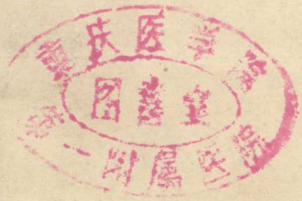
D. M. Weir

Immunology for Undergraduates

Second Edition



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IMMUNOLOGY
FOR UNDERGRADUATES

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PREFACE TO THE SECOND EDITION

The opportunity has been taken in this new edition to improve some of the Figures and to include a few new ones. At the same time some omissions in the text have been rectified and an attempt has been made to clarify some of the explanations and to emphasize the general biological significance of immune phenomena.

I am most grateful to my colleague Dr Andrew Fraser for providing a critical appraisal of the text of the first edition and to many of my colleagues for useful suggestions arising from the use of the book for teaching purposes.

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PREFACE TO THE FIRST EDITION

This short survey of Immunology is derived in the main from lecture material prepared for medical students in the paraclinical stage of their course and for science undergraduates in third year microbiology. The aim of the book is to provide a short text suitable for undergraduates not necessarily intending to specialize in Immunology but who wish to be familiar with the general principles of immunological phenomena and their wide ranging relevance in biology and medicine. For those who may perhaps be stimulated to delve more deeply into the subject there are a number of excellent modern textbooks, including *Immunology for Students of Medicine, Immunology in Clinical Medicine, Structural Concepts in Immunology and Immunochemistry* and *Clinical Aspects of Immunology* for the more advanced students of medicine. These are included in the suggestions for further reading at the end of individual chapters. The text itself in the interests of clarity and simplicity contains no references. The names of individuals associated with particular areas of work are omitted except where they are associated with a phenomenon by common usage.

The Figures are, in the main, highly simplified views of complex situations and the hope is that accuracy has not been sacrificed for clarity.

I am extremely grateful to my colleague Mr W. H. McBride for reading the manuscript and for providing valuable constructive criticism of the text. The Figures were kindly prepared by the late Mr T. C. Dodds of the Medical Photography Department and Mr John Pizer of his staff gave much help in preparing the drawings. My thanks are due to the publishers for their co-operation in producing the text and particularly to my colleague Dr R. R. Gillies for checking the manuscript and for his advice and encouragement in the writing of the book.

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Chapter 1

IMMUNITY

The Scope of Immunology

The tissues and cells capable of exhibiting what is now recognized as an adaptive immune response have an evolutionary history of some 400 million years and the forms taken by the response during this period have maintained a remarkable constancy both at the molecular and the functional level. The meaning of the term 'immunity' as it is used today derives from its earlier usage referring to exemption from military service or paying taxes. It has long been recognized that those who recovered from epidemic diseases such as smallpox and plague were exempt from further attacks and such immune individuals were often used in an epidemic to nurse those suffering from active disease. In England the procedure of cow-pox vaccination developed by Edward Jenner in 1798 for protection against smallpox and that used by Francis Home in Edinburgh for measles protection were essentially empirical measures performed without understanding of the underlying principles. The foundations for an understanding of immunity were laid by the invention of the microscope, the recognition of microorganisms and the advent of Pasteur's germ theory of disease. Pasteur's chance observation that aged cultures of chicken cholera bacillus would not cause the expected disease in chickens led to the development of methods for reducing the virulence of pathogenic microorganisms called attenuation. The protection given to animals by pre-inoculation of such attenuated organisms led to the widespread use of the method for immunization purposes. Immunology as a science began with the demonstration by von Behring and Kitasato at the Koch Institute in Berlin in 1890 of an anti-bacterial substance or factor in the blood of animals immunized against tetanus and diphtheria organisms. The neutralizing ability of such blood serum for the bacterial toxins

was the first demonstration of the effect of what is now recognized as antibody globulin.

The part played by phagocytic cells in clearing away and destroying bacteria was recognized by Metchnikoff, a Russian biologist working in France. Later the helpful effect of antibody (called opsonins by Almroth Wright) in encouraging phagocytosis became apparent thus reconciling two opposing schools of thought on immune mechanisms – one believing the process to be brought about completely by blood factors and the other upholding an entirely cellular viewpoint.

The specificity of antibody for the agent (i.e. the antigen) which induced its formation led to the use of antibody as an analytic tool. Thus the antigenic characters of bacterial and non-bacterial substances could be worked out and systems of classification of microorganisms were developed on this basis. Landsteiner used antibody-antigen interaction to define the ABO blood group system on the basis of antigenic differences in red cell membranes, and was also responsible for performing the ground work on the chemical basis of antigenic specificity.

