IMMUNOLOGY IMMUNOPATHOLOGY and IMMUNITY

third edition

STEWART SELL, M.D.

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The author and publisher have exerted every effort to ensure that drug selection and dosage set forth in this text are in accord with current recommendations and practice at the time of publication. However, in view of ongoing research, changes in government regulations, and the constant flow of information relating to drug therapy and drug reactions, the reader is urged to check the package insert for each drug for any change in indications and dosage and for added warnings and precautions. This is particularly important when the recommended agent is a new and/or infrequently employed drug.

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Preface to the Third Edition

The fields of immunology and immunopathology continue to expand at a mind-boggling pace. The third edition of Immunology, Immunopathology and Immunity contains five new chapters: Chapter 7, The Major Histocompatibility Complex; Chapter 8, Cell-Mediated Immunity; Chapter 10, Accessory Systems in Immune Reactions; Chapter 22, Immune Modulation; and Chapter 23, Lymphoproliferative Diseases. These new chapters reflect areas where major advances (or at least additions) to our knowledge of the immune system, its effects, and its diseases have been made. In addition, major revisions and additions have been made to the chapters retained from the second edition.

As in previous editions, the book is divided into three sections: Immunology, Immunopathology, and Immunity. The major emphasis is on the second section (Immunopathology). In recent years, there has been publication of a number of books on immunology. However, these other books do not include the subject of immunopathology in any systematic manner. The section on immunology presents those basic principles that the author considers necessary for understanding of the remainder of the book. Therefore, attempts have been made to eliminate unnecessary nuances or distractions that may be of interest to immunologists, but are not germane to understanding immunopathology and immunity. On the other hand, I have attempted to include sufficient details to provide a thorough general knowledge of basic immunology.

There are still some areas where the reader may find more details than desired; particularly on subjects such as human immunoglobulin allotypes, histocompatibility restrictions in immune responses, cellular interactions during induction of immunity, the reticuloendothelial system, and complement. Although these are all important topics of modern immunology, it may be advantageous for the reader who is mainly interested in immunopathology to skip these sections and proceed more directly to the sections on immunopathology and immunity.

Finally, I would like to thank a number of individuals who helped me to clarify different sections of this book: Stephen Baird, Richard Dutton, Polly Matzinger, Susan Swain, and Nathan Zvaifler.

A special thanks goes to the artist who provided the final versions of the many new figures, Laurie Newell.

Stewart Sell, M.D.

Preface to the First Edition

Frequently I have been asked by medical and biology students to recommend a text that covers both basic immunology and immunopathology. At best, I could recommend a basic text for immunology and individual chapters in several books for immunopathology—admitting that still, certain fundamental areas would remain uncovered. I could not identify a single text that encompasses the material that I thought important in a manner palatable to a beginner in the field.

In general, medical or pathology texts present immune reactions according to individual diseases or organ systems; they therefore lack a coherent mechanistic organization. Other texts, usually multiauthored, provide excellent reference sources but are too large and detailed and lack the organization necessary to be of general use for students unfamiliar with immunologic principles. My goal in writing this book is to give an organized, concise, yet meaningful presentation of immunology, immunopathology, and immunity, stressing their interrelationships. This book is intended for biology and medical students, house officers, and faculty who wish an introduction to the role played by immune mechanisms in disease.

In order to present both the protective and destructive mechanisms of the mammalian immune system, the text is divided into three parts: Immunology, Immunopathology, and Immunity. The first part, Immunology, presents the basic principles of the induction and expression of specific immune reactions. Aspects of immunology important for the understanding of immunopathologic mechanisms are emphasized. This provides an introduction for the second and major part of the book, Immunopathology. In this section, I have organized the fundamentals of how immune reactions cause tissue damage and disease in order to stress a classification based on immune mechanisms. The last part, Immunity, covers the role of immune reactions in protecting against infection and cancer. Detailed coverage is provided in areas of current interest, such as tissue transplantation and tumor immunity; the more classical topics receive a simplified treatment.

Stewart Sell, M.D.

