RECENT ADVANCES IN 3 RHEUMATOLOGY

Edited by
W. Carson Dick
J.M.H. Moll

Churchill Livingstone

Recent Advances in
RHEUMATOLOGY

EDITED BY

W. CARSON DICK
J. M. H. MOLL

NUMBER THREE

CHURCHILL LIVINGSTONE
EDINBURGH LONDON MELBOURNE AND NEW YORK 1983

CHURCHILL LIVINGSTONE
Medical Division of Longman Group Limited

Distributed in the United States of America by
Churchill Livingstone Inc., 1560 Broadway, New York,
N.Y. 10036, and by associated companies, branches and
representatives throughout the world.

First published 1983

ISBN 0 443 02681 5
ISSN 0309-2283

Library of Congress Catalog Card Number: 80-40621

Printed in Great Britain at The Pitman Press, Bath

Recent Advances in
RHEUMATOLOGY

W. CARSON DICK, MD, FRCP
Reader in Rheumatology, University of Newcastle, Newcastle upon Tyne; Honorary Consultant Physician at the Royal Victoria Infirmary and The Freeman Hospital, Newcastle upon Tyne, UK

J. M. H. MOLL, BSc, DM, PhD, FRCP
Consultant Physician in Rheumatology and Head, Sheffield Centre for Rheumatic Diseases, Nether Edge Hospital, Sheffield; Honorary Clinical Lecturer in Rheumatic Diseases, University of Sheffield, UK

Preface

The immediate questions which need to be answered by editors involved in the Recent Advances Series concern two primary issues. First, what is to be regarded as 'recent' and, second, what should be considered 'advances'? These points, raised by previous editors in this Churchill Livingstone series, need to be examined in the light of a further question — where should the boundaries between one -'ology' and another be drawn?

We hope that the current volume will satisfy these questions, though we fully accept the arbitrariness of the separate ideas implied by the title *Recent Advances in Rheumatology*.

The need for a further edition since Advances 1 and 2 was felt to be amply justified in view of the many exciting changes that have evolved within rheumatology since the last edition only 3 years ago. Furthermore, the fact that one chapter in this book is largely neurological, and that others contain material which could rest as happily in books devoted to other specialties, serves in particular to highlight the *widening*, as well as the *advancing*, thrust of the rheumatological specialty.

The contents of this volume could readily have been arranged in a different order, as they are intended to be digested as individual, self-contained units. However, whether the reader wishes to approach the book from front to back, or simply to dip into chapters of special interest, a general plan has been followed. The first seven chapters are primarily concerned with aetiopathogenesis, the next two with management and treatment, and the last with objective assessment.

The contributions can broadly be summarised as follows:

Drs Bennett and Goodacre discuss the lessons to be learned from animal models in the field of inflammation and immunopathological processes. This combined veterinary/medical approach serves to highlight the place of animal models in furthering our knowledge of the immune system and of inflammation in the aetiology and pathogenesis of several diseases in man, including rheumatoid arthritis and systemic lupus erythematosus.

The impact of monoclonal antibodies in rheumatoid arthritis is the subject of the essay by Drs MacKenzie and Williamson. The authors examine the exciting potential in this field, especially the way in which monoclonal antibodies provide an objective method to monitor changes in the immune system brought about by immunomodulatory substances. However, the therapeutic use of monoclonal antibodies in, say, rheumatoid arthritis seems unlikely at present, although clearly if this can be achieved their impact is likely to be even greater in the future.

Dr Pearson has reviewed recent thinking in the detailed field of proteoglycan biochemistry in relation to connective tissue diseases. Such studies are clearly of seminal importance in leading to a further understanding of the factors involved in the initiation and progression of disease processes in this group of disorders.

Professor Vernon-Roberts has drawn attention to the major areas of progress concerning a better appreciation of cellular, immunological and chemical events in the rheumatoid synovial lesion. However, he emphasises that relatively little progress has been made in other aspects of the joint lesion, apart from those to do with the synovial fluid. He stresses that the synovial rheumatoid nodule is the only histological feature pathognomonic for rheumatoid arthritis. It is concluded that further advances in the field of rheumatoid arthritis should result from an interdisciplinary collaboration, particularly between clinical rheumatologists, pharmacologists, immunobiologists, biochemists, and cell biologists.

