

Px 1813

THE IMMUNE RESPONSE AND CLASSIFICATION OF HYPERSENSITIVITY REACTIONS

James D. Lakin and
Richard A. Strecker

Correct diagnosis and management of the allergic diseases requires thorough knowledge of basic immunologic principles. During the past two decades few areas of medicine have experienced as dramatic a change in the rationale for therapy, from pervasive empiricism to a substantive degree of rational theory, as have allergy and clinical immunology. Our understanding of the pathophysiology of hypersensitivity, autoimmune, and immunodeficiency disorders has paralleled the elucidation of the underlying cellular and molecular structures and functions of the humoral and cellular immune systems and their subsidiary effector systems. This chapter presents a brief outline of current understanding of the immune system, the workings of the immune response, and their role in the various categories of hypersensitivity reactions. Chapters 2 and 3 consider in greater detail the immediate, or atopic (type I), IgE-mediated hypersensitivity reactions at the cellular and molecular level. The scope of current information is such that only the most basic material is presented in this chapter.^{81,155,160,211,216}

THE IMMUNE SYSTEM: RESPONSES AND REGULATION

The selective acquisition of increased resistance to specific foreign substances such as microorganisms and toxins has conferred a substantive advantage in the evolution of complex multicellular organisms. The absence of this advantage is demonstrated clinically by immunodeficient patients. In these patients, variable degrees of impairment of the immune system manifest themselves in a broad spectrum of clinical illnesses, and in the extreme condition of severe combined immunodeficiency disease that is rapidly fatal, if untreated.^{33,100} The understanding of these and the classic allergic diseases is dependent on knowledge of normal development of the immune system, as well as its operation. In this text, as in most current literature, the term immune system is used in its more restrictive sense, to refer to those defense mechanisms that confer specific immunity. Nonspecific bodily defense mechanisms, such as the mucociliary epithelium of the respiratory tract, the cough reflex, various proteolytic enzymes of external secretions, and phagocytic cell functions are not included.

The first characteristic of specific immunity implies the acquisition of a biologic response in which circulating lymphocytes or antibodies interact with a unique molecular configuration, or a very restricted range of molecular configurations. The molecules eliciting the immune response are termed *antigens*, and usually are high-molecular-weight proteins, carbohydrates, or nucleic acids. Antigens that elicit an allergic or hypersensitivity response are termed *allergens*. A second characteristic of specific immunity is that of memory. When the immune system encounters an antigen to which it has previously mounted a primary response, the secondary, or *anamnestic*, response usually is found to be qualitatively and quantitatively increased.

The immune system arises from developing lymphoid tissue during embryogenesis.³² Specific immune response cells differentiate from a pluripotent stem cell derived from bone marrow. Three cell types arise from this stem cell. They are induced to differentiate from the stem cell by anatomic hemopoietic-inducing microenvironments (HIMs). When the stem cell arrives at the proper HIM it differentiates to the resultant immunocompetent cell. (See Fig. 1-1.)

The first of these is responsible for the specific cellular immune response as well as for moderating cellular and humoral immune responses. The HIM for this cell is the thymus, where the progenitor cell differentiates to a T (thymus-dependent) cell. The progenitor cell may be acted upon by humoral factors such as *thymopoietin* or *thymosin*.^{86,212,257} The thymus is thus the central lymphoid organ for the T cell. In mice after differentiation the T cell acquires a characteristic surface antigenic marker termed *Thy 1*. Therefore, cells can be differentiated accordingly by being *Thy 1⁺* or *Thy 1⁻* (non T cells). T cells also may express *Ly* (*Lyt*) antigens, referring to lymphocyte antigen. There are three detectable determinants, specifically *Ly 1*, *Ly 2*, and *Ly 3*. Usually *Ly 2* and *Ly 3* are found together on the cell surface; thus the designation may be *Ly 1⁺ 23⁺*, *Ly 1⁻ 23⁺*, or *Ly 1⁺ 23⁻*. There are additional surface antigens designated *T1* (1 through 6) and *Qa* antigens (1 through 5). By using antisera to these antigens, the various subpopulations of T cells may be differentiated. For example, T-helper cells (*T_H*) can be designated