In more recent years with increasing knowledge of the molecular processes underlying the functioning of cells it became possible to formulate theories on the mechanisms whereby the tissues and cells responsible for producing antibody performed this function. The need for such theories became apparent with the recognition of human diseases where the immune mechanisms had become deranged and were treating the individual's own tissues as if they were foreign antigens. Thus the question of how the immune system distinguished between what was foreign and what was part of self became important and resulted in the formulation of new theories to explain these phenomena, notable among which was the clonal selection theory of Burnet. These attempted to define the scope and limitation of Ehrlich's 'contrivances by means of which the immunity reaction ..... is prevented from acting against the organism's own elements and so giving rise to autotoxin'. The advances made in this area gave a new dimension to the science of immunology which until then was devoted almost exclusively to the prevention of infectious disease by vaccination and immunization. This new field of study – immunobiology – has drawn the attention of biologists to the apparent central importance of immune mechanisms in the evolution of multicellular animals. Knowledge of the genetic

control of protein synthesis is likely to make considerable advances as a result of the study of the synthesis of immunoglobulins.

Modern biochemical techniques have helped to add precision and sensitivity to immunological methods. These include the use of radioisotopes to measure accurately the primary binding of antibody with antigen and to demonstrate the metabolic activity of cells engaged in antibody production. Protein fractionation techniques and peptide analysis of the antibody molecule have thrown light on the chemical basis of specificity of the molecule and the relationship of structure to function as well as confirming a genetic basis for antibody formation and providing factual limitations on earlier theories of antibody formation. The understanding of immunological processes underlying the reaction of the body to tumours, to transplanted tissues and organs and to infectious agents has gained much ground as the result of these advances in immunochemical techniques. Clinical developments have included the recognition of autoimmune and immunological deficiency diseases and the feasibility of organ transplantation. Phylogenetic studies have stimulated investigations into the development and control of the lymphoid tissues leading for example to a new understanding of the role of that previously enigmatic organ, the thymus.

Thus it can be seen that immunity in its original meaning, referring to resistance to invasion by a parasite by means of a specific immune response is only one activity of a cellular system in animals the total activity of which is concerned with mechanisms for preserving the integrity of the individual with far-reaching implications in embryology, genetics, cell biology, tumour biology and many non-infective disease processes.

The subject of immunology can be considered under three general headings: immunity, dealing with the adaptive response to infective agents; immunochemistry, concerned with the chemical nature of antigens and antibodies; and immunobiology, which encompasses a variety of topics of biological importance and deals with the activity of the cells of the immune system and their relationship to each other and their environment.

Chapter 2

INNATE IMMUNITY: NON-SPECIFIC DEFENCE MECHANISMS

The healthy individual is able to protect himself from potentially harmful microorganisms in the environment by a number of very effective mechanisms present from birth which do not depend upon having previous experience of any particular micro-organism. The innate immune mechanisms are non-specific in the sense that they are effective against a wide range of potentially infective agents. The main determinants of innate immunity seem genetically controlled, varying widely with species and strain and to a lesser extent between individuals. Age, sex and hormone balance play lesser roles. In comparison, acquired immune mechanisms, discussed below, depend upon the development of an immune response to individual microorganisms that is specific only for the inducing organism.

Determinants of Innate Immunity

Species and strain

Marked differences exist in the susceptibility of different species to infective agents. The rat is strikingly insusceptible to diphtheria whilst the guinea-pig and man are highly susceptible. The rabbit is particularly susceptible to myxomatosis and man to syphilis, leprosy and meningococcal meningitis. Susceptibility to an infection does not always imply a lack of resistance because although man is highly susceptible to the common cold he overcomes the infection within a few days. Dogs in contrast are not susceptible to the virus agents responsible for the common cold in man. In some diseases, although a species may be difficult to infect (i.e. insusceptible), once established the disease can progress rapidly (i.e. lack of resistance). For example rabies

although common to both man and dogs is not readily established as the virus does not easily penetrate healthy skin. Once infected, however, the resistance mechanisms in both species are not able to overcome the disease. Marked variations in resistance to infection between different strains of mice have been noted.

