Comprehensive Immunogenetics

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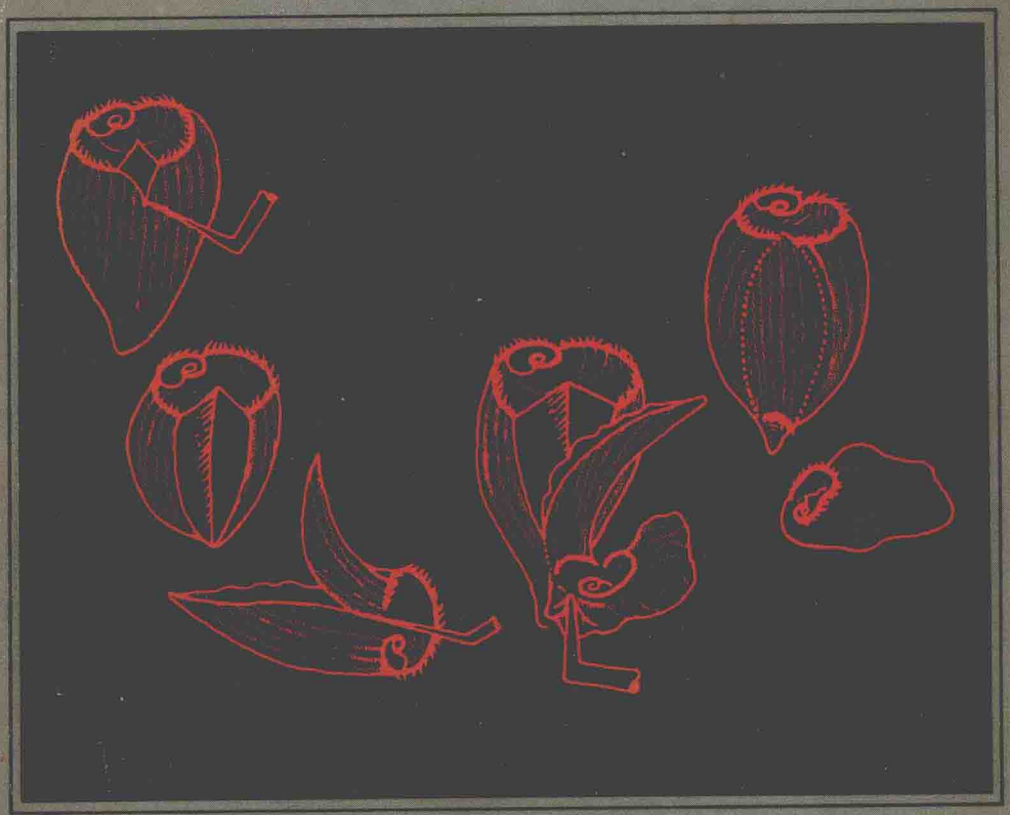

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Blackwell Scientific Publications Ltd.
Osney Mead, Oxford OX2 OEL
8 John Street, London WC1N 2ES
9 Forrest Road, Edinburgh EH1 2QH
52 Beacon Street, Boston, Massachusetts 02108, USA
214 Berkeley Street, Carlton, Victoria 3053, Australia

First published in the United States of America in 1981
by Elsevier North Holland, Inc., 52 Vanderbilt Avenue, New York, NY 10017

ISBN 0-632-00788-5

Desk Editor Robert Glasgow
Design Edmée Froment
Design Editor Glen Burris
Art rendered by Vantage Art, Inc.
Production Manager Joanne Jay
Compositor Publishers Phototype, Inc.
Printer Haddon Craftsmen

Manufactured in the United States of America

COMPREHENSIVE IMMUNOGENETICS

To Dorothy, Yukiko, and Roslyn

PREFACE

The first book entitled *Immunogenetics,* written solo by the senior author and completed in 1968, was also the first attempt to offer a comprehensive overview of this newly emerging field. By that time, the subjects of microbial antigens/serotype patterns, blood group alloantigen systems, and immunogenetics of tissue transplantation were already well explored. However, other topics now at the forefront of immunogenetic interest were still in early stages of study. These newer emphases are genetics of antibody molecules, genetic control of immune responsiveness, immunodeficiency and immunogenetic diseases, and phylogeny of immunocompetence. Although many excellent reviews of different aspects of immunogenetics have been written over the years, no single source of basic principles and their applications has been available for pedagogic or correlative purposes. The need for such a book has markedly increased with expanding emphasis in the interdisciplinary fields of tissue transplantation, genetic regulation of immune responsiveness and cancer.