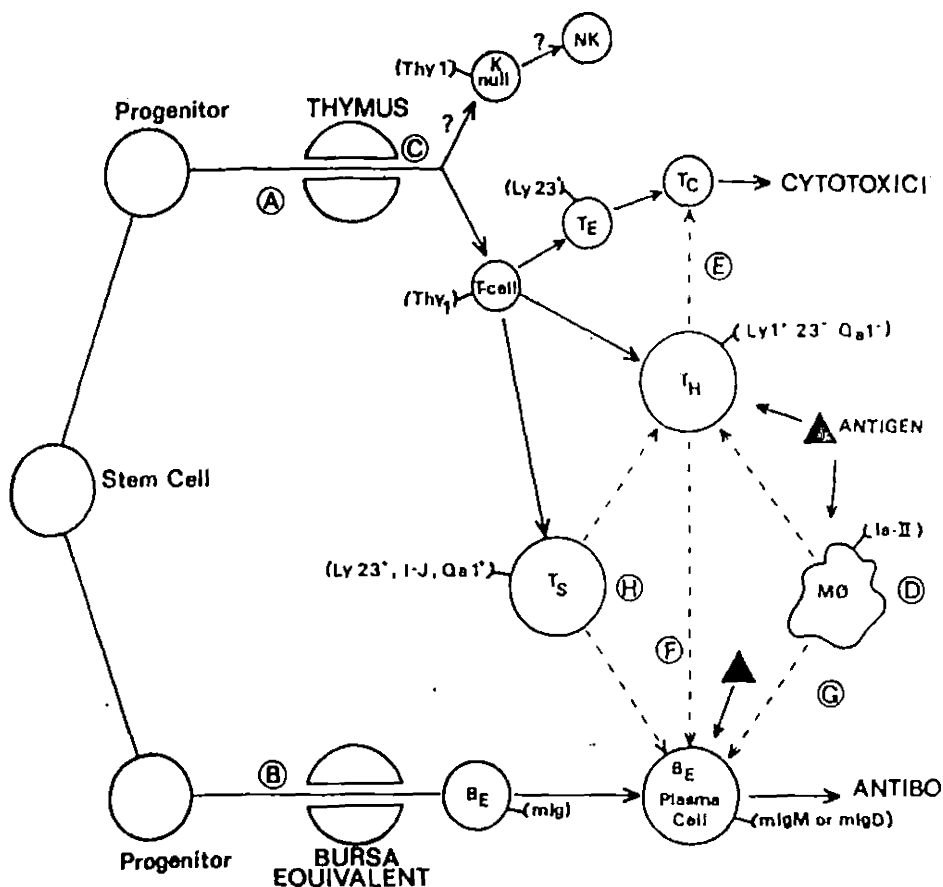


Fig. 1-1. The development of effector cells in humoral and cellular immunity. (A) Stem cells are acted upon by the thymus microenvironment to differentiate into T cells. (B) Stem cells are acted upon by the bursa-equivalent microenvironment to differentiate into B cells (B_E, effector B cells). (C) T_H (T helper), T_S (T suppressor), T_{NK} (T killer), and T_E (T effector) cells are differentiated. (D) Macrophage (Mφ, APC) of the same major histocompatibility complex (MHC) haplotype as T_H processes antigen and presents it to T_H. (E) T_H communicates signal to T_E, which activates to T_C (cytotoxic T cell). (F) T_H communicates with B plasma cell. (G) APC of the same MHC haplotype as T_H processes soluble antigen and presents it to T_H, which communicates to B_E an antigen-specific factor. (H) Suppressor T cells (T_S) effect decrease in immune response by either soluble factor or cell contact. (Modified with permission from Waldman TA et al: Disorders of suppressor immunoregulatory cells in the pathogenesis of immunodeficiency and autoimmunity. *Ann Intern Med* 88:226, 1978, of the American College of Physicians)

Thy 1⁺, Ly 1⁺ 23⁺, Qa 1⁺ and T-suppressor cells (T_S) can be designated Th 1⁺, Ly 1⁺ 23⁺, and Qa 1⁺. In humans, because there are no experimental inbred strains, it has been more difficult to determine surface antigen restricted to T cells. However, monoclonal antibodies have been produced to antigens designated T1-T10. T cells remaining in the thymus (thymocytes) are of different phenotypes.

differentiate to subsets. T_H is $T4^+$ and cytotoxic T cell (T_c) is $T5^+$. The most commonly used marker for the T cell is E-rosette formation. T cells express receptor sites for nonspecific bindings of sheep red blood cells to form the characteristic rosette pattern.^{69,144}

Second, an additional cell line arising from the progenitor cell is responsible for humoral specific immune response. The humoral response was first defined in chickens. In the avian immune system, the bursa of Fabricius, a lymphoid organ contiguous to the cloaca in the chick embryo, provides the necessary microenvironment for the differentiation of progenitor cells into immunocompetent B (bursa-dependent) cells. Removing the bursa from the early chick embryo abolished subsequent antibody formation in the adult bird. No obvious anatomic equivalent of the avian bursa has been found in mammals.¹⁷⁸ However, B cell precursors are demonstrable in the mammalian fetal liver, in the placenta, and in adult bone marrow. These are considered the central lymphoid organs for the B cell.⁷⁸ The B cells express membrane-bound immunoglobulin (mIg) on their surfaces. The first of these to appear are membrane-bound IgM and IgD (mIgM and mIgD). After mIgM and mIgD, either mIgG, mIgE, or mIgA appears on the surface of the B cell.¹⁴⁴

A third cell evolving from the pluripotent stem cell is the monocyte or, in its mature form, macrophage. The ability of macrophages to ingest foreign particles (phagocytosis) has been known since the late 19th century. It now has been determined that phagocytosis of an antigen is highly important to the immune response. Studies have found that portions of the antigen are ingested and portions are maintained on the surface. The surface portion of the antigen is presented to T cell and/or B cell. This communication and presentation of antigen is necessary for maximum response. It is not certain if the antigen has been processed before presentation to the lymphocyte or how the surface antigen differs from the phagocytized portion. It may also be that there are other antigen-presenting cells (APC) than the macrophage.^{69,144}