Dr Brighton, from Pretoria, provides an account of rheumatic diseases occurring in the Third World, a subject that has received only scant attention in the past. Some of the lessons emerging could well be of value in understanding the nature of rheumatic diseases in general. More specifically the differences in the apparent frequency of rheumatoid arthritis in rural and urban Africans deserves closer study, as they might provide a further clue to the aetiology of this disease.

Dr Hudgson, a neurologist, reviews recent advances in diseases of muscle, a chapter which draws attention to the inextricable borderland that exists between neurology and rheumatology. Even in those conditions which are not equally claimed by both specialties the author points out that in many disorders of the lower motor neurone, the neuromuscular junction, or muscle cell itself, in terms of disordered musculo-skeletal function, the clinical picture may be difficult to distinguish from primary joint disease.

Drs Welsh and Black examine the major histocompatibility system and discuss its relevance to rheumatological disorders. The authors cover a wide field and discuss not only the strong associations between HLA–B27 and the spondarthritides, but also associations involving HLA–DR antigens and genes coding for the complement allotypes of C2, C4 and Bf, and for C3b and C3d receptors. Although it is acknowledged that HLA typing has proved of value in the subdivision of some clinical syndromes, the authors stress that the greatest potential in this field lies in its application to preventative medicine.

Drs Amos and Walker have critically surveyed current methods enabling immune manipulation in rheumatoid arthritis. They conclude that although the recent enlightenment in this area has aided the construction of pathogenetic concepts it has presented the clinician with some difficulty in selecting and applying methods based on immune manipulation in a logical way.

In these days of increasing cooperation between rheumatologists and orthopaedic surgeons, and 'combined clinics' to prove it, this volume would have been incomplete without a contribution from an orthopaedic standpoint. Professor Bentley and Mr Dowd have put recent advances in the field of 'rheumatoid surgery' in perspective, and it is hoped that this new information will be of help to all clinicians involved in the surgical management of their rheumatic patients.

Professor Wright reports on several new approaches in the field of objective assessment in rheumatology, and reminds us that the relative lack of objectivity in the speciality in the past has resulted not only in diagnostic imprecision but also confusion regarding the results of treatment. Recent developments and attitudes suggest that this is no longer a rheumatological *bête noire*.

It is hoped that the central message arising from these contributions is one of optimism. Certainly, much more research work needs to be done in the field of rheu-

matology, but it is becoming clear that on several fronts ideas concerning causes, mechanisms, and treatment — as well as approaches to assess these matters of paramount clinical relevance — are rapidly becoming more fruitful.

However, it is likely that several further editions will have passed before the time is reached when 'arthritis' and 'rheumatism' fall more within the province of prevention than those of control or cure.

Newcastle upon Tyne and Sheffield, 1983

W.C.D.
J.M.H.M.

Acknowledgements

We wish to thank Mrs June Thompson (Newcastle) and Mrs Pat Drake (Sheffield) for their continual help in coordinating the editorial work, and also the publishers for their helpful cooperation.

Contributors

R. S. AMOS BSc MB ChB MRCP
Consultant Physician in Rheumatology, Sheffield Centre for Rheumatic Diseases, Nether Edge Hospital, Sheffield; Honorary Clinical Lecturer in Rheumatic Diseases, University of Sheffield

DAVID BENNETT BSc B Vet Med PhD MRCVS
Senior Lecturer in Clinical Studies, Small Animal Hospital, Crown Street, Liverpool

G. BENTLEY ChM FRCS
Professor of Orthopaedics and Director of Clinical Studies and Research, The Institute of Orthopaedics, University of London at the Royal National Orthopaedic Hospital

CAROL M. BLACK MD MRCP
Consultant Rheumatologist, West Middlesex University Hospital, London

S. W. BRIGHTON MB ChB MMed (Pretoria)
Head of the Department of Rheumatology, University of Pretoria

G. S. E. DOWD MD MCh Orth FRCS
Senior Lecturer and Acting Head of Department, University Department of Orthopaedic and Accident Surgery, Royal Liverpool Hospital, Liverpool

