Research Activities in Rheumatic Diseases

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THE RHEUMATIC DISEASES currently subjected to the most intensive investigation in this country are rheumatic fever, rheumatoid arthritis, gout, and the so-called collagen diseases. The following comments are addressed mainly to the first three of these conditions.

During the past year (July 1952 to July 1953) an estimated total of approximately $1,750,000 was contributed in support of research in the rheumatic diseases in this country. Of this amount, 57 percent was advanced by the Federal Government, mostly by the Public Health Service, and the rest (43 percent) by voluntary agencies, universities, foundations, industrial corporations, and private sources combined (figs. 1 and 2).

Rheumatic Fever

The most significant advance made in rheumatic fever as a result of clinical investigation is the demonstration that this disease is preventable. In 1939, it was reported that recurrences of rheumatic fever could be prevented by the continual administration of sulfanilamide to patients who had rheumatic fever. Sulfonamides are effective bacteriostatic agents and suppress the growth of hemolytic streptococci which precede and, it is thought, may incite an attack of rheumatic fever. It was soon discovered, however, that once a streptococcal throat infection developed, administration of sulfonamide was ineffective in preventing the sequel of rheumatic fever. In this regard, penicillin was subsequently found to be decidedly superior to sulfonamides. Although either agent when administered prophylactically to an uninfected person can prevent streptococcal infections and hence recurrences of rheumatic fever, only penicillin can prevent rheumatic fever even when administered after the onset of a hemolytic streptococcal throat infection. This superiority is attributed to bactericidal properties of penicillin in contrast to bacteriostatic action of the sulfonamides. The earlier after onset that penicillin is administered (within 24 hours) the more effective it will be in preventing rheumatic fever.

It is the practice today, therefore, to keep all rheumatic subjects, especially children and adolescents who are most prone to develop recurrences, on daily sulfonamide or penicillin prophylaxis for 5 years or longer following an attack of rheumatic fever and to administer to all patients who develop a hemolytic streptococcal sore throat large doses of penicillin with-

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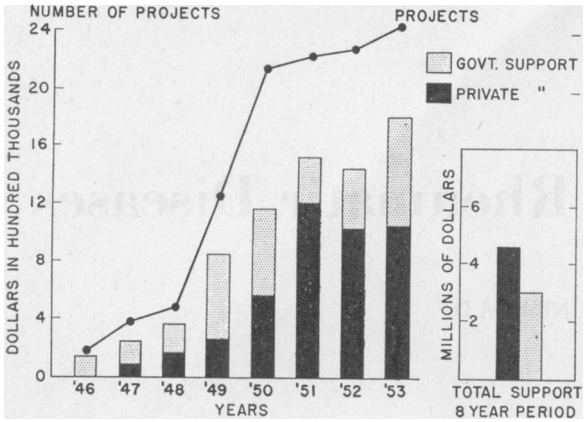
Figure 1. Government and private funds granted for research on rheumatic diseases, 1946–53.



in the first 24 hours of infection. Under such a regimen only 2 percent of known rheumatic subjects will develop recurrences and 0.2 percent of nonrheumatic subjects will develop rheumatic fever. Without these agents the recurrence rate among rheumatic fever subjects following a hemolytic streptococcal infection has been as high as 50 percent.

During the past 2 years, a new repository type of penicillin (Dibenzyl) has been studied. It shows promise of being a useful compound in simplifying effective prophylaxis of rheumatic fever. It now appears that an intramuscular injection of 1,200,000 units once each month will sustain enough concentration of penicillin in the serum and tissues to prevent hemolytic streptococcal infections and even to eliminate the carrier state.