Glossary of Terms

ABC	antigen-binding capacity
ALS	antilymphatic serum
ATP	adenosine triphosphate
B cell	bone-marrow-derived cells (antibody-forming cell precursors)
BCG	bacillus Calmette-Guérin
BGG	bovine gammaglobulin
BSA	bovine serum albumin
BSA*	radiolabeled BSA
CBH	cutaneous basophil hypersensitivity
CEA	carcinoembryonic antigen
CGD	chronic granulomatous disease
Con A	concanavalin A; a plant mitogen
Cyclic Amp	cyclic adenosine 3′,5′-monophosphate
Cyclic Gmp	cyclic guanosine 3′,5′-monophosphate
DH	delayed hypersensitivity
DL	Donath-Landsteiner antibody
DNA	deoxyribonucleic acid
DNCB	dinitrochlorobenzene
DNP	dinitrophenol
DPT	combination injection for immunization against diphtheria, pertussis, tetanus
EAC	sheep cells coated with antibody and complement
EAT	experimental allergic thyroiditis
GA-(GT)	copolymer of L-glutamic acid and L-tyrosine
GL	copolymer of L-glutamic acid and L-alanine
HL-A	histocompatible lymphocytes-antigens
H-PLL	hapten-poly-L-lysine conjugate
Ia	Ir gene-controlled antigen
Ig	immunoglobulins; five classes: IgA, IgG, IgM, IgD, IgE
Ir	immune response (gene)
IrE	immune response (gene) to ragweed
KLH	keyhole limpet hemocyanin
LATS	long-acting thyroid stimulator
LCM	lymphocytic choriomeningitis
LE	lupus erythematosus

LPS	bacterial lipopolysaccharide
M	macrophages
MLR	mixed lymphocyte reaction
MW	molecular weight
OT	old tuberculin
PHA	phytohemagglutinin
PLS	passive leukocyte-sensitizing activity
PPD	purified protein derivative
Ragg	rheumatoid agglutinators
RAST	radioallergoabsorbent test
RNA	ribonucleic acid
SLE	systemic lupus erythematosus
SNagg	serum normal agglutinators
Ss-Slp	genetic locus within the H_2 complex of mice controlling concentration and allotypic variation of a serum alphaglobulin
SSPE	subacute sclerosing panencephalitis
T cell	thymus-derived lymphocytes (helper cells)
TDM	thymus-derived mediator
Tla	thymus leukemia antigen
TPI	*Trepenoma pallidum* immobilization
TSTA	tumor-specific transplantation antigen

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PART I

Immunology

INTRODUCTION

Immunity has come to mean a specific protective response to a noxious agent or organism as the result of a previous exposure to it. The protection is specific in the sense that it is restricted to the agent or antigenically related agents to which the individual was previously exposed. The protection is mediated through the production of specifically modified serum proteins (antibodies) or specifically altered cells (sensitized cells) that have the capacity to recognize, react with, and neutralize the offending agent (antigen).

The terms *immunity* and *allery* are now used interchangeably for manifestations of immune reactions. Von Pirquet originally defined allergy as "altered reactivity" due to a previous exposure to an agent without consideration of the effect of the altered reactivity upon the reacting individual. For the sake of clarity, allergy should be reserved for instances in which the altered reactivity is deleterious rather than beneficial. However, in practice it is difficult to restrict the use of these terms (i.e., autoimmune is commonly used when autoallergic is preferrable). Hypersensitivity is also used for circumstances in which an allergic reaction causes tissue damage or an undesirable symptom. However, hypersensitivity is frequently applied to nonallergic as well as allergic reactions, and restriction of this term to allergic reactions is not practical. Immunopathology is the study of the tissue alterations that result from allergic reactions.

The induction and expression of immune reactivity are the subjects of the first part of this text. The mechanisms and effects of immune reactions in the production of tissue lesions and disease (allergic reactions) are the subjects of Part II. The role of these mechanisms in protection against disease (immunity), the effects of the lack of such protective mechanisms (immune deficiency diseases); and the relationship of immune mechanisms to cancer are the subjects of the third part of this text.

CHAPTER 1

Antigenicity and Immunization

In all types of immune or allergic reactions, an individual acquires specific information (learns) from contact with an antigen without the mediation of the nervous system. The essence of an immune or allergic response is the capacity to recognize and react to an antigen.