HUMORAL IMMUNITY

The process by which antigen stimulates the production of specific antibody is regulated at several stages (i.e., during the stage of immune recognition and during the course of both primary and anamnestic antibody synthesis¹⁹¹). The humoral response, once mounted, may vary widely in its consequences, depending on the type and amount of antibody produced. Antibody activity in humans resides in five major classes of globulins, migrating electrophoretically in the γ and β regions. These immunoglobulin (Ig) classes are termed IgM, IgA, IgD, IgG, and IgE. (See Table 1-1.) Each immunoglobulin class appears to be synthesized by a separate B cell subclass, although within that subclass many clones of different antigenic specificities may arise.¹⁵⁴ In this section, the process of triggering the immune response, the subsequent cellular events, and the properties of the antibodies produced are examined.

INTERACTIONS OF PRIMARY ANTIBODY FORMATION

The division of specific immune response into cell-mediated and humoral subsystems has been found to be less than absolute. By the late 1960s it was

BLE 1-1. Physicochemical Properties of Human Immunoglobulins

Immunoglobulin	Subclasses	Heavy Chain	Molecular Weight (daltons)	Half Life (days)	Sedimentation Coefficient (svedburs)	Molecular Formula	Complement Fixation		Placental Transmission	Skin Sensitization		Adult Serum Concentration (mg/dl)
							Classic	Alternative		Heterologous Species	Hemologous Species	
IgG 1, 2, 3	IgG 1, 2, 3	γ	150,000	23.0	7S	$L_2\gamma_2$	IgG 1, 2, 3	+	+	+	++	800-1800
serum secretions	IgA 1, 2	α	152,000	5.8	7S (9, 11, 13S)	$L_2\alpha_2$	-	+	-	-	-	90-450
			385,000		11S	$[L_2\alpha_2]_2SC, [L_2\alpha_2]_2SC, [L_2\alpha_2]_2$	-	+	-	-	-	60-250 (male) 70-280 (female)
IgM 1, 2		μ	900,000	5.1	119S	$[L_2\mu_2]_5, [L_2\mu_2]_6$	+	+	-	-	-	10-400S
?		δ	175,000	2.8	7S	$L_2\delta_2$	-	-	-	-	-	0-14
?		ϵ	168,000	2.3	8S	$L_2\epsilon_2$	-	+	-	-	+	10-400S

L: Light chain, either κ or λ SC: Secretory component; μ : chain

Several reports indicate skin sensitizing activity at 4 hours but not at 48 hours.

International units/ml

recognized that, for maximal primary antibody responses to occur to most antigens, the presence of T cells was required.¹¹⁷ This has been shown both *in vivo*, using lethally irradiated, immunologically reconstituted mice, and in a number of *in vitro* systems. Therefore, for an uncommitted B lymphocyte to differentiate into a biosynthetically active end-stage plasma cell, the cooperation of a member of a T cell subpopulation is required. This subpopulation has been termed helper T cells (T_H).^{73,93} A few antigens of simple, repetitive polymeric structure can elicit antibody production when there are no T_H cells, and these antigens are designated T-independent antigens, in contrast to the majority, which are T-dependent antigens.¹⁵⁹

Studies have been performed using hapten-carrier conjugates. These conjugates are artificial antigens formed by the covalent bonding of a low-molecular-weight compound unable to elicit an immune response by itself, but immunogenic when combined with a high-molecular-weight carrier molecule.¹⁶⁶ The low-molecular-weight hapten, when free in solution, will specifically bind with antibody at the combining site. Using carrier molecules immunogenic in their own right, it has been found that if the responding animal produces B cells able to recognize the hapten determinant, but does not possess helper T cells to recognize the carrier determinants, a limited antibody response involving only the IgM class of immunoglobulins will be made to the hapten. If the carrier determinant is recognized by specific helper T cells, a full IgM, IgG antihapten antibody response occurs.¹¹⁵ Thus, antigenic specificity is present, at the level both of B cell hapten recognition and of T_H cell carrier recognition. The intimate cooperation of T cells and B cells (Fig. 1-2) has been shown to be important in the effective development of antibody responses of the IgG, IgA, and IgE classes.⁹³

In addition to the cell-cell interactions among B and T lymphocytes and their subclasses, the macrophage plays a very important role in the initiation of the immune response.^{39,243,244} Macrophage function appears to be bimodal. Initially, antigen is taken up by macrophages, processed, and combined with a product of genes that are linked to the major histocompatibility complex (MHC) of the species.¹⁶ The MHC and the possible role it exerts in genetic regulation of the immune response will be discussed shortly. For the moment, note that this gene product, a mucoprotein, is termed Ia, or immune response associated, presumably coded for by a corresponding Ir, or immune response gene. The combination of processed antigen and Ia mucoprotein is presented to T cells for immune recognition and stimulation to helper or effector activity.¹⁶ Thus, for T cell activation, recognition, not only of foreign antigen, but also including Ia compatibility, must occur. This requirement has been termed the self plus X hypothesis. The nature of the receptor on the T cell surface appears to be the portion of the immunoglobulin molecule called the idiotype. This consists of the variable (VH) portion of the molecule combined with a constant (C) portion called tau (τ). The Ia molecule in conjunction with the τ molecule completes the T cell receptor. The T cell-B cell communicating factor is formed by releasing this receptor, combined with antigen.²¹⁵