Rheumatoid Arthritis

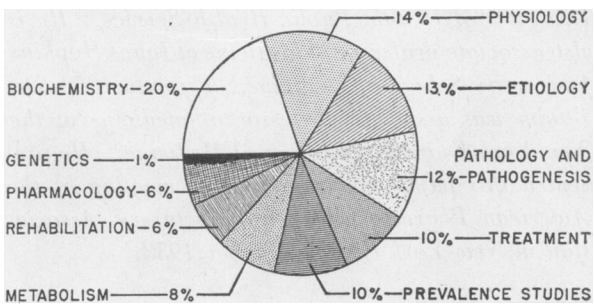
Neither the cause nor the cure of rheumatoid arthritis, the most dreaded of all types of arthritis, is known. Cortisone, hydrocortisone, and corticotropin, when administered to patients who have reversible disease, will very frequently result in dramatic improvement. This may or may not be sustained with prolonged administration. In 80 percent, relapse occurs when the hormone is discontinued. Undesirable effects from this medication are common, and in about 5 to 10 percent they are serious. It is believed that these compounds act by suppressing inflammation. No other adrenal cortical steroid studied thus far has antirheumatic properties. With experience, we have learned to select the proper patients for hormonal therapy more judiciously and to administer these agents more skillfully than in 1949 and 1950.

We are now looking for a steroid whose antirheumatic potency could be enhanced or whose chemical degradation could be inhibited to such a degree as to satisfactorily suppress inflammation of the articular structures and yet produce no undesirable side effects. That this is possible is masterfully exhibited by nature. The pregnant woman with rheumatoid arthritis has a sufficient increase in the steroid concentration of her tissues (as reflected by increased urinary excretion) to experience a striking remission of her arthritis; yet she develops none of the iatrogenic complications seen with prolonged cortisone, hydrocortisone, or corticotropin administration.

The National Institute of Arthritis and Metabolic Diseases of the Public Health Service has made available to responsible investigators in this country radioactive C^{14} cortisone acetate and hydrocortisone. Along with other workers the institute is studying the metabolic fate and physiological disposition of these radioactive steroids.

Phenylbutazone is an effective antirheumatic agent, and, by some mechanism of action which is quite different from the adrenal steroids, it too suppresses inflammation. It also has analgesic properties. Phenylbutazone does not alter the course of rheumatoid arthritis, and when it is discontinued the arthritis relapses. Phenylbutazone cannot be tolerated by approximately 25 percent of the patients. Some of the

Figure 2. Proportion of the arthritis research dollar devoted to different study fields in projects supported by the Public Health Service.



toxic effects are serious, and several deaths apparently resulting from its use have been reported in the American medical literature. Although the mortality rate is a small fraction of 1 percent, nevertheless, many physicians have been discouraged from prescribing phenylbutazone because of these fatalities. It is safe to predict therefore that several derivatives chemically related to this compound will be synthesized and tested with the objective of finding a drug which is free from serious toxic effects and yet retains the desirable antirheumatic properties.

Gold compounds, first introduced in the treatment of rheumatoid arthritis 25 years ago, are still commonly used in this country and Europe. The majority but not all of the experienced clinicians in this field believe that there is considerable merit in gold therapy. Gold may help control the inflammatory phase of the disease. It does not repair damaged cartilage or bone, nor does it free an organically ankylosed or fixed joint. Like cortisone, therefore, it is of value only while the arthritis is active. When gold is discontinued relapse occurs in the majority of cases; therefore, many physicians now maintain their patients on gold therapy for years rather than prescribe interrupted courses. The mode of action of gold is unknown.

Toxicity is severe enough to cause interruption of treatment in 10 to 20 percent of cases. Fatalities today are rare because of greater experience and skill in the administration of this compound, more conservative dosage, and availability of effective agents for combating toxicity, namely, British anti-lewisite (BAL or dimercaprol), cortisone, or corticotropin. There are many patients who can tolerate gold well but who do not benefit from it.

Finally, it is questionable whether gold therapy significantly alters the ultimate clinical course of rheumatoid arthritis even in those patients who derive definite benefit from it during the first few years of treatment. It becomes apparent therefore that gold is not the answer to rheumatoid arthritis. Many physicians believe it is the best available drug; no one will question, however, that it is not an ideal therapeutic agent, hence, the search for a more satisfactory compound is actively in progress today.

Gout

For more than 400 years, colchicine was the only drug known to be of great value in the treatment of gout. In the past 4 years, three important compounds have been accepted as very useful therapeutic agents: corticotropin, phenylbutazone, and probenecid (Benemid).