JOHN GOODACRE B Med Sci MRCP(UK)
Research Associate, Department of Rheumatology, Royal Victoria Infirmary, Newcastle upon Tyne

PETER HUDGSON MB BS(Melbourne) FRCP FRACP
Consultant Neurologist, Northern Regional Health Authority and Senior Lecturer in Neurology, University of Newcastle upon Tyne

A. R. MacKENZIE BTech PhD DIC
Section Head, Immunobiology, Glaxo Group Research Ltd

JEFFREY P. PEARSON PhD
Lecturer in Physiological Biochemistry, Department of Physiological Sciences, University of Newcastle

BARRIE VERNON-ROBERTS PhD MD MRCPath FRCPA
Professor of Pathology, University of Adelaide; Head of Division of Tissue Pathology, Institute of Medical and Veterinary Science, Adelaide

DAVID J. WALKER MA MRCP
Senior Registrar in Rheumatology to the Newcastle upon Tyne hospitals

K. I. WELSH PhD
Head, SE and SW Regional Tissue Typing Laboratory; Honorary Senior lecturer in Chemical Pathology, Guy's Hospital, London

A. R. WILLIAMSON BSc PhD
Research Director, Glaxo Group Research Ltd

V. WRIGHT MD FRCP
Professor of Rheumatology, University of Leeds; Consultant Physician in Rheumatology, The General Infirmary at Leeds and Royal Bath Hospital, Harrogate

Contents

1. Lessons to be learnt from animal models of inflammation and immunopathological processes

D. Bennett J. Goodacre

INTRODUCTION

The test by which a 'model' stands or falls is not whether it does or does not faithfully reproduce the object to which it points; the test is whether it throws light on that object or obscures our understanding of it. The effective model is the illuminating one. D. L. Gardner, 1977

There are many diseases of man where the immune system plays a principal part, often associated with persistent inflammation, and knowledge of the aetiology and pathogenesis of this inflammation is of paramount importance if these diseases are to be treated and controlled. Studies of these diseases in the human patient are necessarily restricted and it is the animal model, both naturally occurring and experimentally induced, which can offer more detailed investigations.

Several experimental models such as the injection of foreign antigenic material into joints, provide certain information on the pathogenesis of inflammation and the involvement of the immune system but can provide no information on the aetiology of the naturally occurring diseases. Studies on possible aetiological agents involve working with animal models where the disease is known to be initiated by a microbial agent. In lymphocytic choriomeningitis, for example, virus infection can lead to tissue damage by immune complexes (e.g. glomerulonephritis) or by sensitised lymphocytes responding to local deposits of viral antigens (e.g. choriomeningitis). Recently genetic factors have become increasingly important in determining immunological responsiveness and susceptibility to immune-mediated diseases (Anon, 1979; Glynn, 1975; McDevitt & Bodmer, 1972) and the use of animal models can reduce genetic variability by using specially bred populations. Thus, the study of animal models of inflammation and immunopathological mechanisms is of importance for (a) investigation of the pathogenesis of diseases and analysis of how immunological reactions can lead to tissue injury; (b) investigation of known aetiological agents particularly discovering how the injurious immunological reaction is set into motion and (c) investigation of genetic factors in the development of immune-mediated diseases especially concerned with tissue types and susceptibility to disease.

It is clearly impossible to review all the relevant animal models in a chapter of this kind, and the authors have therefore selected a few with which they have some first hand involvement and which illustrate some of the important benefits and shortcomings of working with animal models.

INFLAMMATORY JOINT DISEASE

Experimental arthritis in laboratory animals

Innumerable methods have been used to produce arthritis in experimental laboratory animals, particularly in order to study a rheumatoid-like inflammation (Gardner,

1960a). Two methods have received most attention — adjuvant arthritis in rats and allergic arthritis in rabbits, and it is perhaps important that tubercle bacilli play a major role in both models.

