

HEBERDEN ORATION, 1955

RESEARCH AND THE RHEUMATIC DISEASES*†‡

BY

WALTER BAUER

From the Medical Clinic of the Massachusetts General Hospital and the Department of Medicine, Harvard Medical School, Boston, Mass.

(RECEIVED FOR PUBLICATION, OCTOBER 19, 1956)

I am particularly pleased to be privileged to deliver the Heberden Oration this year. Lectureship before this Society constitutes an honour of which I am very proud. The preparation of this lecture has given me an opportunity to review past problems, which we have undertaken with varying degrees of success, to describe work in progress, and to tell of future plans which I believe hold unique opportunity and challenge.

The study of the rheumatic diseases at the present time is not an easy task. The breadth of the field and the lack of clearly defined disease mechanisms and of leads as to cause or cure create a situation in which no single methodological approach seems clearly indicated, and many approaches are possible. I will, however, describe how one arthritis unit functions, and what it hopes to contribute to our understanding of these as well as other problems. Though the course we pursue is uncharted, nevertheless, we have faith in this approach for reasons which I trust will become apparent.

Twenty-seven years ago, when I first became interested in the rheumatic diseases, it was decided that one of our aims should be descriptive accounts of each of these disorders, especially rheumatoid arthritis. Some of the inquiries proposed concerning the latter disease were these:

What is the nature of the disorder?

Is it exclusively a disease of the joints, or is there widespread involvement of many organ systems?

What is its course and what are the factors which influence it?

It was our hope that as rheumatoid arthritis became more clearly defined, we should be able to

* This is publication No. 202 of the Robert W. Lovett Memorial Foundation for the Study of Crippling Diseases.

† The studies herein reported have been supported by grants from the Commonwealth Fund, the United States Public Health Service, the Helen Hay Whitney Foundation, and the Eli Lilly Company.

‡ The Heberden Oration, postponed from 1955, was given at the Royal Society of Medicine on October 19, 1956.

take better care of patients suffering from the disease, and might obtain clues as to the cause of the disease, and if possible its prevention or its cure.

The initial description of the disease was based on a thorough clinical study, and, in many instances, pathological data on a series of 300 cases who have been followed over a period of 25 years. Despite a well-conceived, prearranged plan for the recording by well-trained personnel of historical, physical, and laboratory findings with careful statistical evaluation, several sources of difficulty in the interpretation of the data were encountered. These included problems relating to the comparability of the series of patients and the control subjects, the influence of hidden factors unpredicted in the planning stage on an association between two variables, and finally, the fact that the information was obtained from a sample of hospitalized patients, an important selection factor.

This study did, however, disclose certain features of the disease which are worthy of comment. For instance, an analysis of eighty of the original 300 patients who had experienced complete, or nearly complete, remissions before admission to the hospital revealed that onset before the age of 40 and primary involvement of a single joint favoured an intermittent rather than a progressive course. In a large majority of patients, attacks were "brief"—of one year's duration or less. In a smaller number of instances attacks were "long"—over one year. While attacks lasting over one year were much less likely to be followed by remissions, instances were recorded of complete remissions after 2 to 5 years of active disease. In the whole group with intermittent course, about twice as much time was spent in remission as in exacerbation.

Remissions occurred throughout the year, with a peak in May, but exacerbations were more frequent during the colder months, with distribution corresponding to the few available figures for the season of

onset of rheumatoid arthritis. The majority of the patients exhibited a tendency to experience exacerbations or remissions in the same quarter of the year. The significance of these observations will be referred to later.

In consequence of this long-term, detailed study and extensive pathological examinations, we now have a fuller appreciation of the fact that rheumatoid arthritis is a chronic inflammatory disease, characterized by the manner in which it involves joints, but systemic in nature. This is readily demonstrated by the fact that lesions can be found in such diverse organs as the skin, subcutaneous tissue, muscles, nerves, eyes, heart, and aorta.

Perhaps the most vivid demonstration of other organ or system involvement by the rheumatoid process was the more than chance association of aortitis and aortic insufficiency with what we term rheumatoid (ankylosing) spondylitis. Detailed clinical study of nearly forty cases with this syndrome, together with pathological information on nine, has convinced us that aortic involvement is, indeed, part and parcel of rheumatoid spondylitis. This clinico-pathological entity has been observed almost exclusively in males and is frequently associated with uveitis. The lesion mimics that of luetic heart disease, but tends to remain localized to the region of the aortic valve, rarely, if ever, involving the aorta distal to the ascending portion.