In contrast, B lymphocytes have readily identifiable IgD and IgM monomer present on their cell membranes.^{68,69,74} These receptors appear to recognize the antigenic determinant to which the B cell can commit its antibody-synthesizing activity. After the B lymphocyte has matured into a plasma cell, these receptors are shed, and they are replaced with a surface-bound

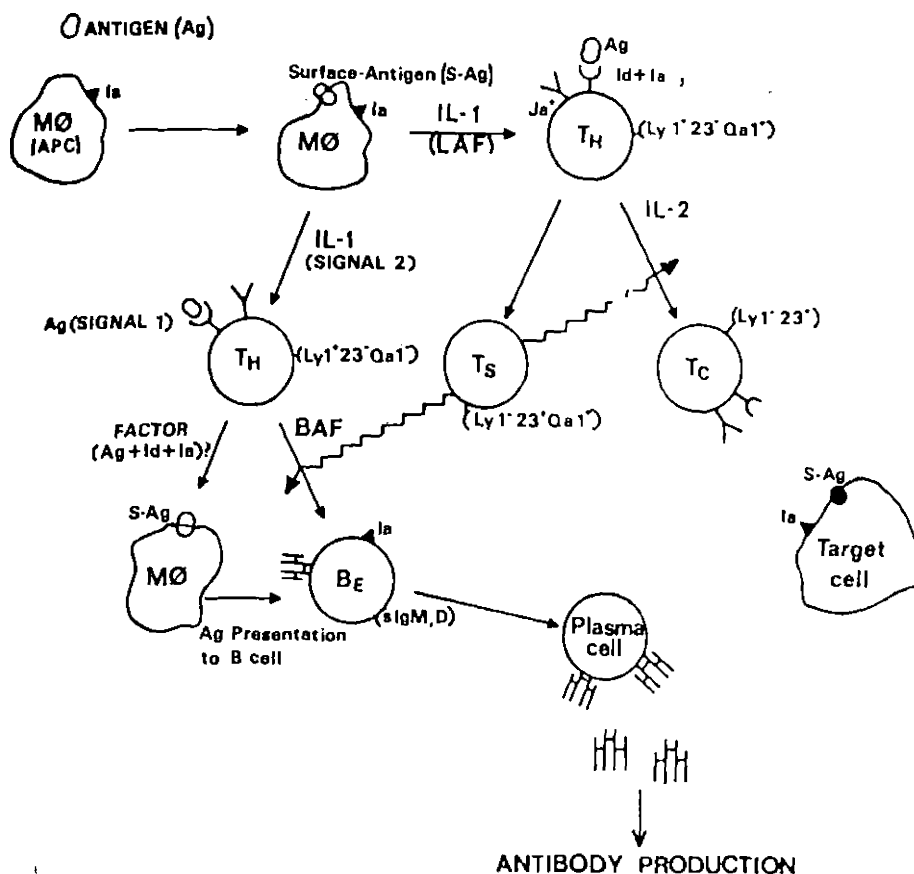


Fig. 1-2. Antigen processing cell (APC, macrophage) is activated by encountering antigen. The activated macrophage elicits IL-1, which induces T_H cells stimulate by antigen to release IL-2, which induces T_C cell proliferation. A separate population of T_H cells requires antigen (Ag) as a first signal and IL-1 as a second signal to produce B cell activating factor (BAF) and a second factor that may be antigen, Ig idiotype (Id), and Ia molecule to communicate with APC, which is required to present antigen to B_E cells. The T suppressor (T_S) cell may block the communicative factors.

immunoglobulin of the same class and specificity as that being secreted by the plasma cell.^{13,83}

REGULATION OF ONGOING ANTIBODY SYNTHESIS

Following the interaction of macrophage, helper T cells, and B cells, a B lymphocyte undergoes blastogenesis and is transformed into a mature plasma cell. Rich in endoplasmic reticulum, the mature plasma cell is committed to biosynthesis of immunoglobulin of one antigenic specificity corresponding to that which initiated the cell's development. There is evidence that a B cell switches from production of IgM antibody to IgG antibody during the maturation of the response to specific antigen. The