Adjuvant arthritis

This form of arthritis was first observed by investigators attempting to induce autoallergic lesions in rats by the intradermal injection of spleen or muscle extract in Freund's complete adjuvant (Pearson, 1956; Stoerk et al, 1954). It was found that the important principal was in the tubercle bacilli and particularly in the Wax D fraction. Interestingly, this model produces polyarthritis as well as occasional lesions in the eyes and skin. The lesions in individual joints are usually of limited duration but chronic lesions lasting several weeks also occur. A rheumatoid-like pathology within the joints was reported by Pearson & Wood (1959). A cellular hypersensitivity reaction has been implicated since the disease can be transferred to syngeneic rats with living lymphoid cells (Pearson, 1964). Delayed hypersensitivity to homologous collagen has also been shown in diseased rats (Steffen & Wick, 1971). Dissemination of tubercle fragments throughout the body has been suggested but radiolabelling experiments are equivocal (Jones & Ward, 1962). The effects of immunosuppressive agents has, however established a need for an unimpaired immunological system. Gery & Waksman (1967) found that the incorporation of bovine serum albumin or ovalbumin into the adjuvant largely suppressed the appearance of lesions. If, however, the rats are previously made tolerant to the foreign protein the development of arthritis is not inhibited. The inhibition therefore seems to be the result of antigenic competition between the albumin and the mycobacterial antigen. Recent work by Kayashima and colleagues (1978) suggested that there were at least two T-cell subpopulations involved in the development of adjuvant arthritis. Pretreatment of the experimental rats with either cyclophosphamide or hydrocortisone enhanced the severity of the arthritis, possibly due to selective depletion of suppressor T-lymphocytes. Pretreatment with anti-thymocyte sera caused marked inhibition of the arthritis reaction. The two T-cell subpopulations could be an anti-thymocyte sensitive T_2 subpopulation that is effective in the induction of adjuvant arthritis and the other a T_1 subpopulation that regulates the disease process.

The ability to produce a chronic polyarthritis by single injections of tubercle bacilli in oil is of immunological importance but its relevance to rheumatoid arthritis is obscure especially since the condition appears to be restricted exclusively to the rat and even this species shows considerable strain differences in susceptibility. The model is still favoured for the study of the pharmacological control of inflammation and for the evaluation of therapeutic substances in controlling inflammation.

Experimental allergic arthritis

Polyarthritis as a feature of serum sickness suggested that allergic reactions can produce inflammatory joint changes (Boots & Swift, 1923). Experimental studies were performed to elucidate the pathogenesis of serum sickness. These generally involved the intravenous injection of foreign proteins such as bovine albumin or gamma globulin into rabbits, mice or guinea pigs. The lesions of serum sickness are produced as antibody production begins and while antigen is still persisting in the blood and tissues. With the continued production of antibody, antigen is hopefully eliminated and free antibody appears in the serum and the lesions of serum sickness disappear. It

has been possible to demonstrate the persistence of antigen/antibody complexes in the circulation at the time of serum sickness symptoms (Dixon et al, 1958; Weigle & Dixon, 1958), and it is also possible to show the localisation of antigen and antibody in the diseased tissues (Dixon et al, 1958). Lesions include necrotising arteritis, endocarditis, glomerulonephritis and granulomatous lesions in the lymphoid tissues (Germuth, 1953; Germuth et al, 1957). The development of different lesions depends on several factors, e.g. mice are more susceptible than rabbits, injection of gamma globulin produces mainly glomerulonephritis, injection of albumin produces arteritis as well as glomerulonephritis, and some animals when subjected to the same experimental protocol do not develop any lesions (Weigle & Dixon, 1958).