These same detailed clinical studies have proved of great value in caring for patients with rheumatoid arthritis. They have taught us what complications can reasonably be attributed to the disease, and do not call for a second or third diagnosis. The increasing awareness that rheumatoid arthritis is a constitutional disease which is not confined to articulations has contributed to our emphasis on rest as one of the cardinal features in its treatment. The demonstration of the high incidence of spontaneous remissions, especially in certain types of case, has led us to considerable scepticism about many remedies alleged to lead to remissions. The evidence concerning the seasonal incidence of a high percentage of naturally occurring remissions and exacerbations provides facts which should not be lost sight of in any consideration of the aetiology of the disease.

On the other hand, as Dr. Albright facetiously remarked some years ago, "Bauer, pretty soon you'll know all there is to know about rheumatoid arthritis except its cause and its cure." This statement is not without its grain of truth, for while the detailed descriptive studies mentioned have contributed greatly to our understanding of the nature of rheumatoid arthritis and its treatment, they have not provided specific leads concerning either the

cause or the pathogenesis of the disease; nor have they led in the direction of a specific cure.

Knowing in advance that such clues might not be forthcoming, a parallel investigation had been begun at a more basic level, in the hope that as one learned more about the anatomy and physiology of connective tissue and its response to various insults, one would be able to learn more about the connective tissue diseases and possible aetiological factors.

These studies have been continued, with increasing intensity, through the years. For example, much of our time has been devoted to studies pertaining to the origin and properties of synovial fluid and its important constituent, "mucin". We are still in need, however, of information concerning the chemical composition of the polysaccharides of synovial fluid, their structural configuration, the enzyme systems concerned with their synthesis and degradation, and the intermediate compounds. As this knowledge comes to hand, the metabolism of mucin in articular diseases can be re-investigated. It is hoped that the results obtained by new approaches will reveal differences in articular disease in terms of both cellular derangements and biochemical alterations. It might then be possible to translate the alterations observed into terms of disease mechanism.

For obvious reasons, considerable attention has been given to the mechanism of exchange between the joint cavity and the body as a whole in both normal and diseased articulations. The analysis of a large number of joint effusions with histopathological findings shows that the changes are sufficiently characteristic to establish synovial fluid examination as an important diagnostic measure.

Another point of interest has been the change taking place in cartilage in ageing individuals and in patients with degenerative joint disease. Here, one is confronted with two considerations. One is the distinctly disadvantageous biological position of articular cartilage when subjected to injury. This is evident, anatomically, in the sparseness of its cellular constituents and its remoteness from blood supply and, physiologically, in an extremely limited faculty of autogenous repair. The other concerns the effect of mechanical stress and strain incident to joint function upon a tissue which is apparently incapable of repairing the damage resulting from constant wear and tear. Therefore, it is not surprising that the most constantly observed correlative to the so-called primary form of degenerative joint disease is increasing age. In fact, of the series of specimens obtained from individuals presumably without joint disease, all those past the second decade of life showed, progressively, evidence of this disorder.

The analytical appraisal, therefore, of the factors which govern maturation, maintenance, and ageing of hyaline cartilage and other mesenchymal tissues would appear to be a most worthwhile effort.

Upon my re-joining the rheumatic disease unit after the last war, it was decided that, in order to implement this research programme, additional investigators, of various backgrounds, should join our unit, to permit the investigation of connective tissue on an even broader level. Since then, much time has been devoted to the structural and chemical characterization of connective tissue components, such as the fibrous proteins, the non-collagenous proteins of the ground substance, the mucopolysaccharides, and the glycoproteins.

The original motivation behind our studies on collagen was the popular assumption that this fibrous protein is the target in rheumatic disease. To date, no convincing evidence for primary involvement of this protein is available. These studies have, however, led to exciting avenues of investigation into the mechanisms of fibre formation and degradation. The major efforts in this area have been directed towards the characterization of the collagen molecule, the process of polymerization of these units to form fibrils, the rate-regulating factors, and the involvement of collagen in growth processes and connective tissue derangements such as scurvy. Much of this work is based on the properties of solubility and the unique molecular configuration of collagen, which permit this protein to be precipitated in the form of fibrils of essentially native structure from cell-free extracts of connective tissue. The unique structural and chemical fingerprints of collagen revealed by electron microscopy and x-ray diffraction plus specific amino acid determination permit ready identification and quantitation.

Another interesting finding is the characterization of the building block or molecule of collagen, called "tropocollagen", and the devising of extraction procedures for obtaining the probable precursor of collagen and its *in vitro* polymerization to apparently native collagen fibrils. A direct correlation of the amount of this collagen fraction with growth rate has been made, and its isolation and characterization in the scorbutic process is under study. Among the questions raised are the nature of the intermolecular forces involved in the precipitation of collagen fibrils in the extracellular spaces; the factors regulating the rate of fibre formation, and the mechanisms responsible for the specific organization of the fibres on a tissue level. It is hoped that, as information of this type is gathered, it will have significant clinical application to problems of wound healing, abnormal sclerotic processes, congenital connective

tissue malformations, bone growths, and certain clinical entities, particularly scleroderma.

