Rheumatism Research: A Survey*

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Although the experimental method was introduced in the seventeenth century as the basic working tool of science, it was used surprisingly little in medicine until the last century, when the alarming prevalence of the acute communicable diseases began to be held as a reproach to the faculty. With the advent of the Industrial Revolution, which led the rural populace to flock to the towns where industries were daily springing up, crowding and lack of sanitation took their inevitable toll. At that time (which would be within the memory of my grandfather), the expectation of life at birth was less than half of what it is to-day.

Once the need for something better than traditional medical empiricism was clearly seen, the problem was tackled with that vigour which we now recognize as a characteristic of our Victorian forebears. The crusade against infectious disease, initiated by such men as Chadwick and Simon, was fortunate in its timing in that it corresponded with the culmination of the great work of Pasteur and his colleagues. The Public Health Act of 1870 may be said to have marked the beginning of the end of the menace of infectious disease and its high death-rate. Thus a problem which had seemed insoluble at the beginning of the century was reduced to the status of a nuisance by the end of it. This achievement, however, inevitably allowed us as a nation more time to develop, and to suffer from, diseases of a chronic and crippling nature; but realization of this did not come until recent years. It was Lord Dawson who first remarked in 1930: "The disorders of degeneration are advancing as the diseases of invasion recede." Flushed with triumph the newborn medical science looked for further conquests. One by one the more specific and "interesting" diseases succumbed; but the field of chronic non-fatal disease remained almost untouched, being considered unlikely to yield easy worth-while results.

Genesis of Rheumatism Research

Thus the situation at the close of the first quarter of our present century remained static until the problem was first systematically set before the medical profession as one which should engage its practical interest. It was a dynamic Dutchman, Jan Van Breeman, and a quiet scholarly London Quaker physician, Fortescue Fox, who founded the International League against Rheumatism, through which they planned that their message should reach every civilized country. In most places branches eventually grew, and gradually results began to appear. In Great Britain the Ministry of Health published its famous "Report on Rheumatic Diseases (1924)," the starting-point of official lay and medical interest in Europe. The report was a

statistical analysis of an extensive inquiry into the incidence of these disorders, and the hitherto unsuspected and devastating toll they were exacting from the industrial population. It was chiefly the work of the late Dr. J. Alison Glover, who made use of the data which were becoming available through the operation of the National Insurance Act. He followed it up with a second official report in 1928, calling attention to the need for special study and treatment of this group of diseases.

These reports encouraged the British Committee of the League to exert its influence upon various sympathetic voluntary bodies, including Friendly Societies and the British Red Cross, both of which allocated considerable funds to the formation of the first special clinic for rheumatic diseases in Peto Place, London. This clinic was opened by Queen Mary in 1930 and is now the Arthur Stanley Institute of the Middlesex Hospital. Thus the special discipline of rheumatology was established in this country and was made "respectable," although the conception of founding chairs in such a subsidiary "growing point" was still a quarter of a century away.

In 1933 the Royal College of Physicians set up a committee to study the chronic rheumatic diseases, the President, Sir Humphry Rolleston, nominating himself as chairman and me as secretary. It was this committee that first endeavoured to bring some order into the classification and nomenclature of these disabilities. Before then rheumatoid arthritis, for instance, was referred to under a different name in no fewer than sixty separate classifications of the rheumatic diseases in Europe and America. The committee published three excellent reports, edited by the late C. W. Buckley, and these were the prototypes of the *Annals of the Rheumatic Diseases*, for which the British Medical Association accepted financial responsibility in 1944 when it undertook its publication. By 1936, however, it had reached a point at which specialized facilities for bedside and laboratory research were essential to further understanding. As the limited financial resources at its disposal were clearly inadequate, a voluntary organization was established to collect funds.

This new body, the Empire Rheumatism Council, was formed at a meeting called for the purpose at the Royal Society of Medicine on 7 February 1936. Lord Horder was elected chairman. The members of the committee were elected *en bloc* as the Medical Advisory Committee, with Sir William Willcox as chairman. Shortly afterwards the Duke of Gloucester accepted the presidency. Since that day the Council has gradually increased its influence and accumulated funds, which it uses to subsidize research both basic and applied. In 1938 the first special department for rheumatic patients was established in a London general hospital with the support of the Council. To-day there are departments for these patients in six others. At a number outside London research work, clinical and basic, is carried out *pari passu* with routine clinical activities.