A similar self-limiting form of arthritis can be produced in most experimental animals by repeated intra-articular injections of antigen or a single injection in an already immunised/sensitised animal (e.g. Bruun, 1940). A more prolonged arthritis resulted when Freund's complete adjuvant was introduced into the immunisation schedule. Dumonde & Glynn (1962) using human fibrin as antigen found that in animals previously immunised with this antigen in complete adjuvant, the intra-articular injection of fibrin led to a chronic arthritis still active when the experiment was terminated after 16 weeks. Further work showed that various proteins could replace fibrin as the antigen and for reasons of simplicity, crystalline ovalbumin was most commonly used (Consden et al, 1971). The pathological changes recorded in affected joints are very similar to rheumatoid arthritis and the inflammation appears to be self-perpetuating as it is in rheumatoid arthritis. The histological picture is consistent with a local immune reaction in the joint against some antigen; local antibody formation has been demonstrated (Jasin & Ziff, 1969). The intra-articular injection of preformed complexes directly into joints has also produced synovitis (Hollister et al, 1973; Rawson & Torralba, 1967). A rheumatoid-like synovitis was also produced by the injection of Fab fragment of rabbit IgG into a rabbit joint, providing the spontaneously occurring serum autoantibody against the Fab fragment was present (Rawson et al, 1969); this autoantibody known as homoreactant, is present in most normal rabbits. The Fab fragment and homoreactant need to complex together before the synovitis is initiated.

The simplest explanation for the persisting inflammation following the intra-articular injection of antigen, is that it is the result of the persistence of the injected material in the joint. Quantitative studies on the amount of antigen required to elicit a chronic inflammatory reaction have been done (Glynn, 1975). Radio-labelled ovalbumin has also been used to monitor the antigen retained (Consden et al, 1971; Cooke & Jasin, 1972) and this work has suggested that active inflammation continues when the antigen level is well below that required for significant immunological stimulation (Webb et al, 1971). The theory that the persisting inflammation could be the result of an infective agent brought to the joints or some latent infection excited by the inflammatory process has not been confirmed (Glynn, 1975). The only other possibility is that the inflammation is in response to some new antigen which has appeared in the damaged joint itself. This could be a derivative of the inflammatory exudate or a product of pathological breakdown or a normal product of wear and tear that has acquired antigenicity because of abnormal handling by the inflamed tissue, or a combination of these. Autoallergic mechanisms, for example, may be in operation. There is some evidence that inflammatory exudate in rabbits can act as an autoantigen (Phillips

et al, 1966) and can be used for the induction of experimental arthritis. Also, the injection of fibrin into joints of rabbits previously sensitised to autologous and heterologous fibrin can cause an inflammatory response (Dumonde & Glynn, 1962). In fact, several species will develop a chronic arthritis when injected with heterologous fibrin, and a few do so with their own fibrin (Lack, 1968).

Other models

Arthritis can be produced in rabbits by repeated intra-articular injection of streptolysin S — a non-antigenic water soluble toxin elaborated by streptococci (Weissman et al, 1965) which disrupts lysosomes and releases proteolytic enzymes (Hirsch et al, 1963; Weissman et al, 1963) as occurs naturally in an inflammatory focus. Rabbits receiving one or two injections developed only a transient arthritis, whereas those receiving longer courses of injections developed arthritis similar to rheumatoid. This observation may be explained by the development of an allergic reaction against some product produced by the repeated enzymatic injections. Weissman et al (1965) also demonstrated the presence of serum complement fixing antibody directed against membrane components of lysosomes. Cook & Fincham (1966) repeated the work in both rabbits and goats and confirmed most of the findings except for anti-lysosome membrane antibodies. Cook and Fincham found that chloroquine which is believed to have a stabilising effect on lysosomes did not modify the lesions produced by streptolysin S. Filipin, another agent capable of disrupting lysosomes, has been used to produce arthritis experimentally in rabbits (Weissman et al, 1967) and horses (McIlwraith et al, 1979).

Gardner (1960b) produced arthritis in rabbits by repeated intra-articular injection of carrageenin, a sulphated mucopolysaccharide extracted from a seaweed *Chondrus crispus*. Similar experiments were reported in the pig by Marroquin & Ajmal (1970). The joint lesions were similar to those seen in rheumatoid arthritis except for the paucity of plasma cells. Carrageenin would appear to act as an antigen (Johnston & McCandless 1968).

