FUNDAMENTAL IMMUNOLOGY

Editor

William E. Paul, M.D.

Preface

Fundamental Immunology is an advanced textbook aimed at providing the reader with a sophisticated treatment of the main areas of contemporary basic immunology. The text is organized so that it will be accessible to students of immunology with very different backgrounds. The introductory chapters—Chapter 1, "The Immune System: An Introduction," and Chapter 2, "The History of Immunology"—should provide those with little or no previous knowledge of immunology with the main concepts of modern immunology and enable them to profitably read the subsequent chapters. The second section, "The Cells of the Immune System," may be regarded as an expanded introduction, providing newcomers and specialists alike with information about the key cellular constituents (the lymphocytes and macrophages) that are the main actors on the immunologic scene. The subsequent sections deal with the principal themes of contemporary immunologic science: "Antibodies and Receptors," "Immunogenetics," "Regulation of the Immune Response," and "Effector Mechanisms of Immunity." The final section highlights some of the critical techniques that have made possible much of the recent progress in basic immunology: hybridomas and monoclonal antibodies, modern approaches to identifying and separating specific cells of the immune system, and techniques to propagate lymphocytes in long-term culture and to clone these functional cells.

Each of the chapters has been prepared by an individual who is actively engaged in research on the topics considered in that chapter. The reader will note that some differences of opinion exist between authors and that on some topics opposing views may be held by equally accomplished scientists. I have taken the position that such differences are intrinsic to any developing field. Thus, rather than attempting a bland consensus, I urge the reader to reach his own judgment or, more properly, to view continued developments as they illuminate these controversial issues.

William E. Paul

Foreword

Immunology, among biological disciplines, is a relatively young science. Our knowledge of the structure of immunoglobulins and of the nature and genetic basis of their specificity has been acquired in the last three decades. Similarly, our understanding of the cells of the immune system and of the role of gene products of the major histocompatibility complex regulating their differentiation and specific interactions is a recent achievement of the greatest significance. Many of the authors of the chapters in this timely volume have contributed significantly to the exciting discoveries that have transformed immunology.

From its beginnings as an applied science in close relationship with bacteriology following the momentous discoveries of Jenner and Pasteur, immunology has become one of the most challenging and creative disciplines of modern biology. Immunology began as a novel therapeutic approach to the prevention of infectious diseases. Animated and acrimonious disputes between proponents of von Behring's humoral theory of immunity and supporters of Metchnikoff's cellular theory of immunity characterized the initial phenomenological phase of immunology. It is of considerable historical interest that both theories were proven essentially correct.

The study of immunological phenomena was followed by the molecular period when the emphasis centered on the study of antibodies and antigens, their specificity, combining sites, and precise molecular structure. This period began with the demonstration by Heidelberger that antibodies are proteins and therefore susceptible to molecular analysis and with the definition by Landsteiner and Avery and Heidelberger of antigenic determinants. This period provided, ultimately, precise and detailed information on antibody classes, antibody structure, amino acid sequence in relation to antibody specificity, and the relationship of structure to function in immunoglobulins.

While immunochemists were still engaged in the successful analysis of antibody molecules, a new phase of immunology was initiated, appropriately characterized by Jerne as the cellular period. Concern with the cells responsible for both humoral and cellular immunological phenomena was prompted by the discovery by Landsteiner and Chase that sensitized lymphoid cells were critical for the transfer of tuberculin sensitivity from an immune donor to a naive recipient. The cellular period, however, owed its major development to the following important contributions: (1) the elaboration of the clonal selection theory of specific immunity by Sir MacFarlane Burnet, later proven correct by Nossal and Green, Vassalli, Nussenzweig, and Benacerraf; (2) the identification of the circulating lymphocytes as the cells responsible for immune phenomena; and (3) the identification of plasma cells as the cells that synthesize and secrete antibodies, by Fagraeus and Coons. The cellular phase of immunological thought also provided insight on the mechanism of antibody synthesis, which we now recognize follows the same laws governing the synthesis of the less diverse proteins. This period culminated in the identification of the various cell types concerned with specific immunological phenomena, the thymus-derived lymphocyte or T cell, the B lymphocyte, precursor of the antibody secreting cell, and the plasma cell.