In 1944 the Ministry of Labour expressed concern at the considerable loss of working time in the war industries attributed to rheumatic diseases. Accordingly the Minister of Health set up a committee, with Lord Cohen of Birkenhead as

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chairman, to consider the provision of better facilities for the specialized diagnosis and treatment of this group of disorders and the organization of further research facilities. The deliberations of this committee were conducted with the knowledge that the Government intended to set up a National Health Service, and high hopes were aroused when its recommendations were approved by the Minister of Health at the end of that year. Unfortunately other problems rendered urgent by the end of the war diverted this newly aroused Government interest in rheumatology. Thus the National Health Service was born with a grave congenital deformity resulting from the lack of the special diagnostic, clinical, and research facilities which had been planned and promised for this field.

The initiative now reverted to the interested voluntary bodies, including the Nuffield Foundation. In 1946 a Chair of Rheumatology was instituted in the University of Manchester. A few years later another was established in London in association with the Medical Research Council unit; while in Edinburgh a readership in Rheumatic Diseases was created within the Department of Medicine. The World Health Organization, always sensitive to trends in medical thought, set up an Expert Committee on the subject. In 1950 a second special committee was formed by the Royal College of Physicians to consider the field anew. It urged the authorities to establish a number of regional centres in association with selected teaching hospitals for consultations, treatment, and research, and the extension of certain of those already existing. The committee took the view that it was desirable to make a number of consultant appointments in rheumatology within the National Health Service who could also conduct research. It felt that "such specialists could improve the average standard of care which patients with rheumatic diseases received throughout Great Britain." These recommendations were reiterated by the College in a further report ten years later (1961) and by the Porritt Review Committee in 1963.

In spite of all these activities much soil remains virgin from the clinical as well as scientific aspects. This fact has a strong appeal to certain types of worker. Many advances in recent years have served to increase clinical subdivision, and now no fewer than fifty different brands of "rheumatism" are well recognized, although their origins remain mostly doubtful. In this field above others, therefore, it is salutary to remember the truth of the epigram: "The limit of ignorance is the first definition of knowledge."

Population Surveys

It was in the field of rheumatology that the need to define the size and shape of the hitherto unprospected problem first led to the present fruitful alliance of academic clinicians and statisticians within the ambit of epidemiology. This resulted in the technique of the population survey, which, largely a British achievement, has proved so valuable in the hands of Bradford Hill, Kellgren, and Lawrence in increasing our knowledge. It was their initial survey in the town of Leigh in Lancashire that laid the foundation of our present information about the extent of rheumatic complaints. They found that frequency increased from 7% in the youngest group to 42% of those over the age of 40. From this it became obvious that there was still a great loss of working time in industry, and in 1956 the E.R.C. Field Unit was formed based on the University of Manchester. Since its inception it has carried out a number of further detailed surveys at home and in the Commonwealth. We now know that in this country there are more than 1.7 million patients who suffer with rheumatoid arthritis alone; that more than 3.7 million persons succumb to osteoarthritis; while degenerative lesions affecting the spine, intervertebral disks, and other parts of the body occur in a further 12% of the population. It has been discovered that, strangely, the majority of all these patients are never seen in hospital departments, so the immensity and importance of the problems involved—medically, sociologically,

and economically—are still not adequately recognized by the academic world.

Rheumatic Fever

In this disease group rheumatic fever has the longest pedigree in research. It was recognized by Hippocrates as a syndrome unconnected with podagra—the prototype of the arthritides. It was given its name by Guillaume de Baillou, court physician to Henri IV of France; and its association with heart disease was first mentioned by Dr. David Pitcairn, of St. Bartholomew's Hospital, in 1788. The great French physician Jean Baptiste Bouillard first demonstrated pancarditis of rheumatic origin towards the middle of the last century, but it was not until 1904 that Ludwig Aschoff described the pathognomonic granulomatous cardiac lesion that bears his name. Soon after the electrocardiograph was introduced, and physical research can be said to have started. Out of this developed modern cardiology and cardiac surgery.

