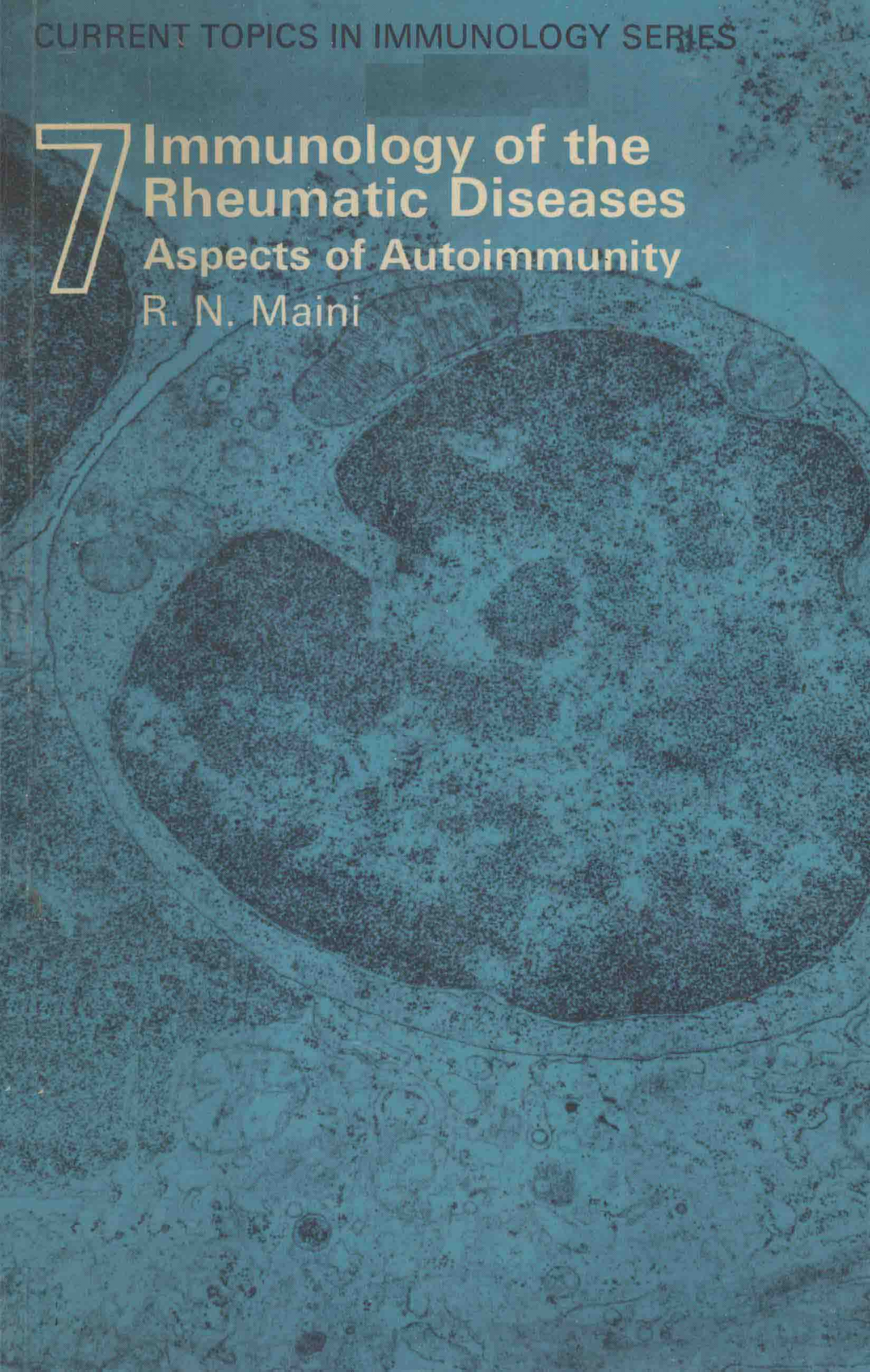
CURRENT TOPICS IN IMMUNOLOGY SERIES

7 Immunology of the Rheumatic Diseases

Aspects of Autoimmunity

R. N. Maini



Immunology of the Rheumatic Diseases

Aspects of Autoimmunity

R. N. Maini, M.R.C.P.

Consultant Rheumatologist to Charing Cross Hospital, London; Deputy Head, Clinical Research Division, Kennedy Institute of Rheumatology, London