This work set the stage for the present phase of immunological research, in which we are concerned with the interaction among the various cells in the system and between these cells and the antigen-presenting cells. This multicellular phase of immunological research has permitted the elucidation of the regulatory mechanisms controlling immune responses and protecting against the development of autoimmunity. Among the critical discoveries that initiated the multicellular phase of immunological research are: (1) the identification of the regulatory functions of T cells in immune responses, (2) the discoveries of helper T cells by Mitchison and Rajewsky and suppressor T cells by Gershon, and (3) the identification by Benacerraf and McDevitt of the role played by gene products of the major histocompatibility complex in the specificity and the regulation of T-cell-dependent immune responses.

Another important regulatory mechanism, illustrating critical cell interactions in the immune system, involves the response of the host to idiotypic specificities present on antibodies and the immune cells that produce them. This form of regulation postulated by Jerne in his elegant Network Theory of Immunity has been proven correct by many laboratories.

Finally, the identification and cloning by Tonegawa and Leder of the genes that code for the variable and constant segments of immunoglobulins has permitted a detailed understanding of the origin of diversity in antibody-combining sites and has demonstrated the contributions of genetic and somatic mechanisms.

This volume describes and documents our knowledge of fundamental immunology and its techniques. It is a stimulating book not only for immunologists but also for biologists and physicians for whom immunological research and its achievements can be an exciting and intriguing story.

Baruj Benacerraf

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The initiation and preparation of *Fundamental Immunology* required the work of a large number of individuals, each of whose contributions was of great importance. I wish to specifically acknowledge the efforts of Anne Patterson, formerly of Raven Press, who worked closely with me at the outset of this project and who encouraged each of the authors and me to complete our chapters on schedule; of Ann Berlin, Assistant Managing Editor at Raven Press, who supervised the production of *Fundamental Immunology;* and, most particularly, of my secretary, Kay McMahon, whose good advice and sound judgment were critical at several stages in bringing this work to fruition.

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Chapter 1

The Immune System: An Introduction

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This chapter is designed to provide the reader with a general introduction to the science of immunology. It is anticipated that the interested individual will read this chapter as a prelude to the other chapters, which provide a detailed treatment of each area. To facilitate this process, references are provided in this chapter indicating appropriate chapters for further reading.

CELLS OF THE IMMUNE SYSTEM

Chapters 3–6

The immune system may be regarded as consisting of lymphocytes, macrophages, a series of macrophage-related cells including the dendritic cells of the spleen and the epithelial Langerhans cells, and specialized epithelial cells, such as those found in the thymus. These cells occur in organized tissues and organs, including the spleen, the lymph nodes, the Peyer's patches of the intestine, the tonsils, the thymus, and the bone marrow. In addition, a very substantial fraction of the lymphocytes and the macrophages comprise a recirculating pool of cells found in the blood and in the lymph.

Individual lymphocytes are specialized in that they are committed to respond to a limited group of structurally related antigens. This commitment, which exists prior to the first contact of the immune system with a given antigen, is expressed by the presence on the lymphocyte's membrane of receptors specific for determinants on that antigen. Any individual lymphocyte appears to possess a population of receptors, all of which have identical combining sites. (A possible exception to this will be considered in the discussion of "histocompatibility restricted" T lymphocytes.) Thus, one set, or clone, of lymphocytes will differ from another set, or clone, in the structure of the combining region of its receptors and, thus, in the range of antigenic substances that may stimulate it to respond. The ability of an organism to respond to

virtually any antigen is achieved by the existence of a very large number of different sets of lymphocytes, each bearing receptors specific for distinct antigens. Lymphocytes are, in consequence, an enormously heterogeneous collection of cells. Although exact figures are not available, it seems quite likely that the number of distinct combining sites of lymphocyte receptors present in an adult human exceeds 10^6.