The nine chapters of *Comprehensive Immunogenetics* now cover the entire field from the perspective of 1980. Indeed, this is the only book available that deals with the ramifications of immunogenetics as a whole. This book is intended to serve multiple needs. It is intended first as a text for advanced undergraduates and graduate students. For this purpose, only a very elementary background in genetics, biochemistry, and immunology is assumed by the authors. The introductory chapter accordingly outlines concepts and first principles—the scope of immunogenetics with emphasis on fundamentals, terminology, and basic methodology. This chapter ends with a consideration of types of genes affecting diverse immunologic characteristics. The stage is thereby set for the more specialized topics of subsequent chapters. The sequential approach adopted has evolved over many years of teaching immunogenetics to a broad range of students at the University of California, Los Angeles. *Com-*

prehensive Immunogenetics should also serve to enrich courses in genetics or immunology, including those offered for medical or professional students. Postdoctoral and faculty-level individuals in various biomedical sciences should find this book a frequently useful reference, suitable for self-instruction.

The first chapter is intended as a general foundation upon which later chapters depend in differing degrees. Chapter 2 deals with the genetics of antibody molecules, their production, structure, diversity, and their generation. Given this understanding, microbial antigens and serotype patterns are analyzed in Chapter 3 with emphasis on genetic polymorphisms and their significance in well-studied bacteria, protozoans, and viruses. At this juncture, the student should have a good basic grasp of the immunogenetics triad of immunogenes, antibodies, and antigens. Chapters 4 through 6 may be regarded as an integrated unit, dealing in turn with blood group alloantigen systems, immunogenetics of tissue transplantation, major immunogene complexes, and lymphocyte differentiation genes. These subjects provide an important background for understanding Chapter 7 on genetic control of immune responsiveness with its dependence on the major immunogene or histocompatibility complex. Chapter 8 then comes to grips with immunodeficiency and immunogenetic diseases. This takes the reader from the genetic basis of infectious disease resistance to immunogenetic correlates of cancer and aging. Finally, Chapter 9 on phylogeny of immunocompetence puts immunorecognition systems, allogeneic polymorphisms, and diversification of immunocyte functions in evolutionary perspective.

Since there are many interconnecting paths among the subjects considered in the separate chapters, attention is repeatedly called to basic interrelationships, especially where frontier questions are involved. This book then emphasizes principles and problem-solving. An entreé to the contemporary literature of immunogenetics is also provided in the text and in the annotated key references at the end of each chapter. These references, which are mostly recent reviews or definitive research articles, contain citations of pertinent earlier work the serious student may wish to pursue in greater detail. Given the new breadth of immunogenetics, an effort was made to achieve a stimulating compromise between the usual textbook and advanced monograph approaches. The illustrations are an integral part of the presentation. For the most part, each chapter may be read or used independently. Thus, instructors may choose to alter the sequence or otherwise select certain chapters to meet the needs of different groups of students.

We welcome the opportunity to acknowledge the lively stimulation of immediate colleagues, postdoctoral fellows and graduate students. For helpful suggestions or personal communications we thank Don Bailey, Nick Cohen, Carol Sibley, George Snell, Clyde Stormont and Paul Terasaki. At the same time, we apologize to investigators whose work may have been cited without pausing to assign credits. Carol Thiele skillfully converted our crude drawings

into the finished illustrations. For innumerable days of typing, proof-reading, and enthusiastic attention to other details, we salute Lois Bigger and Virginia Janczak.

Bill Hildemann
Ed Clark
Bob Raison

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CONCEPTS AND FIRST PRINCIPLES

INTRODUCTION: THE SCOPE OF IMMUNOGENETICS

Immunogenetics was born about 1900 when Landsteiner identified ABO blood groups in humans while Ehrlich and Morganroth discovered individual-specific blood types in goats. This was the first use of immunological methodology to explore genetic variation, coincidentally at the time when rediscovery of Mendel's principles began to revolutionize biology. Some might contend that immunogenetics was really established in the mid-1920s with Bernstein's demonstration from analyses of family data of a three-allelic-gene basis for ABO blood types in man. However, the genetic basis of tissue transplantation incompatibility was already proved in 1916 as a result of experiments with inbred lines of mice by Little and Tyzzer. Numerous studies of blood types and of tissue transplant reactions during the 1920s established the early finding that normal cells of mammals carry individual-specific antigens under the control of Mendelian genes.

