Immunology in Medicine

A Comprehensive Guide to Clinical Immunology

Second Edition

Edited by

E. J. HOLBOROW

W. G. REEVES

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Foreword

It is nowadays widely recognized that the activities of the immune system not only protect against microbial invasion and maintain the integrity of higher organisms, but that exaggeration or aberration of these activities can lead to disease. Much of the knowledge on which this recognition is based has been gained only within the last twenty years, and its application in medicine is even more recent. Although concepts in immunology are by no means static, and the mechanisms whereby the immune response is regulated are still far from clear, the use of an immunological approach has produced plausible experimental models of and possible explanations for a wide variety of human disease processes whose pathogenesis was previously obscure. In some instances, the explanations have proved nearly enough correct to guide therapy or even to indicate new therapeutic approaches. In others, the application of immunological techniques has suggested that immunological factors may play a part in production or control of the disease processes but has left their aetiology tantalizingly unsolved, and has revealed *inter alia* that there is still much to learn about fundamental aspects of the immune response, in respect not only of the part played by lymphocytes but also by mononuclear cells, granulocytes and the complement system. In others still, immunological investigations, even when negative, are important for differential diagnosis.

Because the ramifications of immunology are very wide, and the relevant primary information or review articles are scattered throughout many journals, clinicians, pathologists and students badly need critical compilations of existing knowledge. In a rapidly expanding subject, it is difficult to decide when is the right time to make such a compilation, but to my mind, the present is as near to a nodal point as is likely to occur in the foreseeable future. Clinical immunologists, during the last year or two, have reached a fair degree of agreement about what should be their scope and function, and good manuals have been published lately describing most of the basic techniques in their armamentarium. "Immunology in Medicine" sets out to give an account of the relevance of immunological concepts and of information obtained with these techniques in the whole field of clinical practice, using language which is intelligible to the non-specialist and attempting to assess critically the significance of the observations described. Insofar as these have implications for treatment, this is also indicated. The editors and their fellow authors have succeeded in their aim. Because they write from practical experience, the information which they provide has been predigested sufficiently to inform rather than to confuse the reader. Nevertheless, plenty of facts and raw data are included when these are appropriate, backed up by suitable references to the literature. Although this is a multi-author book, the editors have avoided serious overlap or repetition. The volume is large, but so is its subject matter, and it can properly be regarded as a magnum opus.

April, 1977

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Preface to the First Edition

"Immunology in Medicine" is primarily designed for the practising clinician, be he physician, surgeon or pathologist. The large majority of doctors in practice today escaped any specific training in immunology and many find its unfamiliar jargon and growing complexity formidable. Books abound on the more fundamental and specialized aspects, but there is a dearth of texts which communicate the practical importance of immunological developments across the breadth of clinical medicine. Twenty-three of the 34 contributors to this book are actively involved in day-to-day problems of medical care as well as contributing to immunological advances in their own field.

In an initial chapter we have attempted to give an overview of immunology: its history, jargon, cardinal features and mechanisms. The following eight chapters review the important basic aspects and the highlighted keywords in the general index refer back, predominantly, to this section for important definitions. Chapters 10–12 discuss the means by which immunological mechanisms cause disease, with particular emphasis on auto-immune processes in Chapters 11 and 12. Although the basic defect underlying auto-immune reactivity is poorly understood, clinical observation has almost as many clues to offer as have the various animal models which fascinate immunologists.

The traditional *raison d'être* of the immune response—defence against infection—is emphasized in chapters on infective disease and immuno-deficiency. The largest section deals with the immunology of individual system disorders and is followed by contributions on malignancy and transplantation. Although therapy is mentioned wherever relevant, the last two chapters categorize the various means by which untoward immunological responses may be controlled. Apart from improved methods of diagnosis and increasing knowledge of mechanisms, the immunological manipulation of disease processes offers an exciting prospect for the future. Various non-pharmacological manoeuvres have already proved successful and the growth of disease-specific or antigen-specific treatment will add significantly to the skills required of the clinical immunologist in the future.