In man the habits and environment of a community affect its ability to resist particular infections by acquired immune mechanisms developing early in life. This environmentally determined type of resistance is easily confused with the genetically

Table 1 Determinants of innate immunity

Specific host determinants	*Physical determinants*	*Active anti-microbial determinants*
Species and strain	Skin and mucous membrane barriers, moist surfaces	Anti-bacterial and anti-fungal secretions of skin – sweat and sebaceous secretions
Individual genetic factors	Anatomical traps, e.g. nasal cavity	Anti-bacterial and anti-viral secretions of mucous membranes
Age	Mechanical cleansing, e.g. cilia	Anti-microbial substances of tissue fluids, e.g. lysozyme, basic polypeptides
Hormonal balance		Phagocytosis and digestion

controlled innate immunity and makes it difficult to establish differences in innate immunity in different communities. It is however fairly clear that the American Indian and the Negro are more susceptible to tuberculosis than are Caucasians. It seems reasonable to assume that certain interspecies and interstrain differences have arisen by a process of natural selection.

Individual differences and influence of age

The role of heredity in determining resistance to infection is well illustrated by studies on tuberculosis infection in twins. If

one homozygous twin develops tuberculosis, the other twin has a three to one chance of developing the disease compared to a one in three chance if the twins are heterozygous. Sometimes genetically controlled abnormalities are an advantage to the individual in resisting infection as for example in a hereditary abnormality of the red blood cells (sickling) which are less readily parasitized by *Plasmodium falciparum* thus conferring insusceptibility to malaria. Infectious diseases are more severe at the extremes of life, and in the young animal this appears to be associated with immaturity of the immunological mechanisms affecting the ability of the lymphoid system to deal with and react to foreign antigens. In the elderly on the other hand physical abnormalities (e.g. prostatic enlargement leading to stasis of urine) are a common cause of increased susceptibility to infection.

Nutritional factors and hormonal influences

The adverse effect of poor nutrition on susceptibility to infectious agents is usually not seriously questioned. Experimental evidence in animals has shown repeatedly that inadequate diet may be correlated with increased susceptibility to a variety of bacterial diseases and this has been associated with decreased phagocytic activity and leucopoenia. In the case of infective agents such as viruses which depend upon the normal metabolic function of the host cells, malnutrition, if it interfered with such activities, would be expected to hinder proliferation of the potentially infective agent. There is experimental evidence in support of this view in a number of animal species which when undernourished were less susceptible to a variety of viruses including vaccinia virus and certain neurotropic viruses. The same may be true of malaria infections in man. The parasite requires para-amino benzoic acid for multiplication and this may be deficient when a low level of nutrition exists. The exact role of nutritional factors in resistance to infectious agents in man is difficult to determine by epidemiological data. Poor diet is often associated with poor environmental conditions and increased incidence of infection can correlate with poor sanitary conditions.

There is decreased resistance to infection in diseases such as diabetes mellitus, hypothyroidism and adrenal dysfunction. The reasons for this have yet to be elucidated in detail but it is known that the glucocorticoids are anti-inflammatory agents, decreasing