Lymphocytes differ from one another not only in the specificity of their receptors but also in their functional properties. Two broad classes (or lineages) of lymphocytes are recognized: the B lymphocytes, which are precursors of antibody-secreting cells, and the T, or thymus-dependent, lymphocytes. T lymphocytes consist of a series of subtypes, some of which mediate important regulatory functions, such as the ability to "help" or "suppress" the development of immune responses, including antibody production. Other T lymphocytes are involved in effector functions, such as the production of soluble products that initiate a variety of inflammatory responses, or the direct destruction of agents bearing antigenic substances ("killer" function). Thus, we recognize groups of helper T cells, suppressor T cells, killer T cells, and T cells involved in delayed hypersensitivity and related immune phenomena.

In addition to these two major lymphocyte classes, lymphocytes that mediate certain "nonspecific" cytotoxic responses are known (Chapter 25). These include the so-called natural killer (NK) cells, which kill certain forms of tumor cells, using recognition systems that may be quite different from those used by T or B lymphocytes. Another type of nonspecific killing of target cells is antibody-dependent cellular cytotoxicity (ADCC), which is a function of a lymphocyte (or, in certain circumstances, a variety of other cell types) capable of killing antibody-coated target cells as a consequence of the recognition of a constant portion of the antibody bound to that target cell. Whether ADCC is a function of the cells that mediate NK activity is still uncertain.

B LYMPHOCYTES

Chapter 3

B lymphocytes, which as already noted are precursors of antibody-secreting cells, are originally de-

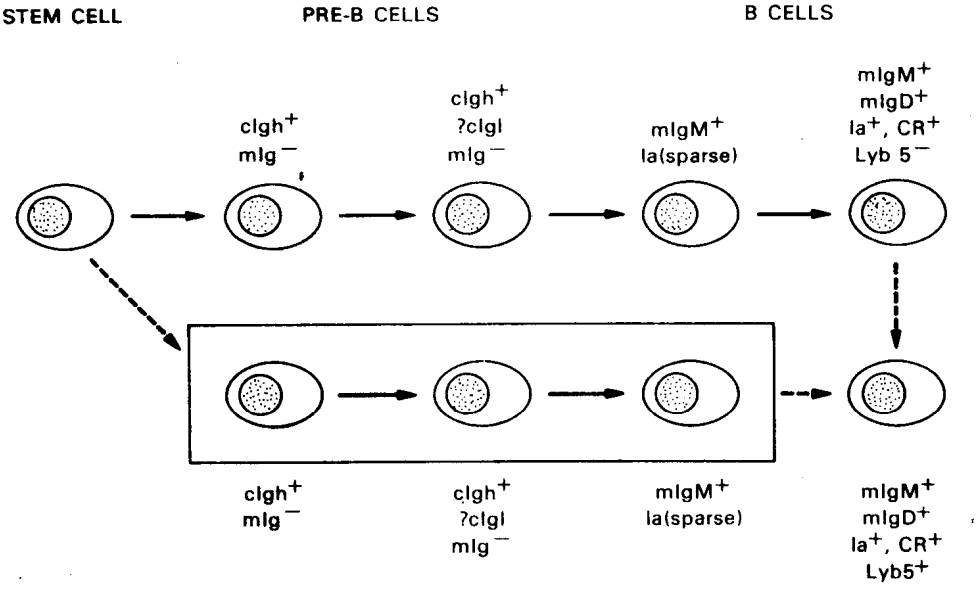

FIG. 1. B lymphocyte ontogeny and heterogeneity. B lymphocytes develop from a stem cell that has not yet been purified and whose characteristics are not well understood. The first identifiable members of the B lymphocyte pathway of development are the pre-B cells. These cells express cytoplasmic immunoglobulin heavy (Igh) chains of the μ class but lack membrane Ig (mIg). Early pre-B cells are large cycling cells. Later pre-B cells are smaller; some may express c Ig light (cIgl) chains as well as cIgh chains. Pre-B cells develop into B cells; the latter are distinguishable by their expression of mIg. Immature B cells generally express mIgM but not mIgD and often have relatively small amounts of class II major histocompatibility complex (MHC) molecules. Class II molecules are also designated as Ia antigens. More mature B cells express mIgM and mIgD and have a higher density of Ia. They also express receptors for complement components (CR). Studies of mature mouse B cells indicate that some express a differentiation antigen, Lyb 5, which distinguishes these cells from those that lack Lyb 5. Lyb 5^+ and Lyb 5^- B cells have distinctive activation requirements. It has not yet been established whether Lyb 5^+ B cells are derived from Lyb 5^- B cells or whether there are two distinct pathways of B cell development resulting in Lyb 5^- and Lyb 5^+ B cells, respectively. [From Stein, J., *Textbook of Medicine*, Little, Brown, Co., with permission.]