Guidelines and training programmes are now established for the various personnel necessary for the pursuit of clinical immunology, i.e. physician, pathologist, technologist and non-medical scientist.[1] We hope that this book will prove of value to each of these. Little space has been devoted to the finer details of laboratory technique which is covered by several recent publications.[2,3,4]

The complexities of producing and collating a multi-author work such as this are exponentially related to the number of authors involved. We owe a special debt to our wives and families for their acceptance and support of the role of immunological medicine within the domestic scene.

March, 1977

E. J. HOLBOROW
W. G. REEVES

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Preface to the Second Edition

Developments in immunology continue to make inroads into the practice of medicine and pathology and considerable changes have taken place since the first edition appeared five and a half years ago. We have continued our aim to communicate the practical importance of advances in immunology across the breadth of clinical medicine and, although the total number of contributors is much as before, we have made various changes in authorship, content and format. Contributors have been encouraged to opt, wherever possible, for a concise and moderately didactic style incorporating key but not exhaustive references.

Although completely revised and largely rewritten, "Immunology in Medicine" is divided into similar sections as before: a general introduction and seven subsequent chapters cover fundamental aspects of the immune system; another five review the role of the immune system in disease; thirteen chapters are devoted to immunological disorders of major body systems or organs; three concentrate on lympho-proliferative and malignant disease and three concluding chapters focus on transplantation and therapeutic aspects of immunology.

Developments in genetic engineering, hybridoma technology and the characterization of various important immunological molecules (e.g. interferons, interleukins, leucotrienes, thymic hormones) in conjunction with advances in immunogenetics, immunoregulation and transplantation all hold promise for therapeutic innovation in the major categories of immunological disorder, i.e. immunodeficiency, allergy, auto-immunity and lympho-proliferative disease.

It is a pleasure to thank Susie McGowan and Emily Wilkinson of Academic Press for the efficient and expeditious way in which they have transformed our manuscripts into the printed word.

March 1983

E. J. HOLBOROW
W. G. REEVES

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Chapter 1

General Introduction

W. G. REEVES and E. J. HOLBOROW

HISTORICAL DEVELOPMENT OF IMMUNOLOGY

Origins in Microbiology

The proposal of the germ theory of infectious disease by Louis Pasteur in 1847 and the confirmation that many important life-threatening diseases were caused by micro-organisms, soon led to a search for factors which might protect individuals from the dire consequences of infection (Reid, 1974). Two of the early investigators in this field were Eli Metchnikoff, first in Messina and later in Pasteur's laboratory in Paris, and Paul Ehrlich, working with von Behring and Kitasato in Koch's institute in Berlin.

Metchnikoff became impressed with the ability of migratory cells, present in most multi-cellular organisms, to detect and defend against the invasion of foreign material. On the basis of experiments on water-fleas and starfish larvae he propounded a general theory which gave pride of place to his wandering "phagocytes". Von Behring and Kitasato on the other hand, found that serum taken from animals or patients who had recovered from diphtheria or tetanus was able to confer specific protection when passively transferred to another host. Paul Ehrlich painstakingly continued this work and proposed his "side-chain" theory of immunity to explain these biological events. There seemed to be no way of reconciling these two opposing views until Almroth Wright described the enhancing effect of antibody on phagocytosis in 1903; a process which he called *opsonization*. Although this work shed important light on the process of defence against bacterial infection, his unbridled enthusiasm for "stimulating the phagocytes" led to derision by Bernard Shaw in his play "The Doctor's Dilemma" (1908). In addition to the serum constituents already described by Ehrlich and his colleagues, Jules Bordet discovered in 1899 that a further heat labile serum factor—soon to be known as complement—was necessary for the lysis of infecting micro-organisms.

Detection of the appropriate antibodies in the sera of patients recovering from infectious disease and the elaboration of specific antisera for use in their treatment was followed by a rest phase in the development of immunological knowledge. The general view was that infecting organisms were "bad" and the host response essentially "good". In support of this was work performed almost a hundred years before by the Gloucestershire general practitioner Edward Jenner on the protection against smallpox which could be conferred by inoculating material from cowpox vesicles. His unethical but courageous experiment on an 8-year-old boy—James Phipps—yielded an effective immunological means of controlling and eliminating a disease which had previously affected 60% of the population in the United Kingdom.

