HANDBOOK OF EXPERIMENTAL IMMUNOLOGY
IN FOUR VOLUMES

Volume 1: Immunochemistry

EDITED BY

D. M. WEIR MD, FRCP

CO-EDITORS

L. A. Herzenberg PhD Caroline Blackwell PhD

Leonore A. Herzenberg DSc

FOURTH EDITION

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Preface

The pace of progress in immunology has not slackened since the last edition of this handbook. The subject now draws heavily on molecular biology and genetics and this has necessitated the inclusion of an additional volume on **Genetics and Molecular Immunology**. The explosion in the development of hybridoma technology and cell culture, since the last edition, can be seen from the many chapters in each volume that employ monoclonal reagents and cell lines. Some idea of the expansion of the field can be gained from the **Cellular Immunology** volume where contributions on phagocytes and lymphocytes now occupy 30 chapters compared to 12 in the previous edition. A new section on immunoregulation contains 14 chapters and there are now 6 chapters devoted to mammalian cell membrane antigens in the **Immunochemistry** volume.

It is now no longer possible for one editor to keep in touch with the enormous expansion in this field, and I am much indebted to my co-editors Len and Leonore Herzenberg who have joined me in the task of co-opting research workers in the wide range of disciplines now contributing to the field of immunology. I am particularly grateful to my wife Dr Caroline Blackwell for her help with the massive editing task.

Amongst the many new features of this edition is the provision of overviews for many of the sections. I am most grateful to our contributors in the methodology sections for their efforts to achieve a consistent style of presentation of the procedures, and I hope that this will help in the accessibility of the descriptive material. A work of this size inevitably takes a number of years to put together but considerable effort has gone into introducing up to date material into the chapters. This has been achieved by enabling and encouraging contributors to introduce new material and references during the proof stages of their chapters.

I wish to thank Hilary Flenley for her careful and thorough index, and Nigel Palmer and his staff at Blackwell Scientific Publications Edinburgh office without whom production of the new edition would have been impossible. Per Saugman has as always, maintained a benevolent paternal interest in the project.

D.M.W.

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Chapter 1
Overview: Antigens

M. SELA

Definitions

The expression '*antigen*' may have two meanings. On the one hand, we mean by 'antigen' the substance capable of triggering an immune response, but on the other hand, we use the same word for a substance capable of reacting immunospecifically with an antibody, even though sometimes it is not able to trigger a response. To distinguish between these two different notions, we have been using the expressions *immunogenicity* and *antigenic specificity*. By immunogenicity we understand the capacity of a substance to provoke an immune response, whatever its specificity, and such a substance is an *immunogen*. A chemical or physical change in a molecule that will result in an increased immune response will increase its immunogenicity, even though it may or may not have changed its antigenic specificity. It is the *antigenic determinant* (also defined as epitope) which is also responsible for the specificity.

Putting it in other words, immunogenicity is a property of substances that can induce a detectable immune response (humoral, cellular, or, most commonly, both) when introduced into an animal or human being. Such substances are therefore generally called *immunogens* or *antigens*. Ultimately, the ability to mount an immune response depends upon the interplay between the chemistry of the antigen and the physiological state of the host. Thus immunogenicity is operationally dependent on the experimental conditions of the system, including parameters such as the antigen, the mode of immunization, the organism being immunized and its genetic background, as well as the sensitivity of methods used to detect a response.

It is worth stressing that we are using the word *antigen* sometimes for a molecule, sometimes for a virus or a bacterium, and sometimes for an organ or a tissue, but the antibodies—or the sensitized cells—have a *combining site* (also defined as paratope), with all its distinctive features, of a more or less similar size and similar cavity. These combining sites are not complementary to a complete bacterium or a complete heart, but they are always complementary to a unique antigenic determinant which is of a limited molecular size.

The antigenic determinants may be parts of proteins, nucleic acids, polysaccharides, lipids or glycolipids, or other biological macromolecules. Very often they have unique steric conformations and are part of a native structure. We have thus to distinguish between *sequential* determinants and *conformation-dependent* (or conformational) determinants. The operational definition holds that if antibodies against, e.g. a protein, react well with a tetra-, penta-, or hexapeptide derived from that protein, then the antibody is against a sequential determinant. The antibody, on the other hand, is against a conformation-dependent determinant if it is made against a juxtaposition of atoms in space which results from a unique conformation of the macromolecule, and any peptide derived from such a protein will not be able, after denaturation, to react with the antibody.

It is of interest that for most globular proteins and native nucleic acids, almost all the antigenic determinants are conformation-dependent, whereas for most polysaccharides, fibrilar proteins such as silk fibroin, and single-stranded nucleic acids, the determinants are sequential. The use of homopolymers of amino acids or sugars, and of peptidyl proteins as antigens has established that the determinant is composed of four to six amino acid or sugar residues which contribute unequally to binding with the antibody combining site.