selection and maturation of the antibody response is displayed in Figure 1-3. It has been found that the mature plasma cell is not self-regulated. Rather, throughout its lifespan it is subject to a number of separate regulatory influences. IgM production usually occurs early in a primary antibody response, produced primarily by T-independent B cells. A number of *in vivo* and *in vitro* studies in several species indicate that IgM B cells are suppressed by circulating IgG antibody directed against the same antigenic specificity.²¹⁷ This process apparently is mediated by direct interaction of IgG receptors on the IgM B cell. As the immune response proceeds, especially with repeated antigenic exposure, IgG-type antibody predominates in the vascular compartment. IgG B cells are subject to a complex network of immunoregulatory signals, generated by a subpopulation of T cells distinct from helper T cells. These thymus-dependent lymphocytes are known collectively as suppressor T cells (T_s).¹⁴⁴ Their physicochemical properties and localization within the lymphoid system differ by a number of parameters from T_H cells. Suppressor T cells appear to proliferate along with their B cell counterparts at the onset of the immune response.²⁶² At least two types of B cell suppression, probably mediated by two subpopulations of T_s cells, have been documented. An antigen-specific, immunoglobulin class-specific suppressor effect on IgG B cells appears to occur. Additionally, a separate suppressor signal is generated that is specific for the B cells of the IgG class, but is not antigen specific, further serving to modulate B cell antibody production.^{221,262} These suppressor signals are transmitted by soluble factors. Thus, direct T cell-B cell interaction is not as critical as in the initiation of the antibody response. Furthermore, there is growing evidence that yet another T cell subpopulation may exist, generating an opposing amplifier signal to which the mature B cell is subject.^{150,151} Amplifier and suppressor T cells may generate complementary effects, to ensure the degree of B cell activity appropriate to antigenic stimulation.^{17,120} It has been demonstrated recently that the macrophage also modulates B cell biosynthesis. This is mediated by elaboration of a monokine that enhances antibody formation.⁵⁵

Indirect evidence of the clinical importance of IgA T_s cells has been provided in the study of isolated IgA-deficient patients who have normal levels of the other immunoglobulins but little or no detectable IgA. In certain of these patients, an enriched population of circulating T cells will suppress IgA-producing B cells of normal persons when cultured *in vitro*. Conversely, removal of T cells will allow the B cells to produce IgA. It was concluded that these patients possess a defect of immunoregulation at the level of the T_s cell for the IgA-producing B cell.^{220,254,255}

Regulation of IgE production is of special concern to the allergist, because antibodies of this immunoglobulin class primarily mediate the allergic reactions observed in hay fever, extrinsic bronchial asthma, and allied conditions. The initiation of a specific IgE response is analogous to the IgG response. A number of elegant studies have demonstrated that ongoing IgE production by B cells is suppressed by both antigen-specific T_s cells and T_s cells specific for IgE B cells, without reference to the antigenic specificity to which the antibody is being produced.^{101,115,239} Additionally, IgE B cell antibody production is decreased by interaction of IgG of the same antigenic specificity with the IgE B cell surface. This effect, originally described by Tada²⁴⁰ in the rat, has been observed in man.¹⁰²