Soon after 1900, several lines of evidence began to

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suggest that the host response to the ingress of foreign material might not always be favourable and could cause serious harm. While cruising on the Prince of Monaco's yacht, Portier and Richet decided to study the effect of injecting jelly fish extracts into various animals. On their return they experimented with an extract prepared from sea anemone tentacles and made the surprising discovery that dogs which survived a first injection were more severely affected upon subsequent exposure to this antigenic material. This caused these workers to propose the term *anaphylaxis* in contra-distinction to the state of prophylaxis brought about by the use of bacterial antisera. At about the same time, Von Pirquet and Schick working at the Royal and Imperial Paediatric Clinic in Vienna found that "immune antisera" could produce untoward effects. They had cause to inject horse antidiphtheria serum into a large number of children during an epidemic of the disease and soon found that a condition characterized by fever, urticarial rash, lymphadenopathy, arthritis and proteinuria was liable to ensue approximately 8 days after the injection. This was most commonly seen following a second injection but in a few instances was provoked by the initial treatment. This response gave rise to the term *serum sickness*, a condition now known to be mediated by circulating immune complexes.

Arthus described a similar phenomenon occurring locally in the skin after the repeated injection of foreign serum and Robert Koch became particularly interested in the nature of the host response to tuberculin, describing the phenomenon of delayed hypersensitivity. Although several workers investigated the nature of "bacterial allergy" it was not until 1945 that Landsteiner and Chase demonstrated the importance of cellular responses in the tuberculin reaction and little thought was given to the relative contribution of "seed" and "soil" in the pathogenesis of infectious diseases until relatively recently.

Studies on lymphocytic choriomeningitis (LCM) in mice have provided dramatic evidence of the role of host factors in the production of immunologically mediated tissue damage (Cole *et al.*, 1971). Adult animals inoculated intracerebrally with the virus die from an acute encephalitis within 6–8 days. If inoculation is performed neonatally then the animals do not succumb and become life-long carriers of the virus. A similar effect can be produced by pretreating the adult animal with cyclophosphamide although either form of "carrier state" can be rapidly terminated by the administration of compatible spleen cells from a normal animal. Studies in man on hepatitis B, various forms of glomerulonephritis and other conditions such as dengue haemorrhagic fever have confirmed the importance of host factors in disease.

The Recognition of Autoimmunity

Ehrlich and Morgenroth had anticipated the prospect of autoimmune disease in 1901 when they suggested the term "horror autotoxicus" for this possibility. Donath and Landsteiner described the first red cell autoantibody in 1904 but it was not until 1938 that Dameshek and Schwartz rediscovered autoimmune haemolytic anaemia and proposed that autoreactivity might be a more general phenomenon. Various experimental models were developed by Witebsky and others: the commonest means of production being to inject animals with tissue extracts in the presence of Freund's adjuvant. That a number of human diseases are characterized by the presence of autoantibodies was soon established following the development of the technique of immunofluorescence by Coons in 1955. More recently, the story has come full circle with the knowledge that viruses have an important role in the development of several spontaneously occurring autoimmune diseases in animals and possibly in man. This adds a further dimension to the role of host factors in the pathogenesis of infectious disease.

Immunological Individuality and Transplantation

The existence of genetically determined tissue antigens was first established by Gorer in the 1930s. The further observation was made (Owen, 1945) that dizygotic twin cattle sharing a placenta each possess red cells of both genetic types. It was also shown that these non-identical twin animals would tolerate skin grafts exchanged between them. This led to work by Burnet's group in 1950 and Billingham, Brent and Medawar in 1953 which attempted to discover whether the introduction of "foreign" material before an animal was immunologically mature would result in that material becoming recognized as "self". The latter group found that this was feasible in newborn mice receiving foreign cells and this phenomenon was termed "actively acquired tolerance".