It was discovered in 1930 that the disease is associated with a group-A haemolytic streptococcus, but more recent observations have shown that rheumatic fever is no simple bacterial infection but is probably the result of a complicated antigen-antibody reaction, which may, moreover, be determined genetically. The recent work by Glynn and Holborow on secretor genotypes may prove to be of great importance in this respect, as they seem to have shown that sufferers with rheumatic fever are invariably of non-secretor type. The inference, therefore, is that this factor constitutes a main component of postulated genetic predisposition of this disease. With the introduction of the sulphonamides and later the antibiotics preventive treatment became possible. In spite of this, and the epidemic decline in the disease from other causes, about 8,000 deaths still occur annually from the resulting valvular disease of the heart, many of these in children.

Rheumatoid Arthritis

Rheumatoid arthritis presents a problem which is now even more serious and far-reaching than that of rheumatic fever. It affects about 1% of all men in the British Isles, and at least 3% of all women. It may also present in its juvenile form—Still's disease. It heads the list of crippling disease and causes untold suffering, and often disrupting homes when the woman can no longer work.

The cause of rheumatoid arthritis remains completely unknown. There is evidence that a hereditary factor is often implicated. Many aetiologies have been ascribed to it, including bacterial and virus infection, nutritional deficiency, "stress," and endocrine and biochemical abnormalities. Some evidence is available of pleuropneumonia-like organisms in the synovial fluid as the result of culturing the circulating leucocytes.

The most important result of recent research has been the discovery that a macroglobulin of high molecular weight and with many of the properties of an antibody to the patients' own gamma-globulin is present in the blood of more than half the sufferers. It was originally detected as the result of its ability to agglutinate erythrocytes which had been coated with antibody globulin. This observation formed the basis of the modern "specific" diagnostic tests for the presence of the disease, such as the Rose-Waaler and the latex. (The Birmingham team of workers has played a leading part in all this.) The presence of such haemo-agglutinating substance in the serum seems to suggest that the aetiology of the disease may be found in some failure in the process of immunological self-recognition and the establishment of a condition of auto-sensitivity which leads to the development of an antibody-like reaction to certain cellular constituents of the patients' own connective tissues.

An aspect of rheumatoid arthritis which particularly interests some workers is the nature and significance of the typical nodules. These have a characteristic structure and may occur

anywhere in the body, even the heart, where they can produce conduction defects, or the eye, where perforation and blindness may occur. They do not occur in certain rheumatoid syndromes.

At least two long-term studies of the natural history of adult rheumatoid arthritis and of Still's disease have been maintained over many years and continue to yield information of great value; while at Taplow an additional group of sufferers with monarticular rheumatoid disease are under long-term observation, as are the mysteries of Sjögren's syndrome.

Osteoarthritis

This widespread affliction of damaged and elderly joints has been neglected on account of its lack of "interesting" features. It was considered that it constituted a simple wear-and-tear phenomenon and as such must be an inevitable concomitant of the ageing process. We must except from this stricture such long-established investigations as those of the Silberbergs into the growth cycle of epiphyseal cartilage and connective tissue in mice (rats are immune to this disease) and its relation to osteoarthritis, as well as certain genetic studies, also American, from which it seems increasingly likely that multiple genes are involved, the major part of the variation being controlled by recessive non-sex-linked genes.

The older belief that the constituent changes of osteoarthritis are purely degenerative in nature is thus becoming discredited. The recent electron-microscopical work at St. Thomas's Hospital and that of Collins in Sheffield into these ageing changes throw fresh light on the functions and reactions and structure articular cartilage as the result of following isotopically labelled sulphur radiochemically, and so estimating the rate of synthesis of chondroitin sulphate in relation to this disease.

It would appear from these and other studies that the process which starts this disease may not be degenerative or due to age but a change in metabolic control whereby loss of bone matrix stimulates the cells to increased synthesis of chondroitin sulphate in order to replenish this. In fact, an increase in local metabolic activity will result, and not the reverse. Thus it seems reasonable to presume that in this disease certain systemic metabolic factors are operative quite independently of either ageing or trauma, and the corollary that degenerative joint disease may not be a necessary part of growing old, in the absence of trauma or joint abrasion.

One clear-cut example of degenerative joint disease resulting from metabolic changes in the human subject is ochronotic arthritis occurring in conjunction with alcaptonuria. In this the systemic constituent is obvious on account of the pigmentation of the affected cartilage. It is possible to conceive of analogous disorders of metabolism in which the guilty metabolites remain unpigmented, and so still remain to be discovered.