ANTIGENS AND IMMUNOGENS

An antigen is classically defined as a molecular species capable of inducing an immune response and of reacting specifically with the products (antibody, sensitized cells) manufactured as a consequence of the immune response (Fig. 1-1). The ability of material to induce an immune response is referred to as immunogenicity, and such a material may be called an immunogen. The ability of a material to react with the products of an immune response is referred to as antigenicity, and therefore such a material is an antigen. Antibodies join to antigen by noncovalent bonding of sites which can be juxtaposed because of a physical "lock and key" relationship (see Chap. 3). Antibodies are present in the serum component of whole blood (blood without fibrin and cells) and serum containing antibody is designated *antiserum.*

Complete and Incomplete Antigens

A complete antigen is one that can both induce an immune response and react with the products of that response. An incomplete antigen (hapten) is a chemically active substance of low molecular weight that is unable to induce an immune response by itself but can, by combining with larger molecules (carrier or "Schlepper"), become immunogenic. A complete antigen is both an immunogen and an antigen, whereas an incomplete antigen is not an immunogen, but is an antigen. For example, a chemically highly active small molecule such as dinitrophenol (an incomplete antigen) may combine with the host's protein (to form a complete antigen) so that sensitization occurs (Fig. 1-2). An individual thus sensitized reacts with the dinitrophenol upon second contact with it (see Chap. 16).

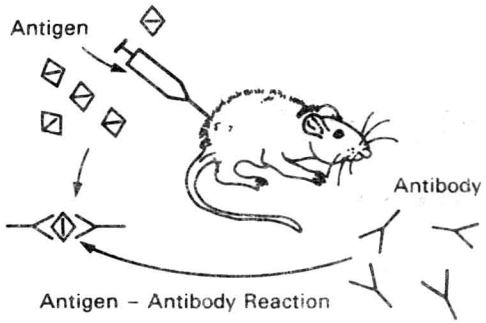

Fig. 1-1. Definition of antigen and antibody. A complete antigen (immunogen) is a material that is capable of inducing an immune response and of reacting with the products of the immune response. Antibody is a protein molecule formed by stimulation with antigen that reacts specifically with the antigen.

Physical Properties of Antigens

The size, shape, rigidity, location of determinants, and tertiary structure have been shown to affect antigenicity.[7,11]

Size

Complete antigens (immunogens) usually have a high molecular weight. Some naturally occurring immunogens may have a fairly low molecular weight, such as ribonuclease (MW 14,000), insulin (MW 6,000), and angiotensin (MW 1,031). The artificial antigen N-acetyl-L-tyrosine$_3$ (MW only 450) has apparently evoked an immune response in some guinea pigs,[11] but one cannot rule out the possibility that such a small molecule may combine with host protein so that the actual immunogen is a complex composed of the small molecule (hapten) and the host protein (carrier).

The sites of antigens that react with antibody are smaller than those that induce antibody formation. Kabat has reviewed the size and characteristics of areas of antigen that react with antibody (antigenic determinants).[5] This information is obtained by determining the ability of a given compound of low molecular weight to inhibit the reaction of antibody with the complete antigen of which the small compound is only a part. Antibodies to dextran polysaccharide are inhibited by six unit saccharides (MW 990), and antibodies to polypeptides are inhibited by four to five amino acid oligopeptides (MW 650). Homopolymers of amino acids are not usually immunogenic, but will function as haptens if added to carrier molecules such as a serum protein. Poly-L-lysine is not immunogenic, but the attachment of a dinitrophenyl group to poly-L-lysine may establish immunogenicity. DNP-L-lysine$_7$ is immunogenic, but DNP-L-lysine$_6$ is not. L-Lysine$_5$ inhibits the reaction of anti-L-lysine antibody with poly-L-lysine$_7$. Therefore a larger molecule is usually required to induce an immune response than is necessary to react completely with antibody.

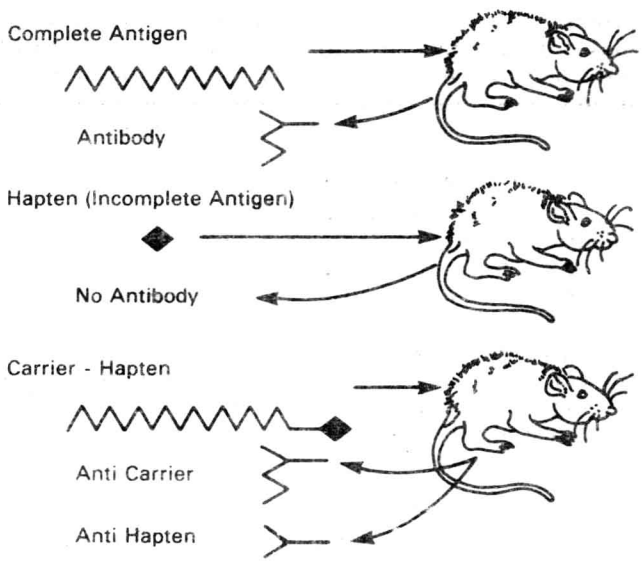

Fig. 1-2. Carrier-hapten relationship in immunization. A complete antigen (immunogen) both induces an immune response and reacts with the antibody produced. Haptens are incomplete antigens. Incomplete antigens are not able to induce an immune response alone, but antibody can be induced if the hapten is complexed to a complete antigen.

