has directed the use of millions of dollars in research and training grants from both federal and private sources, and has served as a consultant to several Washington, D.C. hospitals.

In addition to his expertise and depth of experience as a researcher and teacher, Dr. Brown continues to enjoy patient care. His tireless interest in treating patients has been an outstanding example and inspiration to medical students and physicians alike.

Dr. Clark is a leading expert in microbiology, biochemistry and immunology, particularly as they relate to arthritic diseases. His pioneering efforts in investigating the role of mycoplasmas in arthritis, in both animal models and humans, have earned him well-deserved worldwide recognition in the form of federal and private research grants. Dr. Clark has published more than 50 scientific papers.

An alumnus of Wooster College, Dr. Clark received a Ph.D. in biochemistry from the University of Rochester, where he also served as a Fellow in the U.S. Public Health Service. He was Associate Research Professor of Medicine and Director of Research in the Rehabilitation, Research, and Training Center of George Washington University, also holding the position of Laboratory Director in the University's Arthritis Research Institute.

Dr. Clark joined the Arthritis Institute with Dr. Brown in 1970 as a founding member, serving as executive officer and chief administrator for the Institute after his 18 years of service at George Washington University.

Dr. Hicks, a recent addition to the Arthritis Institute staff, has had considerable experience in research, investigating the possible viral cause(s) of arthritis, and overseeing drug testing and patient care. As Group Director, Medical Affairs in the Rheumatology/Immunology Division of Smith Kline Beckman Corporation, Dr. Hicks was responsible for worldwide controlled trials of oral gold therapy involving more than 1,000 patients at more than 100 medical centers. During that time he also developed, organized and directed clinical trials of long-acting drugs in double-blind, placebo-controlled comparison studies.

A graduate of the University of Michigan, Dr. Hicks received his M.D. degree from Columbia University College of Physicians and Surgeons. He was a resident and Fellow in Rheumatology at Georgetown University Hospital, served as a Senior Investigator in the Division of Virology, Bureau of Biologics, F.D.A., and was a Fellow in Rheumatology at West Virginia University. While in private practice in Philadelphia before joining Smith Kline, Dr. Hicks was Clinical Assistant Professor of Medicine and Rheumatology at Temple University.

In addition to his patient care responsibilities at the Hospital and Clinic, Dr. Hicks will direct controlled clinical trials of antibiotic therapy for RA and related disorders.

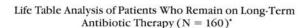
Retrospective Research Studies

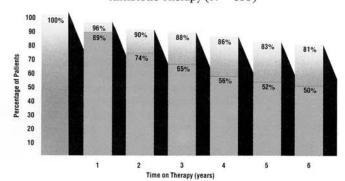
... 81% of patients would still be benefiting from antibiotic therapy at six years... an impressive success rate for a long-term therapeutic regimen. As a means of providing background for further research studies, and to analyze the results of antibiotic therapy over an extended period of time, the Arthritis Institute commissioned a biostatistical research corporation to analyze data on 98 patients treated over five years—a total of 451 patient-years of treatment. The study was conducted by an independent group of statisticians and epidemiologists whose purpose is to review raw medical data and prepare specific statistical analyses and reports. Independent clinical and epidemiologic consulting on the project was furnished by M. C. Hochberg, M.D., M.P.H., Associate Professor of Medicine (Rheumatology) and Epidemiology at the Johns Hopkins Medical Institutions.

The results of this retrospective study indicated that 70% of patients were likely to remain on antibiotic therapy for at least five years. About 84% of patients reported 50% or greater improvement in the number of tender and swollen joints, and 75% reported improvement in systemic symptoms (weakness, fatigue, depression, lack of wellbeing). Over 50% of patients in the study had previously failed on gold therapy.

In another retrospective review, Dr. Hicks analyzed data on 160 patients with classic and definite RA who had received antibiotic therapy for at least five years since 1978. Life table analysis, shown in Figure 1, indicated that 81% of patients would still be benefiting from antibiotic therapy at six years, excluding those who stopped therapy because of adverse drug reaction or insufficient therapeutic effect. Even when those who had died or were lost to followup for other reasons were included in the analysis, 50% would remain on therapy at six years. This is an impressive success rate for a long-term therapeutic regimen.

Figure 1





Figures include discontinuations due to adverse drug reaction or insufficient therapeutic effect.

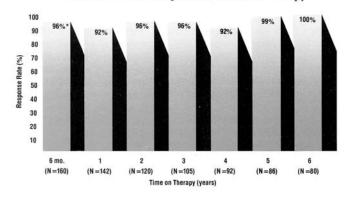
Figures include discontinuations for all reasons, including adverse drug reaction, insufficient therapeutic effect, death, intercurrent illness, loss to followup, and remission.

*Data presented at 1985 ILAR Meeting, Sydney, Australia

Figure 2 illustrates calculations of the therapeutic response rate over time. While at the end of one year the rate was excellent—96%— these figures show an even better response rate over greater time. During the sixth year of antibiotic therapy, 100% of the patients had a favorable response.