rived from hematopoietic stem cells. A self-renewing B cell progenitor appears to exist but its properties are poorly understood. This specialized stem cell is found, in adult mice, in the bone marrow and, to a lesser extent, in the spleen. The first member of the B cell series that can be directly visualized is the pre-B cell (Fig. 1). The pre-B cell lacks receptors for antigen on its membrane but contains within its cytoplasm at least one of the chains of antibody molecules (the heavy immunoglobulin [Ig] chain). Pre-B cells are first found in the liver of the developing mouse fetus at about 12 to 14 days of gestational age. Pre-B cells continue to develop during postnatal life. Both in humans and mice, malignant forms of pre-B cells exist, namely certain acute lymphocytic leukemias and Abelson virus-induced tumors.

Mature B cells differ from pre-B cells in that they express receptors for antigens on their membranes and are activated as a result of the binding of antigen to their receptors. This activation generally requires that the B cells interact, at the same time, with specific helper T cells or bind certain soluble growth and differentiation factors. Alternatively, B cells, particularly immature members of the B cell lineage, may become inactivated if they bind antigen without receiving signals from soluble growth factors or from helper T cells. Such inactivation can lead to B cell tolerance (Chapter 20).

The activation of B cells has two distinct phases: proliferation and differentiation (Fig. 2) (Chapter 12). The role of proliferation is to expand the number of cells capable of reacting against antigenic substances that have been introduced into the individual. Such proliferation is of obvious importance since the frequency of B cells specific for any individual antigen in an unimmunized animal is very low. Proliferation has two consequences: it increases the number of cells that may immediately differentiate into antibody-secreting cells and it provides an expanded number of B cells, in many respects similar to the original precursor, so that a second immunization with the same antigen leads to a prompter response of greater magnitude than the primary response. That is, expansion of the number of precursors leads to a state of immunological memory. The proliferative phase of B cell responses is driven, at least in part, by a T cell product designated B cell growth factor (BCGF) (Chapter 21).