Running parallel with research on fibrous proteins are studies on the intimate chemical structure and properties of the acid mucopolysaccharides of connective tissue. Interest in these compounds was a product of our long-term study of the changes in the synovial fluid mucin so characteristic of rheumatoid arthritis. The connective tissue carbohydrates are ubiquitously distributed and are involved in many physiological functions. Interesting changes are found in their types, amounts, and distribution during embryo-genesis, growth, and ageing. A general scheme for the analysis of chemical structure of high polymer polysaccharides as well as low molecular weight substances, such as the aminosugar-containing nucleotides, has been devised for use on both macro- and micro-amounts of substances. This procedure involves methylation, degradation and comparison of the product with a host of methyl derivatives of various sugars synthesized in this laboratory. Elucidation of the structure of hyaluronic acid is now nearing completion. Knowledge of the detailed chemical organization of these biologically important substances should permit better understanding of their behaviour and functional role in the intact tissue. Among the questions raised are these:

- Can reactive high polymers such as chondroitin sulphate function in an ion exchange capacity in developing bone or in loose connective tissue?
- What types of proteins or lipids can they bind and what physical properties will such complexes impart to the tissues?
- How are the kind, amount, and state of such substances related to the normal and abnormal histology of connective tissue?

With this baseline biochemical experience, it may be possible to devise an attack on pathological tissue as well as to speculate as to the possible roles of such materials in the pathogenesis of disease.

Among the widely distributed carbohydrate-containing substances are the glycoproteins, which are present in both body fluids and tissues. These protein molecules contain relatively large amounts of tightly bound carbohydrate. Dramatic changes in concentration of serum glycoproteins occur in many disease states, including the rheumatic diseases, the significance of which, however, is still unknown. Several of the serum glycoproteins have been fractionated and purified in our laboratory with the aim of elucidating their structure and studying their biological significance. In addition to physical

chemical and analytical studies on the blood proteins, we have undertaken the fractionation of synovial fluid by a modification of the meticulous fractionation procedures developed for blood in the laboratories of the late Edwin J. Cohn at Harvard Medical School. Examination of the synovial fluid in rheumatoid arthritis and other arthritides has revealed the distribution of proteins to be very similar, if not identical, to that seen in plasma. Studies on normal human synovial fluid proceed more slowly because of the difficulty in obtaining it. It is hoped that now that we have a model and the experience required, we can extend these fractionation and purification procedures to other more complex tissues, both normal and pathological. These methods may make possible the isolation and mass preparation of relatively pure and unaltered tissue components for the study of their biological properties. The pharmacological properties of certain purified glycoproteins are being investigated at the clinical level, and the nature of the proteins and carbohydrates in amyloid and abnormal bone are being pursued in the laboratory.

Another line of inquiry has been undertaken in order to compare connective tissue and synthetic poly-electrolytes, as these might modify perfusing blood proteins. This work, still in its early stages, can only point to evidence of selective protein retention and modification in the two systems. Special interest attaches to the obvious fact that such reaction is favoured by conditions of column flow. The relatively avascular pattern of compact tissue such as articular cartilage and aorta might favour this sort of reaction.

In the field of enzymology, work is in progress on amino sugar metabolism as part of the endeavour to unravel the mechanism of mucopolysaccharide and glycoprotein synthesis. Another phase of this problem concerns the isolation from connective tissues of coenzyme-related compounds.

A problem more immediately related to the rheumatic diseases, especially rheumatoid arthritis, is the study of amyloid. In order to determine its origin, pathogenesis, and significance in both clinical and experimental material, careful analytical studies are being performed on amyloid tissue obtained from these sources. To date, the amount and the identity of the sugars contained in nearly pure amyloid have been established. Work in progress should characterize and identify the source of the proteins in both human and experimentally-induced amyloid.

Basic investigation in an entirely different direction was established in our unit twenty-odd years ago, when detailed studies on pleuropneumonia-like organisms and L-forms of bacteria were undertaken.

These observations indicated that bacteria may survive and reproduce in a variant form which is indistinguishable from the morphology of that class of agents known as the pleuropneumonia-like organisms. Although no L-form of a bacterium has been demonstrated to be virulent, their similarity to, if not identity with, the pleuropneumonia-like organisms, which are frequent pathogenic agents for a number of animal species, provides stimulus for further investigation of their possible aetiological role in human disease.