Shape

The shape of a determinant is important, as certain components, such as the DNP in DNP-L-lysine, give form to a molecule that is evidently not found in the homologous polymer. Copolymers of two amino acids are immunogenic for some species, whereas polymers of three or four amino acids are required for other species. The presence of more than one amino acid in a polymer results in a configuration not available in the polymer of a single amino acid. The location of a structure within a determinant may also be important. In some cases antibody can be demonstrated to bind more strongly with certain structures within a determinant than with other structures. For instance, in determining the binding of antibody to D-alanine-glycine-E-aminocaproic acid, it was found that the terminal alanine was responsible for most of the antibody binding. In this case, the D-alanine group is termed the immunodominant part of the determinant.[5,11]

Rigidity

The role of rigidity and location of determinants in antigenicity is exemplified by the work of Sela in regard to the alteration in immunogenicity and antigenicity of gelatin by the addition of poly-L-tyrosine to a gelatin backbone.[12] Gelatin, which may have a very high molecular weight, is almost completely nonimmunogenic. Addition of 1 per cent tyrosine increases the immunogenicity and antigenicity of gelatin, and the specificity of antibody

produced is directed toward the gelatin. Addition of the tyrosine evidently makes the gelatine structure more stable or rigid. Addition of 3 to 10 per cent tyrosine to gelatin results in the production of antibody with specificity directed toward the tyrosine, that is, all the antibody activity can be removed by absorption with poly-L-tyrosine and none by gelatin.

Determinant Location

Sela also demonstrated that if the tyrosine is buried inside the tyrosine-gelatin molecule, it does not function as an antigen, but if the tyrosine is placed on the surface of the molecule, it is recognized.[11] This finding, along with the observations that new determinants may be exposed by partial denaturation of proteins, indicates that important antigenic determinants may be secluded inside large molecules and may be exposed by unfolding of the molecule. Denaturation of a protein generally decreases or destroys its immunogenicity and antigenicity. However, partial denaturation may result in exposure of different molecular configurations because of alteration of the tertiary structure of the molecule. This creates new antigenic determinants.

Tertiary Structures

The tertiary structure of proteins (spatial folding) is important in determining the specificity of an antibody response. Antibodies produced to the A chains of insulin do not react with the natural molecule.[13] Reduction and reoxidation of ribonuclease under controlled conditions produce a mixture of protein molecules different in only third-dimensional structure. Some antisera to native ribonuclease are unreactive to these denatured molecules; other antisera to the native molecule do react with the denatured forms.[9] These results indicate that the tertiary structure of immunogens is recognized by the immunologically reacting systems. Therefore no significant breakdown of the immunogen can occur before it is recognized by the specifically reactive cells. If catabolism did occur, the tertiary structure of the immunogen would be destroyed.

Catabolism

The optical activity of synthetic antigens has suggested that the ability to catabolize or break down the antigen is important for the induction of an immune response. Thus, L-amino acid heteropolymers are catabolizable and are immunogenic, whereas D-amino acid heteropolymers are not catabolizable and are poorly immunogenic.[7] However, pneumococcal polysaccharides are not digested by mice, but are highly immunogenic. The inability of D-amino acids to function as immunogens is not due to an inability of the reacting animal to recognize D-amino acids as foreign, since copolymers of L- and D-amino acids are immunogenic and some of the antibody formed reacts specifically with D-amino acid polymers. The immunogenicity of D-amino acid polymers is dependent upon dose in mice and rabbits. The response to D-isomers exhibits a strong maximum at about 1 μg. per mouse, but that to L-isomers is largely independent of dose. Therefore, the failure to detect responses to the poorly catabolized D-isomers may be due to selection of the wrong immunizing dose. Antibody formed to poorly catabolized immunogens may be difficult to demonstrate because of blocking or binding of the antibody formed with the noncatabolized antigen still present in the serum (see Chap. 9).