In those cases where degenerative joint changes are seen to accompany the general ageing process, several interesting mechanisms have been suggested. Sokoloff and his colleagues at Bethesda have postulated that thermal degradation of collagen fibres and synovial connective tissues can occur at body temperature throughout life in certain subjects. Alternatively, the chemical interaction of collagen with naturally produced aldehydes or other metabolites may serve to "tan" it, and so facilitate premature degenerative changes.

All this, and much more of which I have not spoken, carries the germ of hope that medical means whereby degenerative joint disease may be modified or prevented are in sight.

Current Trends of Research

One of the important lessons learnt during the past twenty years has been that individual research into chronic disease, where clinical progress is slow, is apt to be unrewarding until

the value of special units is recognized, manned by specialized teams in everyday touch with clinical medicine but sheltered from overwhelming routine demands.

Clinical research in rheumatology has now reached the point where a large number of rheumatic syndromes are clearly recognized but in which aetiology remains mostly obscure. If available clues in this respect are to be followed up, we need the interest of many disciplines, basic and clinical. It is at this stage that it behoves us to remember that "it is the formulation of the right question which is the first step to wisdom"—a truism which is inevitably sometimes overlooked by the specialist.

Of the many fields in which fundamental research is active, possibly the most fertile may prove to be those of immunology and serology, and biochemistry as applied to steroid and enzyme metabolism. The histo-anatomical and chemical studies of collagen and other connective and synovial tissues, as enlarged by the electron-microscope, remains a basic necessity, and will be rendered more profitable if, as seems likely, we shall shortly be able to produce rheumatoid arthritis in the experimental animal. Recent studies have seemed to show that sufferers with rheumatic diseases differ in their genetical constitution from the rest of the population, so it is the nature of this genetical predisposition that remains to be determined. For instance, the highly significant difference in disease incidence between relatives of spondylitics and control populations is now being investigated and is yielding important results.

Of research into the auto-immune mechanisms, and more particularly investigation of the rheumatoid and antinuclear factors, we hear much, and Birmingham has pioneered in this field. It now seems likely that a number of factors are involved in each instance, and their spreading inter-relationship is occupying the attention of many workers. For example, the antinuclear antibodies detected by micro-fluorescent technique are now being used for the analysis of possible changes in the distribution of nuclear antigens in lymphocytes and other tissue cells, while recent work from Oxford also suggests that these substances may become localized in the synovium and the lymph-nodes. Much interest has lately become centred upon the probable role of the thymus gland in this milieu. The relationship between the auto-immune factors and the specific Hargreave cells found in disseminated lupus erythematosus is still unsolved and may constitute the aetiological key to this disease. A comparatively recent observation that thyroïd auto-antibodies are found more frequently in the serum of rheumatoid sufferers than others, and the relationship of their disease to Hashimoto's syndrome, is stimulating renewed interest in the thyroïd function of these sufferers. Pioneer work is being done by workers at the Middlesex Hospital, led by Roitt and his colleagues, where a research institute of rheumatology, on similar lines to your own, is being built.

The increasing knowledge and importance of the activity of enzymes in the rheumatic diseases is striking, while the biological significance of the muco-polysaccharides in cartilage and synovial tissue and fluid, together with other skeletal connective tissues, continues to demand attention.

Work which is proceeding on the basic phenomena of inflammation, by Spector and others, bids fair to throw additional light on the underlying process of the rheumatic diseases, while mention must also be made of the "pain substance"—a polypeptide isolated from the blood of both normal persons and sufferers by Keele.

More general problems, such as intra-articular joint temperature and its reaction to therapy, and the significance of sacro-iliitis in certain rheumatoid syndromes, attract interest, as well as the relationship of polyarthritis with psoriasis, which still remains undetermined, as does that of ulcerative colitis.

A somewhat novel multicentre study, initiated a few years ago, is concerned with 198 pairs of twins with rheumatoid

arthritis, and also 65 pairs with osteoarthritis. It is hoped that this will shortly serve to elucidate certain environmental and inherited aetiological factors affecting both these diseases.