The scope of immunogenetics has progressively widened to include microbial antigens, the genetics of antibodies and other macromolecules, and the phylogeny of immune responsiveness. Immunogenetics may now be broadly defined to include studies in which the principles and techniques of both genetics and immunology are employed together. Studies of individual-specific and tissue-specific cellular antigens have become a major focus of immunogenetics, with important ramifications both in molecular biology and in medicine. Almost every facet of modern immunological research and its application involves important genetic considerations. Elucidation of host–parasite relationships depends upon understanding the inheritance of host immune-response capacities as well as antigenic characteristics of particular pathogens. Intraspecific differences are reflected in individual variations in chemical structure of cellular and soluble macromolecules. This intraspecific diversity is so great that, except for identical twins or equivalent highly inbred animals, ev-

ery individual within a species may be regarded as unique. Such uniqueness is best demonstrated across the whole spectrum of animal species by tissue transplantation. Given appropriate techniques, self-to-self transplants survive, whereas nonself exchanges reveal their lack of molecular identity by rejection. Incompatibility leading to eventual graft rejection is the universal rule within species of multicellular animals, both invertebrates and vertebrates. A normal, adult recipient reacts against the genetically and antigenically different tissue of the donor. This highly discriminating recognition of nonself applies to species ranging from corals to tunicates and fishes to mammals. The "uniqueness of the individual" and the "uniqueness of separate breeding populations" emerge as tenets of immunogenetics.

One of the most fundamental generalizations in biology is that genes specify and regulate the synthesis of macromolecules required for growth and development. In addition to nucleic acids containing the genetic code, the essential macromolecules that distinguish cells as well as individuals of all species are proteins and polysaccharides. The structural complexity and functional specificity of these molecules have only begun to be characterized. Animals dispose of nearly all foreign macromolecules that enter the body in a predictable manner. Some of these macromolecules are antigenic and may induce an immune response. All multicellular animals appear to recognize foreignness at the molecular level—whether introduced by a pathogenic microorganism or by intraspecies tissue graft. Invertebrates respond to such antigens with cell-mediated immunity associated with leukocyte-type cells, while vertebrates additionally respond with production of circulating antibodies.

The phylogenetic emergence of immunorecognition systems will be considered in detail in the last chapter. For introductory purposes, antigens may be defined as molecules that will induce an immune or antibody response when inoculated into an animal. Antigens will react specifically with the antibodies they have induced in vertebrates. Although antibodies are represented by diverse molecular classes in higher vertebrates, all are found in the globulin fractions of serum or plasma proteins (Figure 1–1). Antigen–antibody reactions are usually highly specific, and yet single antigens may evoke a multiplicity of antibodies of varying reactivities. A macromolecular "antigen," in the crude sense, is composed of various structural groups or sites, each capable of reacting with antibodies of corresponding stereospecificity. Small molecules, even ions associated with proteins or polysaccharides, may serve as antigenic determinants or haptens but will induce antibodies only when conjugated to a large molecule. In general, immunogenic molecules exceed 8,000 in molecular weight and are polyvalent with respect to determinant groups. The combining sites of individual antigens can be as large as six or seven sugar residues in polysaccharides and five or six amino acids in proteins. However, single sugars or amino acids within such sequences usually provide the predominant complementary configuration for specific antibodies (see Figures 3–2 and 4–1). Although nearly all antibodies have two identical combining sites per molecule or subunit, antibody molecules formed to a single antigen are not iden-