Figure 2

Rates of Favorable Response to Antibiotic Therapy



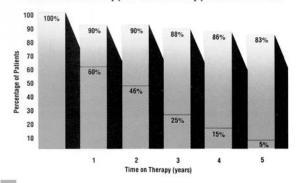
*Response rate is calculated by comparing the number of patients responding favorably at the end of each time period to the total number whose data were available for analysis during that time period.

The percentage of patients still receiving benefit from antibiotic therapy over time is considerably higher than the percentage of patients who continue to receive benefit from gold therapy –83% as opposed to 5% at the end of five years.

The percentage of patients still receiving benefit from antibiotic therapy over time is considerably higher than the percentage of patients who continue to receive benefit from gold therapy—83% as opposed to 5% at the end of five years (Figure 3).

Figure 3

Comparison of the Probability of Remaining on Antibiotic Therapy or Gold Therapy after Five Years



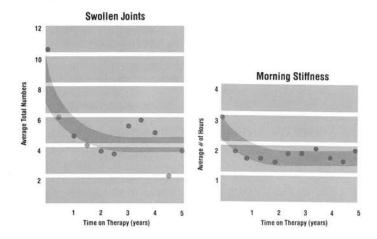
Antibiotic Therapy

Gold Therapy

The average number of swollen joints was reduced from 10 to 3 in 73% of patients over the five-year treatment period, and the duration of morning stiffness decreased from three hours to less than two hours in 50% of patients over the same time. Figure 4 illustrates these results graphically. A striking observation was that improvement in these common indicators of RA developed by six months and improved over 6-18 months. These rates of response are statistically significant and clinically important. It is important to note that these curves of improvement are remarkably similar to improvement curves found in clinical trials of both injectable gold and auranofin.

Figure 4

Average Reduction in Number of Swollen Joints and Duration of Morning Stiffness in Patients on Antibiotic Therapy



Adverse drug reactions requiring discontinuation of antibiotic therapy were very low—only 14 patients of 160 discontinued antibiotic therapy over six years for this reason (Table 2).

Table 2

Because of Adverse Drug Reaction ($N = 160$)	
Gastrointestinal	8
(nausea, diarrhea, cramps)	
Sinus congestion	2
Rash (tetracycline)	1
Vaginitis	1
Headache	1
Nonspecific subjective symptoms	1
Total over 6 years	14/160

Prospective Research Studies

... the Arthritis Institute is now planning large-scale, long-term clinical studies that should provide definitive answers about the safety and sustained efficacy of antibiotic therapy for treatment of [RA]... With the extensive information and experience obtained in using antibiotics to treat more than 10,000 RA patients over a 40-year period, and with the recent encouragement of the NIH and other respected research groups, the Arthritis Institute is now planning large-scale, long-term clinical studies that should provide definitive answers about the safety and sustained efficacy of antibiotic therapy for treatment of this serious chronic disease. Controlled prospective studies, double-blinded whenever possible, should provide sufficient evidence to resolve these uncertainties to the satisfaction of the medical community.

The Institute is now actively soliciting financial support to conduct prospective clinical studies. The goal of the proposed research program is to conduct large-scale multicenter controlled double-blind studies to clarify the role of antibiotic therapy in the management of RA

Outside support of the research programs of the Arthritis Institute is vital in the fight to conquer RA, one of the most crippling and costly diseases known.

With this support, the Institute can continue its work to determine the cause(s) of RA and develop optimal treatment for patients with this potentially devastating disorder.

For Further Information

The Arthritis Institute would welcome the opportunity to talk with you about supporting the research mentioned in this booklet. Please call or write to:

Research Office
The Arthritis Institute of the National Hospital
for Orthopaedics and Rehabilitation
2455 Army Navy Drive
Arlington, Virginia 22206
Phone: (703) 553-2431



The Arthritis Institute of the National Hospital for Orthopaedics and Rehabilitation 2455 Army Navy Drive, Arlington, VA 22206

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In his technical career, which spanned more than 30 years, Mr. Reddan was involved in a spectrum of technical fields from computers and missile guidance systems to electronic instrumentation. He participated in the design of numerous missiles and satellites, as well as in the design and implementation of the world's first fully rotational sports complex, the Aloha Stadium in Honolulu. As both engineer and entrepreneur, Mr. Reddan was instrumental in the founding of several advanced technology companies, including Infrared Industries, Inc., Electronuclear Laboratories, Nash Controls, I.R. Development Corporation, and Rolair Systems. He also helped to establish affiliates Europe and in the Orient.

Currently, Mr. Reddan is a Trustee and member of the Executive Committee of the Santa Barbara Medical Foundation Clinic, and is a director of the Financial Corporation of Santa Barbara and Santa Barbara Savings. He is listed in Who's Who.