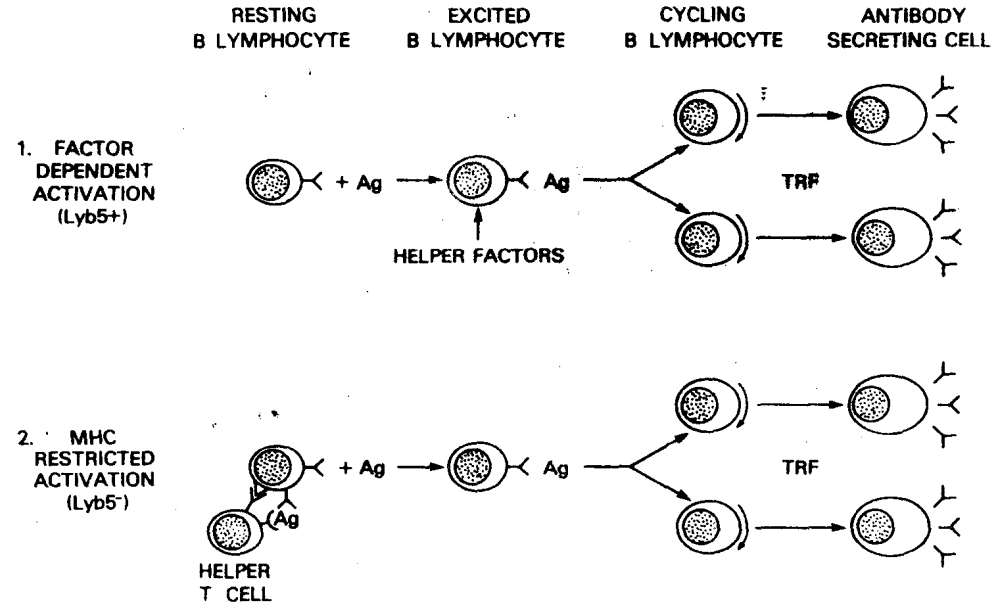

FIG. 2. B cell activation. Resting B cells may be activated to proliferate and then to differentiate by two distinct mechanisms. One mechanism, designated factor-dependent activation, appears to be limited to Lyb 5^+ B cells. In this pathway, resting B cells are activated to an excited, or G_1, state by the action of agents that appropriately cross-link their receptors. Excited cells are acted upon by soluble factors, including B cell growth factor (BCGF) and interleukin 1 (IL-1), and enter the S phase. Differentiation factors, often designated T cell replacing factors (TRFs), act upon these cells to cause them to synthesize and secrete Ig. The second major pathway involves the interaction of "histocompatibility-restricted" helper T cells with resting B cells. These T cells recognize antigen and class II molecules on the B cell surface and stimulate the cell to enter an excited state. This activation pathway is often designated as "cognate" activation and acts upon Lyb 5^- B cells. Whether Lyb 5^+ cells are subject to cognate activation is still uncertain. The subsequent progress of the excited B cell may depend upon further interaction with helper T cells or soluble factors. Differentiation factors are probably necessary for the differentiation of these cells into cells secreting Ig. [From *Annual Review of Immunol.*, 1, 1983, with permission.]

A fraction of the cells that proliferate on stimulation with antigen differentiate into antibody-secreting cells. Several morphological types of antibody-secreting cells are recognized, of which the best known are the plasma cells.

B Cell Subsets

Two major B cell populations have been demonstrated in the mouse (Fig. 1). They differ from one another in the membrane antigens they express, the immunogens against which they respond, and the nature of the regulatory processes that control their responses. One class of B cells bears the Lyb 5 antigen; these cells are referred to as Lyb 5^+ B cells. Lyb 5^+ B cells appear to be mainly responsible for antibody responses to soluble polysaccharides, such as the capsular polysaccharides of pyogenic bacteria, and to hapten conjugates of such polysaccharides (Table 1). A hapten is a low molecular weight (MW) substance that is not by itself capable of initiating an immune response; however, antibodies can be made against it if it has been conjugated to an immunogenic molecule. T cell help for Lyb 5^+ B cells can be mediated by soluble nonspecific lymphokines, such as BCGF and a set of differentiation factors (Chapter 21). Much of our current understanding of the functions of Lyb 5^+ B cells derives from studies of mice with an X-linked immunodeficiency ("xid" mice) that lack this B cell subpopulation.

Lyb 5^- B cells respond to soluble protein antigens, many cellular antigens, and certain products with intrinsic B cell mitogenic capacity, such as bacterial lipopolysaccharide (LPS). They are unresponsive to soluble polysaccharides. The mechanisms through which Lyb 5^- B cells receive help from T cells appear to be quite different from those of Lyb 5^+ B cells. Lyb 5^- B cells appear to require a direct physical interaction with a T cell specific for the same antigen for which the B cell is specific. Such T cell-B cell interactions are often referred to as cognate help (Chapter 18). An important property of cognate help is that it displays histocompatibility restriction of cellular interactions (Chapter 15); this phenomenon will be discussed in greater detail below.

Table 1. *Mechanisms of T cell help*

Type of help	Histocompatibility restricted	B Cell involved	Types of antigens
Cognate	Yes	Lyb 5^- (?Lyb 5^+)	Thymus-dependent (TD) (e.g., soluble proteins, cellular antigens)
Factor dependent	No*	Lyb 5^+	Type 1 (e.g., polyclonal B cell activators [LPS])
			Type 2 (e.g., soluble polysaccharides)
			Some TD antigens

* T cell–B cell interaction is not histocompatibility-restricted. However, in "factor dependent" responses, T cell activation by APC is histocompatibility-restricted.