D. N. Glass, M.R.C.P.

Arthritis and Rheumatism Council Research Fellow at Robert B. Brigham Hospital, Boston; formerly Senior Registrar, Charing Cross Hospital, and Maynard-Jenour Fellow at the Kennedy Institute of Rheumatology, London

J. T. Scott, M.D., F.R.C.P.

Consultant Physician to Charing Cross Hospital, London; Deputy Director and Head of Clinical Research Division, Kennedy Institute of Rheumatology, London

Edward Arnold

First published 1977
by Edward Arnold (Publishers) Ltd.
25 Hill Street, London W1X 8LL

ISBN: 0 7131 4279 0

Set in 10 on 11pt Imprint at Western Printing Services Ltd.
Reproduced and printed by photolithography and bound in Great Britain at The Pitman Press, Bath

CURRENT TOPICS IN IMMUNOLOGY

General editor: Professor John Turk

No. 7 Immunology of the Rheumatic Diseases

For our families, for their patience.
With love and thanks

General Preface to Series

The impact of immunological thought on medical practice has been increasing at a steady rate now for nearly twenty years. There appear to be very few fields to which the immunologist cannot contribute. Initially the immunological approach was limited to assistance in diagnosis and in sera and vaccine production. New approaches in the field of therapy are not only in the use of vaccines, sera and immunosuppressive agents, but also in the more rational use of conventional therapeutic agents. Immunological knowledge is especially necessary in the field of tumour therapy, particularly in the balanced use of surgery and radiotherapy. Moreover, immunological knowledge in other fields has allowed us to understand more readily the mechanisms whereby a single aetiological agent can produce a wide range of different clinical manifestations. Different disease patterns occur depending on the nature of the immunological reaction causing tissue damage. A completely different symptom complex from reactions involving soluble immune complexes reacting with the complement cascade will be found in those involving the reaction of specifically sensitized lymphocytes with antigen as part of a cell-mediated or delayed hypersensitivity reaction.

As a massive amount of new scientific material accumulates in this field, the clinician is frequently left behind and perplexed. Each year a new scientific journal is published specializing in fields as diverse as immunogenetics, immunochemistry or immunological techniques. We have journals emanating from continents as well as countries. The wealth of material is often bewildering. Simple textbooks of immunology are often too simple, whereas review articles may be too complicated for the specialist physician or surgeon who wants a treatise on those aspects of the subject particularly relevant to his own field of interest. It is hoped that this series will fulfil some of these needs by giving comparatively short reviews that will lay emphasis on immunological subjects which should appeal to both clinicians and those working in clinical laboratories. The aim is to provide the busy clinician in a particular field of medicine with a short volume relevant to his practice written by a specialist. It should introduce the reader to the immunological approach to his subject and indicate how modern immunological thought might influence his day-to-day work in the wards or clinical laboratory.

JOHN TURK

The Royal College of Surgeons of England
London

Preface

It is now nearly thirty years since three independent and almost simultaneous observations—the discovery of rheumatoid factor, the description of the LE cell phenomenon, and the dramatic effect of cortisone on rheumatoid arthritis—heralded the present era in which rheumatic diseases have come to occupy a pre-eminent place in the rapidly developing science of clinical immunology.