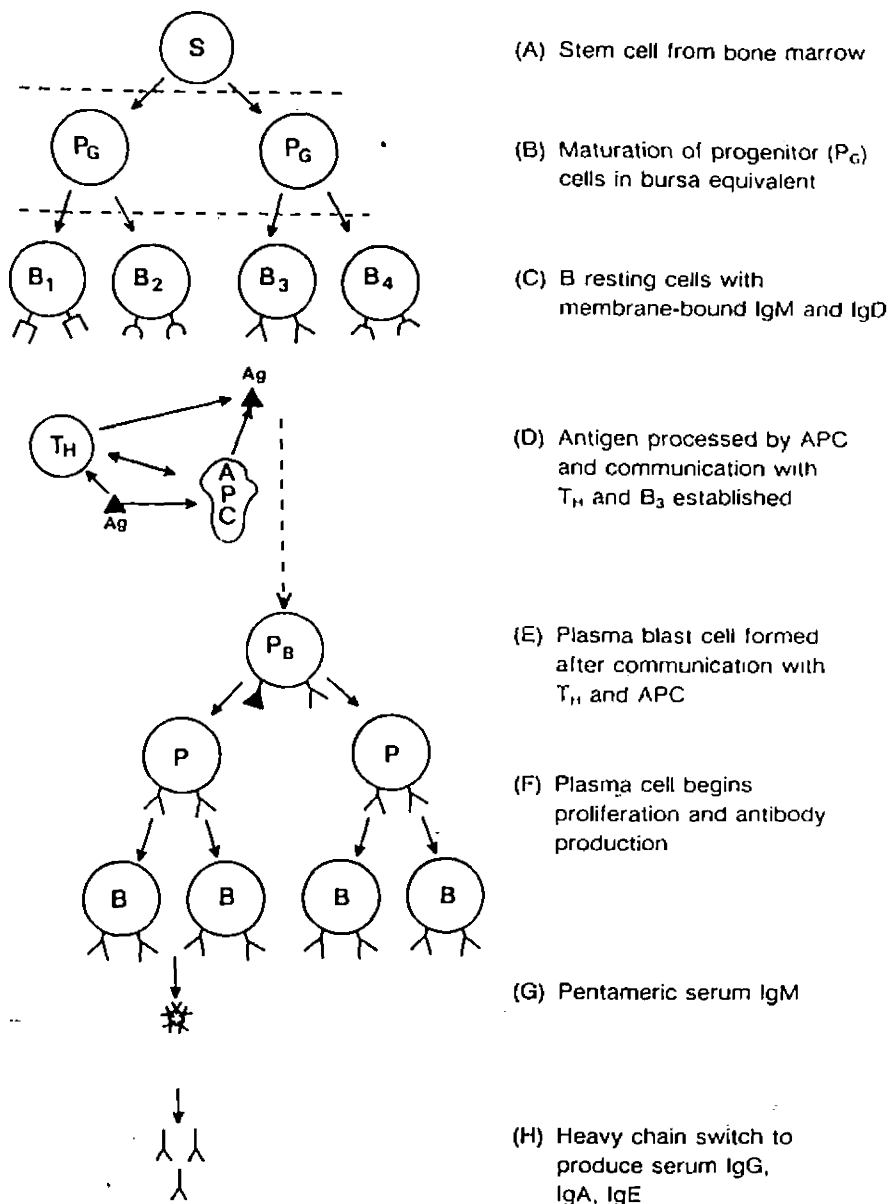


Fig. 1-3. Schematic representation of antibody production: (S) pluripotent stem cell; (P_G) progenitor cell after S enters bursa equivalent; (B) B cell (B₁₋₄) with different receptor specificities expressed by membrane IgM and IgD. B cell specificity (B₃) is selected by antigen (Ag). B cell processes antigen (APC) and presents to T-helper cell (T_H), which mediates the specific factor communicating with immunocompetent B cell and the nonspecific factor communicating with plasma blast cell (P_B). Plasma cells begin producing pentameric serum IgM, then switch to heavy chains to produce monomeric IgG, IgA, or IgE. (Modified with permission from Zaleski MB et al: Immunogenetics, p 158. Marshfield, Pitman Publishing Inc., 1983)

DR), consist of two polypeptide chains. The α chain is approximately 33,000 daltons with at least one disulfide domain and the β chain approximately 28,000 daltons with one or two disulfide domains. The class II molecules are restricted to certain cells, including B cells and macrophages. It is uncertain if they are expressed on T cells. Class III molecules in the mouse and in humans by convention are components of complement.^{142,268}

The importance of the class I molecules in generating cytotoxic T cells is that the T cell must recognize class I molecules as well as foreign antigen before activation of cytotoxicity (see Fig. 1-2). The T_c cell activation is induced only by class I molecules of the same haplotype. In generating humoral immunity, class II molecules are pivotal. Macrophages and B cells express class II molecules on their surfaces. The T_H cell responses are restricted by class II molecules on the macrophage, and they respond to the carrier portion of the antigen presented by the macrophage. The process of communication with the B cell is as yet unclear. Whether the hapten portion of the antigenic molecule is (1) presented to the B cell by T_H cell or APC, or (2) if the secretion by the T_H cell of antigen specific and/or antigen nonspecific products is necessary, or (3) if cell contact between B cell and T_H cell is necessary is not clear. The induction of the subset T_c cells capable of suppressing the immune response are MHC restricted and also appear to be responsive to class II molecules.²⁶⁹

As the multiple activities of the mammalian MHC have come to be understood better, an increasingly large number of diseases suspected to be "autoimmune" in etiology have been found to correlate significantly with specific HLA alloantigens. The presence of HLA-B27 antigen in 81% of patients with ankylosing spondylitis and only 4% of the normal population is perhaps the most striking correlation observed to date. Less striking associations with certain HLA antigens have been found in myasthenia gravis (D/DR3), psoriasis vulgaris (Cw6), dermatitis herpetiformis (D/DR3), Reiter's disease (B27), multiple sclerosis (D/DR2), insulin-dependent diabetes (D/DR3), idiopathic Addison's disease (D/DR3), and rheumatoid arthritis (D/DR5). As the Ia-like cell alloantigens of humans have been better defined serologically, recent reports have indicated very high levels of association between D/DR3 and systemic lupus erythematosus.^{231,236} Sjögren's syndrome also shows similar B lymphocyte alloantigen patterns. The meaning of these associations is controversial.²⁰⁵ It is believed, however, that the genes coding for the antigen in the MHC are closely linked to the loci responsible for actually conferring susceptibility to the disease. As the HLA complex is characterized more completely, stronger associations are anticipated.¹⁹⁹

IMMUNOGLOBULIN STRUCTURE AND FUNCTION

When serum proteins are subjected to electric current in a gel support (electrophoresis), they migrate from the cathode to the anode. There are two groups separated into peaks by this procedure. Albumins migrate the farthest from the cathode. The globulins separate into three areas defined as alpha following albumin; beta following alpha; and gamma remaining near the point of origin at pH 8.6. Antibodies reside in the gamma peaks. Immuno-