IMMUNOGLOBULINS

Structure

Chapter 7

The products of antibody secreting cells are Ig molecules. Igs are a group of proteins that have several structural features in common. They are constructed of one, or several, units, each of which consists of two heavy (H) polypeptide chains and two light (L) polypeptide chains (Fig. 3). Each unit possesses two combining sites for antigen. The H and L chains are made up of a series of domains, each of about 110 amino acids. The L chains, of which there are two major types (κ and λ), consist of two domains. The carboxyterminal domain is essentially identical among L chains of a given type and is referred to as the constant (C) region. The aminoterminal domain of L chains varies from antibody to antibody. This domain represents the L chain's contribution to the binding site of the antibody molecule. Because of its variability, it is referred to as the variable (V) domain. The variability of this domain is actually concentrated in three segments of the region, designated the hypervariable or complementarity determining regions (CDR). The CDRs appear to contain the amino acids that line the antibody's combining site. The three CDRs are interspersed in four regions of much lower degrees of variability, designated framework regions (FR). Immunoglobulin L chain (and H chain) V regions can be classified into groups based on similarities in the structure of their FRs.

The H chains of immunoglobulin molecules are of several types, including μ, δ, γ (of which there are several subclasses), α, and ϵ. An assembled immunoglobulin molecule, which consists of one or more units of two identical H and L chains, derives its name from the H chain that it possesses. Thus, there are IgM, IgD, IgG, IgA, and IgE antibodies. The H chains each consist of a single amino terminal V domain and several (generally three or four) C domains. In many H chains, a hinge region separates the first

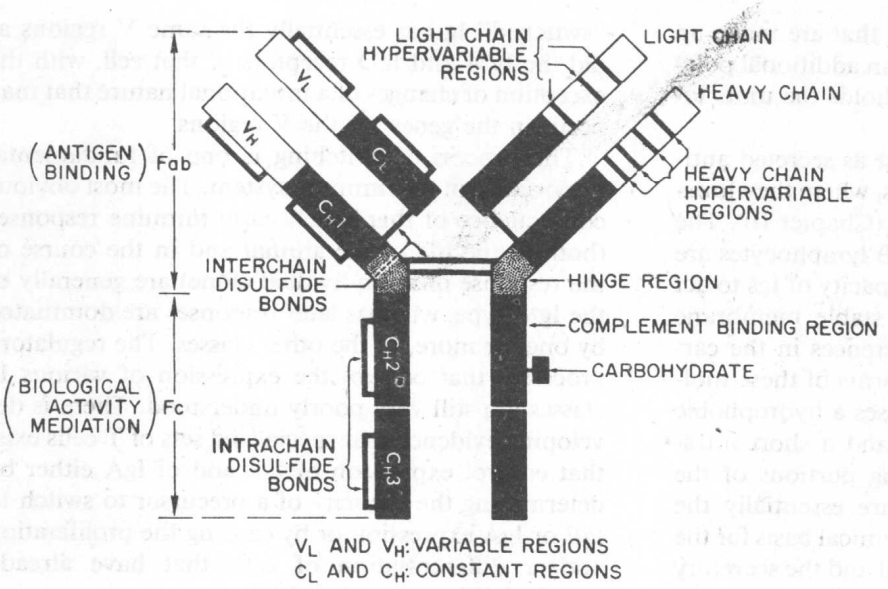

FIG. 3. Structure of an Ig molecule. A schematic representation of an IgG molecule indicating the chain and domain structure of the molecule and the existence of hypervariable regions with variable regions of both H and L chains. (This figure also appears in Chapter 8, where it is explained in greater detail.) [From Wasserman, R. L., and Capra, J. D.: Immunoglobulins. In: *The Glycoconjugates*, edited by M. I. Horowitz and W. Pigman pp. 323–348. Academic Press, New York, 1977, with permission.]