IMMUNIZATION

Immunogenicity is determined not only by the nature of the antigen, but also by characteristics of the responding animal and the manner in which the antigen is presented to the responding animal. The contact of immunogens and responding persons may occur by natural exposure to organisms, chemicals or other immunogens in the environment, or may be artificially induced by controlled immunization. The following factors are involved in any controlled immunization and the detection of a subsequent immune response: 1) the source of the antigen, 2) the preparation of the antigen, 3) the form in which the antigen is given, 4) the route of immunization or anatomic location of initial contact, 5) the dose of antigen, 6) the time between the immunizing event and the testing for antibody or sensitized cells, 7) the number of immunizations given (primary or secondary response), 8) the type of test procedure employed, 9) the genetic makeup of the responding animal, 10) the condition of the responding animal, and 11) the presence of bacterial products in the immunizing mixture. Given such a number of variables, some generalizations may be made, but in practice each immunizing situation must be evaluated individually. Therefore, for the results of laboratory tests to be evaluated satisfactorily, the conditions under which an antiserum or population of sensitized cells is obtained must be thoroughly described.

Immunization is performed clinically to induce a protective reaction, as in vaccination with polioviruses or diphtheria toxoid (see Chap. 20). Experimental immunization may be performed to explore immune reactions or to produce an antiserum that might be used as an immunochemical reagent. The reasons for performing a certain immunization determine, to a large extent, how it is given.

Source of Antigen

The source of antigen depends upon the purpose of the immunization. For protective immune responses, individuals may be immunized with killed infectious agents or with nontoxic extracts (see Chap. 20). In experimental situations, an individual may be immunized with the serum proteins or tissues of another individual of the same or a different species, or with artificially synthesized materials such as polypeptides.

Preparation of Antigen

The final preparation of an antigen used for immunization depends upon the degree of specificity desired. For example, immunization of a rabbit with whole rat spleen produces an antiserum that reacts with various cell populations in the spleen (erythrocytes, lymphocytes, macrophages) and with as many as 30 different plasma proteins. By careful removal of the cellular elements or by immunization with rat serum (defibrinated rat plasma), a rabbit antiserum that reacts with rat serum proteins may be obtained (rabbit anti-whole-rat serum). By fractionation of the rat serum, an antigen preparation may be obtained that contains only one serum protein. Further fractionation of an antigenic molecule may be accomplished by breaking the molecule into smaller units; an antiserum that reacts with only part of the molecule may thus be obtained.

Forms in Which Antigen Is Given

The form in which an antigen is administered also may vary. A serum protein may be administered in soluble form. It may be precipitated with alum to obtain a greater antibody response. An intense mononuclear infiltration at the site of injection is induced by injection of antigen incorporated into an emulsion with Freund's adjuvant (water in oil emulsion)[1] to which mycobacteria may be also added (complete Freund's adjuvant). This greatly enhances the immune response (see Adjuvants, Chap. 22). Many other variations may be employed to modify the nature and extent of the immune response.

Route of Immunization

The routes of immunization include intradermal, subcutaneous, intramuscular, intraperitoneal, intravascular and intracranial injection, as well as injection into any organ. In addition, immunization may be accomplished by ingestion, inhalation, skin application, rectal infusion, or intratracheal infusion. The type of immune response elicited depends upon the route used. Those routes that lead to distribution in vascular spaces generally lead to the formation of humoral antibodies, whereas those routes that lead to focal deposition in peripheral lymphoid tissue (intradermal injection or application on the skin surface) tend to induce cellular sensitivity. Inoculation into organs of external secretion such as salivary glands, breast, or nasal mucosa may result in the production of antibodies of a different class of immunoglobulins (IgA) than would be found following intramuscular injection (IgG). (For a discussion of immunoglobulin classes of antibody, see Chap. 2.)

Dose of Antigen

The amount of antigen given is extremely important because too little or too much may result in a loss of immune responsiveness (see Chap. 9). A few milligrams of any antigen is usually enough to induce an immune response. Much smaller amounts may actually be more effective, depending on the nature of the antigen. If a specific antiserum is desired, relatively small amounts of the antigen preparation should be used. If large amounts are used, trace contamination with undesirable antigens may result in the production of an antiserum with multiple specificities.

Interval Between Immunization and Testing

Antibody may be detected within a few hours following immunization, if very sensitive detection techniques are used. However, in most controlled immunizations circulating antibody does not appear in significant amount until 7 to 10 days following immunization. The immunoglobulin class of antibody produced also may change with time. Early antibody tends to be of the IgM class, whereas later antibodies are of the IgG class.[12] Also, late antibodies may bind more strongly to antigens than early antibodies (see Chap. 3). Usually after 3 to 5 weeks the amount of antibody produced starts to decline so that later blood analyses give lower titers of antibody.