ulins are glycoproteins with less than 20% carbohydrate, the rest polypeptide. The immunoglobulin molecules have two sets of polypeptide chains; one is almost twice as large as the other. The larger is called H for heavy chain, and the smaller L for light chain. The pair of H and L chains are thought to have evolved through gene duplications of a primordial gene.²²⁵ The normal structure is one H chain associated with one L chain, with two disulfide bonds joining these structures to an additional H-L pair forming an H_2L_2 molecule, with these also joined by disulfide bonds. (See Fig. 1-4). The two subgroups of L chains are termed κ and λ , depending on the basis of structural differences in the chain. These κ and λ chains are found among all Ig classes. The H chains are different for each of the five classes of Ig, and are designated by the lower case Greek letter for the appropriate class. These are γ , α , μ , δ , and ϵ for IgG, IgA, IgM, IgD, and IgE. Both the H and the L chains consist of two discernable regions. The carboxy end of the chain is a constant (C) region and the amino end of the chain is a variable (V) region. These regions are named based on the relative heterogeneity within the class of antibody, and are folded upon themselves and contain interchain disulfide linkages. These folded areas are termed domains. There is one domain in the variable region. It is designated VH on the heavy chain, and V κ or V λ in the L chain. The constant region domains are numbered from the amino end, and are designated C κ or C λ on the light chain and CH1, CH2, CH3, and CH4 on the heavy chain. The first two domains on the amino end—the V λ with C λ , and the VH with CH1—constitute the antigen-binding site. There are two of these on each molecule. Antigenic differences found on the V region are referred to as *idiotypic* differences. The constant region begins after the hinge region and contains subsequent CH domains. Papain digestion will produce three fragments—antigen binding fragments (Fab) and one consisting of the constant portion, which was found to be crystallizable (Fc). The break was in the hinge region at the site of interchain disulfide bonds. Antigenic differences found in the constant region are referred to as *allotypic* differences.^{51,75} (See Fig. 1-5.)

Polymers of the basic monomeric antibody molecule are made with the addition of a J chain, which is a polypeptide. The J chain completes dimers, hexamers (IgA), and pentamers (IgM). In addition, another polypeptide, the secretory component, is found with IgA.^{51,75}

Immunoglobulin M

IgM is found in lesser concentrations in serum than IgG is, but it appears to serve several important functions. It is the earliest antibody produced in the primary immune responses. Usually it binds to antigen with less avidity than the later-appearing IgG directed toward the same specificity. IgM is more effective in complement activation to produce immune cytolysis, and is more efficient in agglutination. Therefore, it has been suggested that IgM is especially useful in eliminating particulate antigens from the circulation. Human IgM has a molecular weight of 900,000 daltons with a large percentage (10%) of carbohydrate. Its quaternary structure is that of a pentamer composed of five subunits. The monomeric structure is similar to that of IgG. Several subclasses have been described, IgM1 and IgM2. A monomeric IgM has been described in the serum of certain fish and in the milk of certain mammals.

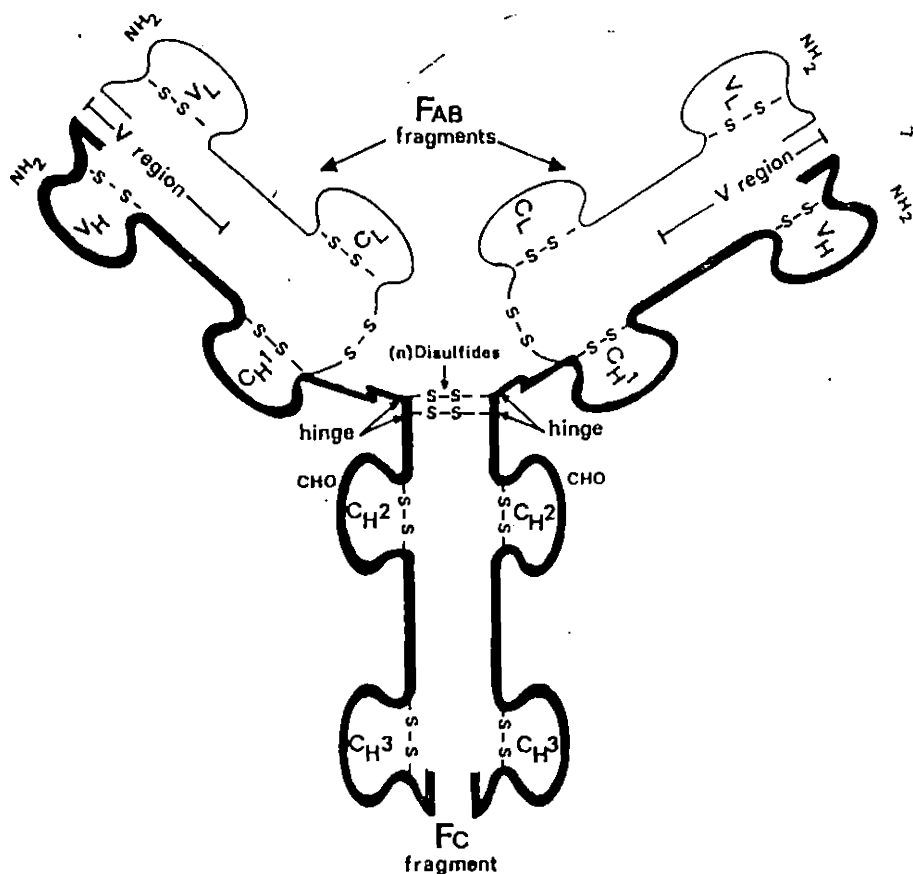


Fig. 1-5. The structure of immunoglobulin monomer is depicted. The domains are shown as loops in the peptide chains. The heavy line indicates the heavy (H) chain (not the actual structural relationship), and the light line represents the light (L) chain. The variable (V) region is located at the NH₂ end of the Fab fragments. (Modified with permission from Golub ES: *The Cellular Basis of the Immune Response*, 2nd ed, p 208. Sunderland, Sinauer Associates, Inc., 1981)