and second C domain and conveys flexibility to the molecule, allowing the two combining sites of a single unit to move in relationship to one another. The H chain V region, like that of the L chain, consists of three CDR, which line the combining site of the antibody, and four FR. Thus, the antigen-combining site of an individual antibody molecule is created by contributions from specialized regions of both the H and L chain V regions. The H and L chain V regions, because of their structural uniqueness, can themselves act as antigenic determinants (Fig. 4). Such immunoglobulin V region antigenic determinants are designated idiotopes and the collection of idiotopes on any antibody molecule is its idiotype (Chapter 9). Idiotopes can be constructed of conformations on H or L chain V regions only or, as seems to be true in a majority of cases, of contributions from both chains. Some idiotopes are closely related to the antigen-combining site and the occupation of the site of antigen prevents anti-idiotope antibody from binding to the immunoglobulin. Such idiotopes are designated "site-related" idiotopes. Other idiotopes appear to be less closely related to the combining sites. T cells and antibodies specific for idiotopes may play an important role in the regulation of the immune system (Chapter 22). An influential theory (the network theory of the immune response) has proposed that they may be the critical regulatory elements of the system.

The C region of each H chain class differs from those of the other classes and is responsible for the distinct biologic functions of each class of antibody: (a) IgM antibodies can activate the complement system (Chapter 24); (b) IgA antibodies are secreted into a variety of bodily fluids and provide secretory immunity; (c) IgE antibodies fix to specific receptors on mast cells and basophils and, when they are cross-linked by antigens, cause these cells to release their biologically active products which result in allergic-type phenomena (Chapter 27); (d) IgD antibodies act almost exclusively as membrane receptors for antigen (Chapter 10); and (e) the IgG antibodies express a variety of functions, including the capacity to be transferred across the placenta.

IgD, IgG, and IgE antibodies generally consist of a single unit of two H and two L chains. IgM antibodies are constructed of five such units, although they consist of a single unit when they act as membrane receptors, and IgA antibodies may consist of

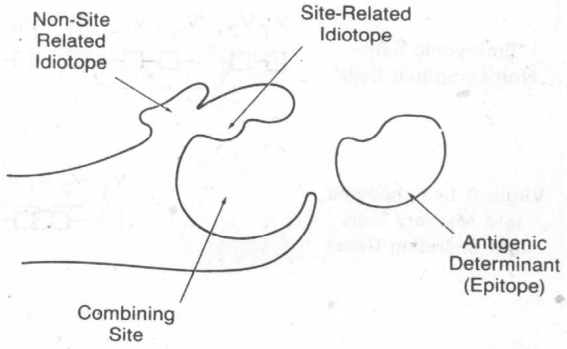

FIG. 4. Idiotopes. Antibody molecules possess combining sites through which they bind antigenic determinants (epitopes). Since distinct antibodies differ from one another in their variable regions, each possesses structures that may themselves be antigenic and elicit the production of antibodies. The antigenic determinants of the variable regions of antibodies are idiotopes. Idiotopes may actually be within the combining site of the antibody (site-related idiotopes) or may be outside the combining site (non-site-related idiotopes).

one or more units. The antibodies that are made up of more than a single unit contain an additional polypeptide chain, the J chain, which holds the units together.

Each of the distinct Igs can exist as secreted antibodies and as membrane molecules, where they function as receptors on B lymphocytes (Chapter 10). The receptors of the great majority of B lymphocytes are of the IgM and IgD classes. The capacity of Igs to act as both secreted proteins and as stable membrane receptors is accounted for by differences in the carboxyterminal regions of the two forms of these molecules; the membrane form possesses a hydrophobic region, spanning the membrane, and a short intracytoplasmic region. The remaining portions of the membrane and secretory forms are essentially the same. This provides an obvious chemical basis for the similarity of the receptors of a B cell and the secretory products of the antibody-producing cells that derive from it.