Therapeutic Research

MacLagan and others noted with high hopes the anti-inflammatory ("antirheumatic") effect of aspirin soon after its introduction into practice at the turn of the century. The discovery of the far more effective suppressive substance cortisone fifteen years ago, and its subsequent host of analogues, threw no new light on the basic process which is responsible for rheumatoid arthritis; there remains no evidence of a steroid deficiency nor of any endocrinological defect. The remarkable effect of the steroid hormones in suppressing the inflammatory manifestations of the disease have, however, when properly used, been of great value to the internist, while a similar although less effective anti-inflammatory effect has been found to be inherent in drugs of the phenylbutazone family, and more recently indomethacin, which are still the subject of clinical study. An interesting suggestion has been made that the common factor in all these substances which produces relief lies in their power to inhibit adenosine tri-phosphate (A.D.P.) in connective tissues.

However, none of these substances is curative, but intensive research is pursued into the pharmacological bypaths which it is hoped will one day enable us to control the basic disease factors, whatever these may be. Therapeutic investigation of all types inevitably suffers from its mostly empirical nature and the difficulties of human assessment, and again in this field we are indebted to Bradford Hill for having introduced the technique of the double blindfold controlled clinical trial, which has kept us on sound therapeutic lines.

It now seems that the effects of the adrenal steroids and A.C.T.H. in rheumatoid arthritis may not be confined to their suppressive influence but may alter enzyme action at cellular level. Bush and others are doing outstanding work in this field of steroid chemistry. At the West London Hospital the long-term action of these substances has been studied over a number of years, more particularly, with the recent help of pituitary function tests, their effects upon the pituitary-adrenal axis. Of therapeutic interest also is the recent promise of synthetic A.C.T.H. polypeptides.

Antirheumatic drugs are being subjected to renewed study at the Unit on Drug Action which was recently founded at King's College Hospital to discover and define in biochemical terms the action of such drugs on cell metabolism. Much study has been devoted to the salicylate group there and elsewhere, particularly as regards its side-effects in the gastric and renal tracts.

The multicentre trial of the long-term effect of gold salts which was carried out by the Empire Rheumatism Council a few years ago remains a model of its kind, and for the first time established proof of its beneficent effect in rheumatoid arthritis. Perhaps a similar trial of the antimalarial drugs which are currently being used for this purpose should be undertaken also in the near future.

In the rather special field of gout the metabolic factor is reasonably well understood, but, largely as the result of tracer studies in America, the clearance of urate and phosphates from the body is now known to vary under differing conditions. The development of true uricosuric drugs has, however, revolutionized the long-term outlook for sufferers.

Clinical Research

Such purely clinical problems as electro-myography in correlation with muscle-biopsy appearances, joint stiffness, the mode of localization of radioactive gold preparations in the synovial tissues, and the ocular effects of some of the anti-malarial preparations used in the treatment of rheumatic diseases, and many other such projects are all the subject of intense investigation in various centres in this country and elsewhere.

Another field in which clinical research of a new kind is yielding useful and interesting results is the correlated medical-orthopaedic approach, notably in Edinburgh. Long-term operative results are being examined and the role of surgery in arthritic disorders is being reappraised. New proceedings have already been introduced, particularly in association with the prevention of early deformities and the restoration of function in the crippled hand. New types of splintage and appliances are being devised in a special appliance research workshop which has been set up. Elsewhere much thought and experiment is being devoted to the various techniques and materials used for arthroplasty, and such matters as the physiology of joint-surface lubrication. The work of Charnley in Manchester is notable in this respect. It is in such fields that the importance of linking the research institute directly with a clinical department of rheumatology shows most clearly.

Even that hoary piece of folk-lore regarding the effect of weather changes upon the pains of arthritis and non-articular rheumatism is being subjected to elaborate objective study by Hollander in Philadelphia. Series of patients live for several weeks inside his "climatron," a chamber in which he can accurately control the climate. He has already confirmed the general suspicion that peri-articular pains of this type can be exacerbated at will by increasing the humidity and concurrently lowering the barometric pressure temporarily, unknown to the occupants.

Conclusion

I have endeavoured briefly to summarize the lines along which investigation seems to be developing in this young field of rheumatology. Within the last twenty years it has increased from isolated individual effort to a large and increasingly international volume of research which explores many fields with profit. Much information of a basic nature is now available and it seems reasonable to believe that this will fit together much like a jig-saw in the foreseeable future. Thus if progress is the sum of many minor advances, it will be evident that already the prospect for to-morrow's rheumatic patient is becoming bright.