Although colchicine has the capacity to terminate promptly and dramatically an attack of acute gouty arthritis, it does not increase uric acid excretion nor reduce uric acid level in the blood. In fact, we do not understand how colchicine acts, although it has been used for centuries. Corticotropin can also promptly terminate acute attacks of gouty arthritis. It is superior to colchicine in that the unpleasant gastrointestinal disturbances that appear simultaneously with the therapeutic effect of colchicine do not occur when the corticotropin is used. Although uric acid excretion is increased when this hormone is given, the improvement which follows does not result from this incidental effect.

Phenylbutazone, like corticotropin and colchicine, can terminate an acute attack of gouty arthritis within 24 to 48 hours. It causes a prompt and marked fall in the serum urate level and often but not always a rise in urinary uric acid excretion. Phenylbutazone has certain advantages which makes it more desirable in many cases than either corticotropin or colchicine.

These three drugs are used chiefly to abort acute attacks. For prolonged treatment during the quiescent intervals between attacks probenecid, or Benemid, has been found of definite value in gouty patients who have deposits or uric acid tophi in their tissues. Benemid, which is relatively nontoxic, reduces the level of urates in serum and other extracellular fluid from excessive to normal levels by increasing urinary excretion. The daily increase may be as high as 67 percent over premedication level and is accomplished by specifically blocking reabsorption of urates at the renal tubular epithelium. In some cases, it has been demonstrated that Benemid mobilized long-established tophaceous deposits. Some observers have claimed that prolonged Benemid therapy reduces the frequency of acute attacks of gouty arthritis.

Although these new agents make the outlook for the gouty patient more hopeful, they have not given us an insight into the nature of the intrinsic error in purine metabolism which occurs in gout. At the National Institute of Arthritis and Metabolic Diseases and in a few other centers in this country, studies are in progress on intermediary purine metabolism in gouty and nongouty patients using isotopically labeled glycine and uric acid.

Areas for Research

Important problems that will require thoughtful consideration, careful planning, and sustained scientific pursuit in the immediate future are:

1. To obtain a better understanding of the biochemistry, biophysics, and function of connective tissue which apparently is the primary site of reaction in most of the rheumatic diseases.

2. To elucidate the mechanism of inflammation in these diseases and to develop laboratory methods for satisfactorily screening and evaluating effective anti-inflammatory agents.

3. To determine the role of hypersensitivity or antigen-antibody union in the pathogenesis of certain diseases like rheumatoid arthritis, rheumatic fever, polyarteritis nodosa, and lupus erythematosus.

4. To find a more satisfactory method than is at present available for measuring objectively clinical improvement in arthritis that may result from the administration of a given compound.

5. To collect accurate information on the prevalence and incidence of the various types of arthritis and nonarticular rheumatic disorders in this country.

Characteristics of Needy Aged Persons

A "typical" needy person receiving old-age assistance is a 75-year-old woman living alone in her own home or rooms and taking care of herself. She receives about $14 a month from her children, from social security benefits, or other sources and about $51 a month in old-age assistance, giving her a total income of $65 a month. She will receive old-age assistance for about 7 years.

This description is a composite picture which the Bureau of Public Assistance, Department of Health, Education, and Welfare, formed on the basis of preliminary data from its nationwide study of persons served by the State-Federal old-age assistance programs. The data are based on a statistical sample of the 2.6 million recipients.

Four-fifths of all persons receiving old-age assistance are 70 years of age or older; a fourth are 80 or older, and more than 1,000 are over 100 years old, according to the findings of the study. In spite of their extreme age, 82 percent are able to care for themselves, and less than 4 percent are bedridden.

Most of the old-age assistance recipients (69 percent) are widows, widowers, or single persons, and most of them (60 percent) live outside of metropolitan areas, chiefly in towns of 2,500 or less, on farms, or other rural places. Sixty percent of the recipients are women.

The study also indicates that 59 percent of the needy aged persons live with a relative, that over 25 percent live alone; and that less than 5 percent live in any type of institution or nursing home. Others live with friends, in hotels, or in boarding homes. More than half (54 percent) have been dependent on public assistance for less than 5 years, and only 5 percent have received it for 15 years or longer.