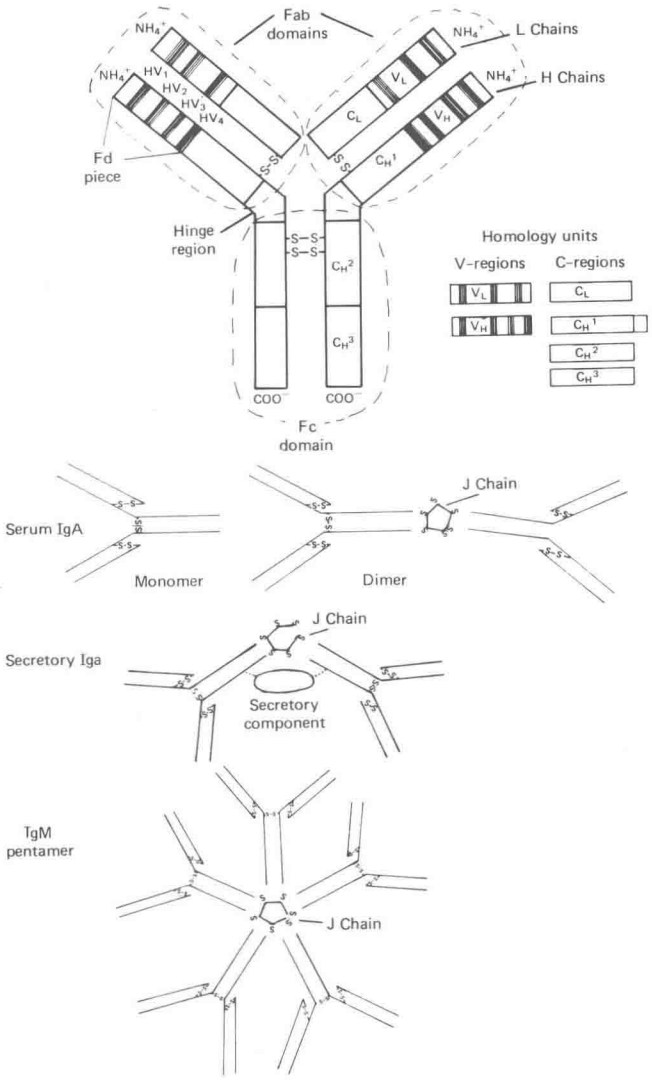

FIGURE 1–1. Schematic diagrams of mammalian antibody molecules of different immunoglobulin (Ig) classes. The essential molecule consists of four polypeptide chains, two identical heavy (H) chains of about 55,000 daltons and two identical light (L) chains of about 25,000 daltons, joined by interchain disulphide bonds (S-S). The antibody-combining site with complementary configuration for an antigenic determinant is located in V_H and V_L hypervariable (HV_1-HV_4) amino-terminal regions of each heavy–light chain pair. Immunoglobulin classes (e.g., IgM, IgA, IgG) are distinguished by heavy chain composition, polymerization involving joining or J chains, carbohydrate content, serum half-lives, and other properties. See Chapter 2 for genetics of antibody structure.

tical. They often have different molecular weights and electrophoretic mobilities as well as different biological effects following combination with antigen. Thus, antibodies in a particular immune serum may be described as populations of antibody molecules, heterogeneous with respect to various properties, but all able to combine with the inducing antigen. Nevertheless, the essential specificity of antigen–antibody reaction systems is their most noteworthy attribute.

Apart from its specificity, the other major attribute of an immune response is its selective memory. Upon a secondary encounter with an antigen, a normal animal usually exhibits an elevated and more rapid response. The stereospecific characteristics of antigens and antibodies are determined by the genetic constitutions of the cells and of the individuals from which they are derived. In many instances, these characteristics are identified with particular genes and stages of development, as we shall see in succeeding chapters. Our focus will range from intraspecific polymorphisms to the genetics of antibody synthesis and the complexities of transplantation reactions. Despite these many ramifications, a relatively few concepts of genetics and immunology do suffice as a basis for coping with this field.

FUNDAMENTALS OF IMMUNOGENETICS

Genes of diverse species have been characterized in terms of mutation, recombination, and, of course, phenotypic effects. Thus, a *gene* can be defined as: (a) a unit of mutation, (b) a unit of chromosomal structure not divisible by crossing over or breakage, or (c) a unit of morphologic or physiologic function. As the essential relation between genes and protein synthesis was revealed in the 1940s, George Beadle suggested that the individual gene provides the specificity for a single primary characteristic which is, moreover, generally associated with an enzyme. This equation was revised to "one gene → one polypeptide" (or subunit thereof) when independent genes were found to specify separate polypeptide chains comprising certain proteins, such as hemoglobins and immunoglobulins. In this book, the term *gene* will refer to distinctive hereditary units located on chromosomes at specific loci in a linear order. *Locus* designates the chromosomal position or site of a gene, as determined by frequency of recombination with separate but linked genes. *Allele* is one of two or more genes belonging to the same gene locus. Alleles then are regarded as functional alternatives which have not been separated by tests for recombination. A locus which has multiple alleles is said to be *polymorphic.* The term gene *complex* or *system* means a functional unit of multiple, closely linked genes. Why cells of different types, even from the same individual, express only some of the potentialities inherent in their *genome* (i.e., one complete set of genes or a haploid set of chromosomes) is the subject of the frontier realm of developmental regulation. Two classes of genes—*structural* and *regulatory*—may often be conveniently distinguished in immunogenetic studies. Structural genes are identified by their coding of amino acid sequence in a polypeptide