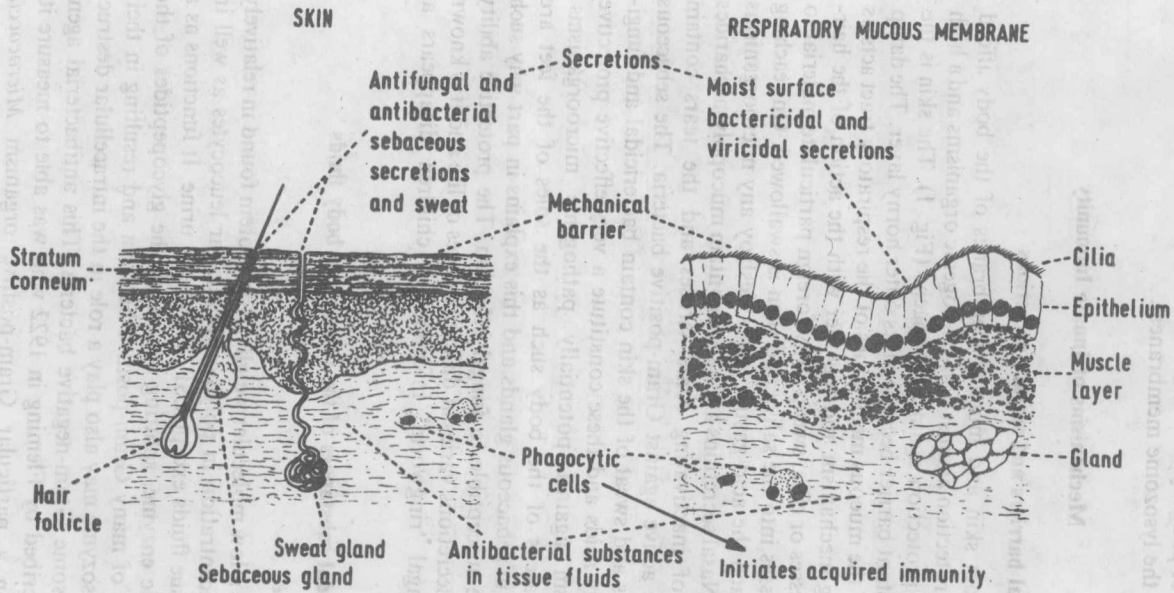

Fig. 1 Innate immune mechanisms

the ability of phagocytes to digest ingested material (probably by stabilizing the lysozome membranes).

Mechanisms of Innate Immunity

Mechanical barriers and surface secretions

The intact skin and mucous membranes of the body afford effective protection against non-pathogenic organisms and a high degree of protection against pathogens (Fig. 1). The skin is the more resistant barrier because of its outer horny layer. The damp surface of the mucous membranes of the respiratory tract acts as a trapping mechanism and together with the action of the hair-like processes or cilia, sweep away foreign particulate material so that it passes into the saliva and then is swallowed. On reaching the stomach the acid gastric juices destroy any microorganisms present. Nasal secretions and saliva contain mucopolysaccharides capable of inactivating some viruses and the tears contain lysozyme active against Gram-positive bacteria. The sebaceous secretions and sweat of the skin contain bactericidal and fungicidal fatty acids and these constitute a very effective protective mechanism against potentially pathogenic microorganisms. Certain areas of the body such as the soles of the feet are deficient in sebaceous glands and this explains in part why such areas are susceptible to fungal infection. The protective ability of these secretions varies at different stages of life and it is known that fungal 'ringworm' infection of children disappears at puberty.

Bactericidal substances of the tissues and body fluids

Lysozyme

This is a low molecular weight basic protein found in relatively high concentration in polymorphonuclear leucocytes as well in most tissue fluids except CSF, sweat and urine. It functions as a mucolytic enzyme, splitting sugars off the glycopeptides of the cell wall of many Gram-positive bacteria and resulting in their lysis. Lysozyme may also play a role in the intracellular destruction of some Gram-negative bacteria. This antibacterial agent was described by Fleming in 1922 who was able to measure its effect on a particular Gram-positive organism *Micrococcus*

lysodeikticus. Human tears contain a large quantity of lysozyme and egg white is a rich commercial source.

Basic polypeptides

A variety of basic proteins, derived from the tissue and blood cells damaged in the course of infection and inflammation, have been found in the tissues of animals. This group includes spermine and spermidine, which kill tubercle bacilli and some staphylococci, and the arginine and lysine containing basic proteins protamine and histone. The ability of these basic polypeptides to destroy bacteria probably depends on their ability to react non-specifically with the nearest acidic substance.

Phagocytosis and the inflammatory response

Microorganisms or inert particles such as colloidal carbon entering the tissue fluids or blood stream are very rapidly engulfed by various circulating and tissue-fixed phagocytic cells. These cells are of two types, the polymorphonuclear leucocytes of the blood – or microphages as they are sometimes called – and the mononuclear phagocytic cells distributed throughout the body both circulating in the blood and fixed in the tissues. The latter cells make up the cells of the reticuloendothelial system or RES and are given the generic name macrophages. Macrophages in the blood are known as monocytes, those in the connective tissues as histiocytes, those in the spleen, lymph nodes and thymus as the sinus-lining macrophages (sometimes called reticulum cells). It is now established that the macrophages of connective tissues are derived from peripheral blood monocytes as are the Kupffer cells of the liver, the alveolar macrophages of the lungs, and the free macrophages of the spleen, lymph nodes and bone marrow. In the spleen and lymph nodes, both free and fixed macrophages occur in close association with the reticular cells which act as a framework for the macrophages. The reticular cells themselves although able to ingest particulate material are not regarded as mononuclear phagocytes nor are the dendritic cells (p. 50) of the follicles of the spleen and lymph nodes. The term *mononuclear phagocyte system* to describe actively phagocytic cells is now gaining favour as a more satisfactory description of the function, origin and morphology