This book is intended mainly for clinicians who are interested in discovering how immunological concepts have contributed to our understanding of the pathogenesis of certain rheumatic diseases, and how immunological methods have been applied to the clinical management of patients. Rheumatic diseases involve primarily the joints and locomotor structures but they also manifest systemic features and involvement of other organs, so that rheumatology is now recognized as an integral branch of internal medicine. It is hoped that our readership will include all those who want to enlarge their knowledge about the application of immunology to clinical medicine, in particular practising rheumatologists, immunologists, post-graduate students, physicians, pathologists and research workers.

The first section of the book begins with an account and analysis of the biology of the immune response and its relevance to protective immunity, tolerance, hypersensitivity and the cellular basis of autoimmunity. The following two chapters discuss the relationship of immune responses to tissue injury and the significance of antibodies and cell-mediated reactions against a large variety of autoantigens. The final chapter of this section is intended to familiarize clinicians with immunological methods and their application to investigative rheumatology.

Section B is essentially concerned with phenomenology. Diseases such as rheumatoid arthritis and systemic lupus erythematosus have been chosen to demonstrate in some detail the application of immunological studies to their clinical manifestations. Sjögren's syndrome is chosen because of its close relationship to both rheumatoid arthritis and systemic lupus erythematosus, and because it perhaps exemplifies the importance of impaired immunological surveillance in the pathogenesis of the disease itself and accompanying predisposition to malignancy. In contrast to these disorders, in which immune complexes have been implicated as an important pathogenetic mechanism, cellular immunity appears to be of primary significance in polymyositis. In myasthenia gravis the pathological basis of impaired neuromuscular transmission remains unsolved but some interesting ideas have been put forward about the hormonal role of the thymus gland and the possibility of autoantibodies directed against cell membrane receptors. Relapsing polychondritis has been chosen because immunological responses to connective tissue components (antigenic sites in matrix) make it a possible contender as the only true example of 'autoallergic connective tissue disease'. A chapter on infections in arthritis deals with the ways in which infection may involve joints and provides an insight into possible

interactions between organisms, the immune response and joint inflammation. Vasculitis mediated by immune complexes and possibly by cellular mechanisms is, in a sense, central to the pathology of inflammation observed in a variety of rheumatic diseases. Some of the more recent investigations summarized in this chapter suggest unifying pathogenetic concepts, but many interesting questions remain unanswered; for example, the reason why different blood vessels and sites of localization are observed in well recognized clinical syndromes. The final chapter in this section considers briefly the therapeutic implications of immunological pathogenesis, particularly the use of immunosuppressive agents. Although a good theoretical case can be made for such treatment, the evidence for their value in some of the rheumatic diseases is controversial.

In the last section the possibility is considered that these diseases evolve against a background of genetic susceptibility. In fact, epidemiological evidence for such predisposition is conclusive only for ankylosing spondylitis and, to a certain extent, systemic lupus erythematosus. The possibility that diseases result from deficiency of genetically controlled capacity to synthesize immunoglobulin or complement on the one hand, and development of antigen-specific immune responses peculiar to the individual, on the other, is discussed in this section.

We should like to acknowledge the help of Miss Lindsay Roffe of the Kennedy Institute in drawing the line diagrams and Dr David Woodrow, Professor John Sloper and Dr David Yates of Charing Cross Hospital for Figures 5.2 and 6.1. A word of grateful thanks is also expressed to our secretaries Miss Teresa Kearney and Mrs Mary Wheeler who have patiently typed the numerous drafts and produced the final version of this book without protest and at great speed, and to Marianne Maini for her help with proof reading.

R.N.M.
D.N.G.
London 1976 J.T.S.