Viral leukoencephalomyelitis-arthritis of goats

Viral leukoencephalomyelitis-arthritis (VLA) of goats was first reported as a naturally occurring disease in the dairy animal in the U.S.A. and has since been studied experimentally. The pathological lesions include demyelination and necrosis of the white matter of the central nervous system and an interstitial pneumonia. Animals which survived the acute encephalomyelitis had active lesions up to three years after the onset of clinical disease and in addition suffered a chronic proliferative synovitis (Cork, 1976; Cork & Davis, 1975; Cork et al, 1974a, b; Cork & Narayan, 1980). The importance of this model is that a rheumatoid-like joint disease has been conclusively linked with a virus infection and persistence of the disease has been associated with the continued presence of the virus in the affected joints (Cork & Narayan, 1980). The virus of VLA is similar to visna virus of sheep (Narayan et al, 1977; Pétursson et al, 1976). It is not yet certain how the virus produces the pathological lesions. Presumably, local replication in cells of the host tissues could cause direct cytopathic changes. Alternatively, this local infection could be a source of viral antigen on the cell surface which could stimulate a direct immune cytotoxic process or some other immunopathological reaction. The failure of the animal to clear virus in the later stages of infection

may be due to persistence of proviral DNA in tissue cells as has been shown for visna virus in sheep (Haase & Baringer, 1974). Alternatively, since the virus can infect lymphocytes and macrophages, these cells may play a role in mediation of pathological changes. This model is interesting since a single aetiological agent can produce a disease complex involving the nervous system, lungs and joints. Of obvious interest would be serological studies of human rheumatoid patients to check for any possible similar viral infection. Further studies of this model are in progress at the Johns Hopkins University.

Erysipelas arthritis of pigs

After infection with *Erysipelothrix insidiosa* the disease in pigs may take one of three possible courses (Drew, 1978). The most acute form is a septicaemia which can be fatal. A less acute form is characterised by rhomboidal erythematous areas in the skin and the third possibility is that no clinical evidence of infection is seen but the pig becomes a carrier with the organism harboured in the spleen, tonsils, gut or bone marrow. The chronic stages of the disease involving the development of chronic arthritis, and less commonly of endocarditis, may follow apparent recovery from either of the acute forms of the disease, or the onset of lameness and joint swelling may be the first signs of the disease after inapparent infection. The articular pathology which has been described in chronic porcine erysipelas is very similar to that of rheumatoid arthritis of man (Ajmal, 1970a; Drew, 1972; O'Brien et al, 1973; Sikes, 1959).

It is in the development of the arthritis lesions that there is uncertainty as to the relative roles of infection and immunity in the pathogenesis of the disease. It is thought that the presence of the organisms in the tissues is sufficient to produce the initial synovitis but that in the later stages, immunological mechanisms are important in the production of the chronic lesions (Renk & Wellman, 1963; Wellman, 1954, 1958; Wellman & Liebke, 1959, 1960). Other workers considered that a previously developed hypersensitivity to the organism, i.e. from previous contact, is of prime importance in the production of the acute joint lesions as well as the chronic lesions (Freeman, 1964; Hughes, 1955; Neher et al, 1958). It is well known both in naturally occurring clinical cases and in experimental animals that the pathological process persists and progresses even though no viable organisms can be cultured from the joints. The period of time taken for joints to become sterile in the experimental animal has varied in different reports but has been in the range of 20–33 weeks (Collins & Goldie, 1940; Hughes, 1955; Sikes et al, 1955). The failure of vaccination to prevent the development of chronic erysipelas arthritis and also reports that arthritis due to *E. insidiosa* occurs more often in vaccinated than in non-vaccinated pigs has been cited as evidence that hypersensitivity is responsible for the onset of joint changes following exposure to live erysipelas organisms. However, Ajmal (1970a) has shown that gnotobiotic pigs receiving a single injection of organisms intravenously develop macroscopic and histologic changes of arthritis within 7–14 days suggesting that prior sensitisation to *E. insidiosa* is not needed for the development of acute arthritis following subsequent infection. Further critical discussion of the investigations performed on the immunopathology of chronic erysipelas infection is given by Ajmal (1970b).

Even though viable organisms cannot be cultured from an affected joint showing active disease, erysipelas antigens can be detected within the synovial membrane — within synovial lining cells, macrophages and also extracellularly (Bennett, 1983;