Human organ grafting became a reality in the early 1960s with the advent of renal allo-transplantation. Although elegant animal experiments have suggested the possibility of inducing specific unresponsiveness to foreign antigens, this has not yet proved to be widely applicable as a means of immunosuppression in man

and transplanted patients still have to be maintained on relatively large doses of non-specifically immunosuppressive drugs. However, some form of "immunological enhancement" may become a practical possibility in the relatively near future (see Chapter 32).

Protein Chemistry and Antibody Structure

The presence of an unusual protein—now recognized as free antibody light chains—in the urine of a patient with myelomatosis was described as long ago as 1847 (Clamp, 1967). Following the development of plasma protein electrophoresis by Tiselius and Kabat in 1938, antibodies were characterized as γ-globulins and in 1948 Fagraeus demonstrated their synthesis by plasma cells. Porter showed in 1959 that the antigen combining sites of antibody molecules could be chemically separated from the biologically active sites that trigger the various effector systems such as serum complement. Soon after, Edelman discovered that antibody molecules contain four protein subunits—two "heavy" and two "light". These two lines of evidence enabled the asymmetrical four-chain structure of antibody molecules to be elucidated (see Chapter 3).

The development of gel diffusion methods for studying antigen–antibody interactions by Elek, Oudin and Ouchterlony in the late 1940s as well as the application of immunoelectrophoresis by Grabar and Williams in 1953 enabled great strides to be made in the analysis of antibody reactivity.

IgG (γG) and IgM (β_2M) were soon recognized as different kinds of antibody molecule but it was not until 1961 that Heremans identified IgA (β_2A) as a separate class of antibody synthesized predominantly in the gastrointestinal tract. The recognition of myelomatosis as a condition associated with the neoplastic proliferation of a single clone of antibody-producing plasma cells and the discovery of myeloma proteins that did not type with existing reagents made possible the identification of two further classes of antibody molecule—IgD in 1965 by Rowe and Fahey, and IgE in 1967 by Johansson and Bennich.

Cellular Immunology

Rudolf Virchow had noted in 1858 that circulating mononuclear cells could be either large or small, and was aware that "the more the glands become enlarged ... the larger and more perfectly developed are the individual colourless cells of the blood wont to be". There was little addition to this state of knowledge until Gowans and his group described the heterogeneity and recirculation of lymphocytes in the 1960s (Gowans, 1966). Since then study of the cells and tissues of the lymphoid system has been one of the most prolific areas of investigation. Glick and his colleagues described the accidental discovery of the importance of the bursa of Fabricius in antibody production in the chicken in 1956 and Miller drew attention to the key role of the thymus in immunological development in 1961. Cell mediated responses and their clinical counterpart "delayed hypersensitivity" had already been shown to function independently of antibody and in the 1960s it was found that some lymphocytes are capable of synthesizing soluble factors of their own which are responsible for many of the phenomena seen in cellular responses (see Chapter 7). In 1970 the presence of surface immunoglobulin was detected on those lymphocytes (B cells) destined to transform into plasma cells and secrete antibody (Raff, 1976) and many other markers have since been identified for lymphocytes of both T and B lymphocyte series (see Chapters 2, 27 and 29).

Evidence from various immunodeficiency states has given adequate confirmation of the compartmentation of the immune system into T and B cell components although the phenomenon of "co-operation" between these two kinds of lymphocyte is well established. Initially, this was thought only to operate in terms of T cells providing help toward optimal B cell function but evidence now exists for several varieties of suppressor cell (Benacerraf, 1981) and proposals for immunoregulatory circuits abound (Cantor and Gershon, 1979; Herzenberg *et al.*, 1980).

The Problem of Diversity

Each individual immunological response is remarkably specific in its reactivity but yet there are potentially millions of different responses. The means by which such a wide range of specificity of response could be elaborated within a single multicellular organism has produced various theories. Haurowitz initially proposed an "instructive" theory of antibody formation in which the reactivity and specificity of the resultant antibody was largely determined by the nature of the immunizing antigen: the latter acting as a template for the synthesis of antibody molecules. The rival view that pre-existing clones of cells with their "ready-made" specific receptors are "selected" by antigen still holds sway (Burnet, 1954), although the differential contribution of the various possible sources of variation, i.e. germ-line genes, somatic

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