Not all the antigenic determinants express themselves all the time: some are more *immunopotent* than others. Some do not express themselves at all under a certain set of conditions, and we call them *immunosilent*, even though under other conditions they may provoke an efficient immune response. Thus a determinant may be immunosilent within a complete macromolecule, but may be quite immunopotent when a segment of that macromolecule on which it is present is used for immunization. Situations are also known where a determinant is immunosilent but

becomes immunopotent in animals made tolerant to other parts of the immunogenic macromolecule of which the determinant discussed forms a part. We may thus define *immunopotency* as the capacity of a region of an antigen molecule to serve as an antigenic determinant and induce the formation of a specific immune response. For all the above reasons, one should never use the expression immunogenic determinant when discussing a determinant within an immunogen which expresses itself; this expression (*immunogenic determinant*) should be used only to define a portion of an antigen of the size of a specificity determinant which can be cut off by chemical or enzymatic methods, and is still able to provoke an immune response when used for immunization by itself.

The term *hapten*, in its strictest sense, designates any substance, large or small, which does not elicit an immune response by itself but can be shown to react with antibody provoked by immunization with a complete immunogen of which the hapten formed a part. In practice, most haptens investigated are small chemical substances, in most cases of a size definitely smaller than that of a complete antigenic determinant. When attached to a protein, haptens such as dinitrophenyl or penicilloyl might be defined as *immunodominant* parts of an antigenic determinant (an epitope). In studies of determinants of polysaccharide or polypeptide nature it is of interest to establish which is their immunodominant portion.

The common response to an immunogen is either the production of antibodies, which find their way usually into the bloodstream, or exclusively cell-mediated immunity, e.g. delayed hypersensitivity. Still other responses may result in specific *immunological tolerance*, i.e. induction of the inability to form antibodies or cellular reaction towards a specific antigen. Generally an organism distinguishes between 'self' (material which is its own) and 'non-self' (any foreign material). The immune system of an organism reacts against any foreign compound (antigen), and is *tolerant* (unable to react) towards its own body components, which may be good immunogens in other organisms. This *self-tolerance* is acquired during fetal or neonatal development, and the immune system can be made tolerant even to foreign material or tissue introduced during this period. Such material, which can induce immunological tolerance or unresponsiveness, is called a *tolerogen*.

Another phenomenon which should be mentioned here is *antigenic competition*. This may occur between different antigens (intermolecular), or between different specificity determinants on the same antigen (intramolecular), in which case we define it as *competition between antigenic determinants*. The existence of this phenomenon may account for some determinants being *immunosilent* under certain circumstances. Antigenic competition may be defined as the inhibition of the immune response to one antigen or determinant by the administration of another antigen or determinant.

Molecules as antigens

The two types of natural macromolecules most investigated as antigens are proteins and polysaccharides. These also include glycoproteins, nucleoproteins, lipoproteins, etc. as well as peptidoglycans, glycolipids, and other conjugates. Nucleic acids are also antigenic. Lipids are poor immunogens, but antibodies against them can be obtained, and liposomes play a role here, as they do in enhancing the immunogenicity of various other antigens. Synthetic antigens, especially synthetic polypeptides, have played an important role in the elucidation of the molecular basis of antigenicity and many other immunological phenomena, and they will be discussed here in more detail below, as well as in a separate chapter (Chapter 2). Other synthetic polymers have also been shown to be immunogenic, e.g. polyvinylpyrrolidone.

All proteins are probably immunogenic, although individual proteins differ markedly in their immunogenicities. Similarly, although a foreign protein can induce the synthesis of both circulating and cell-bound antibodies, the relative distribution of these responses varies considerably for different proteins. Denatured proteins are often less immunogenic than the corresponding native proteins. Self-aggregation of a protein is usually associated with a negligible change in its antigenic specificity, but with a considerable increase in immunogenicity. Like other antigens, proteins possess a finite number of antigenic determinants that correspond to discrete portions of the surface structure and that are preferentially located in those regions most exposed to the external environment. The relationship between structure and antigenicity is, however, more complex for globular proteins than for other antigens in that it depends to a very large extent upon the overall conformation of the molecule. The exploration of antigenic regions on the surface of proteins has become easier with the advent of monoclonal antibodies and rapid methods of peptide synthesis. The antigenic sites may be described as surface domains made up from amino acid side-chains which may be distant in sequence but close in space (conformation-dependent determinants). Such domains are probably overlapping and cover most of the protein surface. On the other hand, fibrous proteins possess sequential determinants, whose size may be determined with synthetic peptides to be in the range of three or four, up to five or six amino acid residues.