Contents

Section A

Aspects of Basic Immunology, Tissue Damage, Autoimmunity and Methods of Study

1

Biological Aspects of the Immune Response

Introduction

Numerous changes indicating involvement of immunological responses are observed in some of the rheumatic diseases, particularly the inflammatory disorders of connective tissue such as rheumatoid arthritis and systemic lupus erythematosus. These changes can be defined in terms of cellular and humoral immunological events which are believed to result from the interaction of the lymphoreticular system with antigen. The ensuing reactions evolve around: (1) cells derived from a lymphocyte lineage or related to macrophages; and (2) humoral factors such as antibody and other molecular products originating from these cells. These phenomena have been investigated and documented in tissues and fluids most readily available, which in patients with rheumatic diseases has in practice meant investigating extracellular fluids, such as blood and synovial fluid, and tissues obtained by biopsy, surgery or autopsy. Many of our ideas about immunological responses in rheumatic diseases have also been obtained from animal models.

A study of immune mechanisms in connective tissue diseases is of fundamental importance in understanding the emergence of autoimmune reactions frequently observed in these diseases, and the mediation of various clinicopathological features. Evidence from experimental studies has drawn attention to the central importance of cells belonging to the lymphocyte and macrophage lineage which are intimately concerned with the development of immune responses upon challenge with antigen. Of equal importance is our increasing understanding of the cellular and chemical basis of immunological unresponsiveness (tolerance), which, as postulated by Burnet (1959) is highly selective and allows discrimination by the immune system between 'self' and 'non-self'. Lymphocytes, however, are a heterogeneous cell population in terms of their developmental origins, structure, surface characteristics and diversity of function. Further, their function is determined by complicated patterns of interaction with antigens; cell division; passage via blood and lymphatic channels through lymphoid tissues, thymus, bone marrow and gut; and by interaction between subpopulations of lymphocytes themselves and with other cells, particularly macrophages. Any unitary concept to explain a basic derangement in disease is at risk of being too naïve.

Many types of defect are possible, and numerous current hypotheses are sometimes contradictory and hard to reconcile. Nevertheless, we are now in a position to define at least a hypothetical model for the development of immune responses and tolerance to antigens, and to see whether the predictions prove to be of value in understanding the immunological pathogenesis of rheumatic diseases.

Lymphocytes and macrophages in induction of immune responses and tolerance

Introduction of antigen under appropriate conditions either stimulates an immune response or leads to an immunologically unresponsive state (tolerance) which is antigen-specific. At least two distinct lymphocyte populations (in addition to macrophages) are concerned with the development of the immune response (see Roitt *et al.*, 1969) and tolerance in a number of ways.

THYMUS-DEPENDENT T LYMPHOCYTES

Thymus-dependent T lymphocytes are responsible for cell-mediated immunity. Interaction of antigen with sensitized T cells leads to activation of metabolic processes of the cell, increased DNA synthesis, cellular enlargement, and mitosis. These cells operate both by direct contact with other cells and by synthesizing and releasing mediators of cellular immunity, collectively termed 'lymphokines'. They are responsible for: (1) surveillance against tumours and infections; (2) graft rejection; they also (3) participate in the synthesis of antibody in response to most antigens ('helper' effect).

B LYMPHOCYTES

B lymphocytes (thus termed because of their origin in the bursa of Fabricius in the fowl) are the precursors of cells which will synthesize antibody. B cells respond to some antigens independently of T cells, possibly with the involvement of macrophages (in which case IgM antibody is usually exclusively produced), but generally require the 'helper' effects of antigen-stimulated T cells.

While administration of antigen normally produces an immunological response, Dresser and Mitchison (1968) have shown that its introduction in certain circumstances (e.g. repeated very low doses) induces T cell tolerance so that B cells remain in a dormant state but under special circumstances are capable of activation; or T and B cell tolerance in which neither T nor B cells respond to antigen (e.g. by appropriate administration of very high doses) (reviewed by Weigle, 1973). Such circumstances were regarded by Allison (1971) and Weigle (1973) as being accountable for tolerance to soluble autoantigens, a postulate that does not entirely support Burnet's original concept of unresponsiveness due to elimination or seclusion of clones of immunocompetent cells during fetal or infantile life. The current concept of unresponsiveness to autoantigens is thus complex and the demonstration of B cells reactive against certain autoantigens lends support to the T cell tolerance mechanism. In accordance