That natively-occurring pleuropneumonia-like organisms may be human pathogens has been suggested by studies on Reiter's syndrome, non-bacterial urethritis, and some infections of the female genital tract. Since some members of this group of organisms are saprophytes in the normal male and female genital tracts, evaluation of their role in the diseases mentioned must await better methods for their isolation, classification, and serological study. Attempts to demonstrate the presence of L-forms of bacteria in the tissues of experimentally-infected animals, and later in tissue obtained from patients with rheumatic fever and rheumatoid arthritis are in progress.

In addition to their possible clinical significance, study of the variant forms of the beta-haemolytic streptococcus has led to the discovery that the L-form of this species lacks the cell wall polysaccharide of the bacterial form. It has been suggested that the absence of this constituent accounts for the pliability and fragility of that form of the organism. Further, it would seem reasonable to speculate that this structural deficiency is a direct result of exposure to penicillin, the procedure used in obtaining L-forms.

From the foregoing, it must be apparent that I believe that fundamental research must be an integral part of the modern teaching hospital and can no longer be considered a luxury. The full-time scientist in a hospital must be regarded as the professional equal of the clinician. On the other hand, I hope that this presentation of some of the basic work in progress in the unit does not create the impression that our primary attention has been diverted from the sick patient and his care, for such is not the case. No catalogue of publications or research projects can come to grips with the central aspect of our work—a group of sick people who come to our clinic with their various needs. Whether it is a decision between lymphoma and rheumatoid arthritis, or an evaluation of some environmental factor which may underlie a flare-up in a patient's disease, instruction in the prevention of a deformity, or help in arriving at some compromise between the limitations imposed by disease and a patient's

concept of a life that's worth living—it is concerns such as these which marked our early endeavour in this field. To predict that our increasing interest in basic research would in any way displace this earlier interest would be to misread completely our attitude to the working relationship between these two pursuits.

I have told you something of our work in fundamental science and in clinical medicine—all this in an effort to come to grips with the idea of an exchange between these dissimilar endeavours, or, more accurately, between the dissimilar individuals who give themselves unreservedly to contrasting vocations. How can one guarantee, or at least, create an atmosphere which favours a productive, enjoyable, and mutually instructive collaboration within a group of this sort?

I believe that one of the most essential ingredients is to allow its members complete independence and the right to work on any problem of their own choice and to collaborate or not as they see fit. The success of such a unit will depend ultimately on the correct choice of individuals. They must be able, imaginative, independent workers with broad common interests, and with the ability and personal security necessary to allow good contact with their colleagues. The institution must provide the stability that men and women of tenacious spirit require for bringing long-term operations to a successful end. In this environment, each individual can establish his reputation on his own merit and thus look forward with confidence to a successful research career in the basic sciences or in clinical medicine, either with us or elsewhere. We believe that a collaborative effort made voluntarily by equals through mutual respect and honest belief in the merits of the project will probably be more productive than a team effort instigated and driven by a team leader.

I believe there is a peculiarly useful role to be played by the individual schooled in the disciplines of both care of patients and basic science in sustaining an awareness of the problems in the rheumatic disease field. In my opinion, the training of a new "breed" of investigator of this type is as vital to advance in the rheumatic disease field as is our need

for the acquisition of new knowledge. An environment such as I have described is particularly useful in fostering the development of such an investigator. Here he can sustain both interests, but particularly he can appraise his dependence on others, his limitations from lack of breadth, and the loss of effectiveness that this entails, especially so when it comes to making significant decisions on incomplete evidence.

It must be recognized that at the present time it is relatively rare that the lessons of the laboratory can be directly applied in the clinic. Usually there is not enough knowledge on either side to bridge the gap. However, this gap will be narrowed more rapidly by permitting clinicians and basic scientists to live and work in close harmony. If the clinical department of the future is to have a lively interest in, and an understanding of, the role of fundamental biological research, it must have a certain number of key clinicians who have had more than a smattering of experience in its disciplines. Likewise, we believe that if the basic investigator is to acquire an active interest in medical problems, he must be willing to train young medical people and to contribute, at least as consultant, to the solution of the problems of the clinic. It should be possible under these conditions to produce increasing numbers of individuals who can speak both languages, thus opening new channels of communication and better rapport between scientist and clinician. As phrased so nicely by Himsworth: "Integration of knowledge occurs within men not between men. If medicine is to maintain its unity then it must include among its members not only the whole range of specialists in its component subjects, but men who, within their own persons, link relevant disciplines."

The success of a study unit such as ours, be it concerned with rheumatic or other diseases, requires the discharge of three responsibilities: the care of the sick, the investigation of the basic mechanisms of disease, and the teaching and inspiration of younger men. Each of these activities is enhanced by virtue of the other two. If we maintain and keep in perspective these three activities, we shall be in a better position more nearly to approach our goal—the alleviation of the rheumatic diseases.