Switching

Chapters 7, 8, and 19

An individual B cell, although it always expresses the same L chain and the same H chain V region, can "switch" the Ig class that it produces. Thus, a cell that expresses receptors of the IgM and IgD classes may differentiate into an antibody-secreting cell that produces IgA (or IgG or IgE) antibodies. This "switched" Ig has essentially the same V regions as did the IgM and IgD receptors of that cell, with the exception of changes of a mutational nature that may occur in the genes for the V regions.

The process of switching is one of fundamental importance in the immune system. The most obvious consequence of this is that early immune responses (both in the life of the animal and in the course of the response of an individual clone) are generally of the IgM type, whereas later responses are dominated by one, or more, of the other classes. The regulatory processes that control the expression of various Ig classes are still very poorly understood. There is developing evidence that specialized sets of T cells exist that control expression of IgE and of IgA either by determining the capacity of a precursor to switch to IgE or IgA expression or by causing the proliferation and/or differentiation of cells that have already switched (Chapters 18 and 19).

Genetics

Chapters 8 and 9

It is now recognized that the H and L polypeptide chains of Igs are each encoded by multiple genetic elements that are physically separated from one another in germline DNA but that are brought together to create a single active gene in B lymphocytes and antibody-secreting cells (Fig. 5). The variable domains of the κ L chains are each constructed from

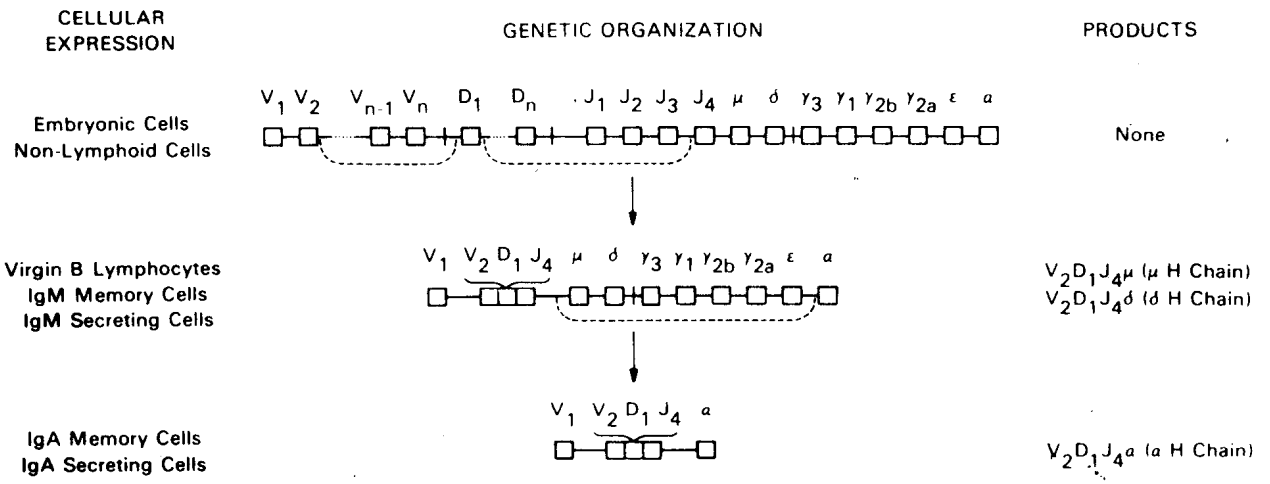

FIG. 5. Organization and translocation of Igh genes. Immunoglobulin H chains are encoded by 4 distinct genetic elements—Igh-V (V), Igh-D (D), Igh-J (J), and Igh-C genes. The V, D, and J genes together specify the variable region of the H chain. The Igh-C gene specifies the C region. The same V region can be found in association with each of the C regions (e.g., μ, δ, γ_3, γ_1, γ_{2b}, γ_{2a}, ϵ, and α). In the germline genome, the V, D, and J genes are far apart and there are multiple forms of each of these genes. In the course of lymphocyte development, a VDJ gene complex is found by translocation of individual V and D genes so that they lie next to one of the J genes, with the excision of intervening genes. This VDJ complex is initially expressed with μ and δ C genes but may be subsequently translocated so that it lies near one of the other C genes (e.g., α) and in that case leads to the expression of a VDJα chain.