tosus, Waldenstrom's macroglobulinemia, and rheumatoid arthritis. In addition to the five H₂L₂ monomers, intact pentameric IgM also contains a unique polypeptide chain with a molecular weight of 25,000 daltons that is rich in cystine residues. This polypeptide chain is called the J chain. It appears to bind to the Fc domains of the polymerized monomers, and may fulfill a special role in the polymerization of these molecules.

Immunoglobulin G

IgG is the major protective antibody. It is important in the neutralization of soluble antigens, for example, bacterial toxins. Its concentration usually increases with repeated antigenic stimulation and is the most abundant antibody in the serum.

As shown in Fig. 1-5, the molecule is composed of four polypeptide chains of two distinct types. The smaller polypeptide chains are light (L) chains, with molecular weights of 25,000 daltons. The larger or heavy (H) chains have molecular weights of 55,000 daltons. Gamma chains carry antigenic determinants that form the bases for the division of IgG into four subclasses: IgG1, IgG2, IgG3, and IgG4.²²⁵ These subclasses vary in their biologic activities. The Fc portion mediates such biologic activities of IgG as complement fixation, reactivity with rheumatoid factors, membrane transmission, skin fixation, macrophage fixation, and regulation of catabolism. The Fc region connects through the hinge region to the two Fab regions.

Immunoglobulin A

IgA comprises about 20% of the serum immunoglobulins. Its protective role in serum, however, is probably smaller than the part it plays as the major protective antibody of the external and internal secretions.¹⁷¹ It is found in large amounts in parotid saliva, colostrum, and lacrimal fluid, and in nasal, bronchial, and intestinal secretions. From these observations the concept has emerged that IgA may serve as the principal effector of an immune barrier against macroorganisms on exposed and potentially vulnerable mucosal surfaces. This hypothesis is supported by the observation that many IgA-deficient patients experience repeated sinopulmonary infections.^{77,235,255} Isolated IgA deficiency, however, actually appears to represent a heterogeneous group of immunopathologies. In other IgA-deficient patients, the immune defect is asymptomatic. In these patients it appears that secreted IgG, or perhaps other factors, is adequate to compensate for the absence of IgA antibody. In blood, IgA circulates as either a monomer or dimer, predominantly the latter. A J chain is found in the polymeric form of IgA. Human IgA monomer has a molecular weight of 170,000 daltons. The IgA in secretions, however, is dimeric, with a molecular weight of 385,000 daltons. Secretory IgA differs from serum IgA in additionally possessing a secretory component (mol wt 58,000 daltons). This polypeptide is synthesized and fixed to the IgA dimer before secretion.

Immunoglobulin D

IgD is found free in the circulation in low concentrations.⁶⁹ Its role in the immune system, long enigmatic, appears primarily to be that of serving as an antigen receptor or recognition site on the uncommitted B cell.^{74,208,215} Monomeric IgM has also been described in this role. Recent reports indicate that uncommitted thymus-dependent B cells carry both IgD and IgM recognition receptors on their membranes. In contrast, thymus-independent B cells appear to carry IgM almost exclusively.¹³⁷ IgD is composed of two heavy chains and two light chains, either κ or λ , with a molecular weight of 184,000 daltons.

Immunoglobulin E

IgE has been shown to be the principal, if not the sole, mediator of immediate (type I) hypersensitivity reactions.^{173,215} IgE binds to tissue mast

combines with antigen (allergen) and causes basophil degranulation, with release of histamine and other mediators.¹⁴ The process will be discussed further in this chapter under type I hypersensitivity reactions, and in Chapters 2 and 3. It is thought that IgE may have a protective role against certain parasitic infestations.^{35,56,166} IgE is composed of two ϵ heavy chain and two light chains, either κ or λ . Its molecular weight is 190,000 daltons. Serum IgE concentrations are the lowest of any of the immunoglobulin classes, and are measured in nanograms. IgE concentrations are generally higher in the allergic population, although there is considerable overlap with nonatopic persons.¹⁰⁰

IMMUNOGLOBULIN SYNTHESIS

The process by which immunoglobulin is produced has three general phases: synthesis, assembly, and secretion.⁶ Most studies concerning these processes have been performed on plasma cells, usually murine plasmacytomas. It appears, however, that the events described apply equally well to the less fully developed B lymphocyte and uncommitted B cell surface immunoglobulin receptor synthesis.

Production of Immunoglobulin Polypeptide Chain

There are about ten separate genes that code for each class and subclass of CH chain. There are three genes for the CL chain, one for κ , and two for λ . In addition, for the variable region there are three genes for $V\kappa$ and four for $V\lambda$, which may combine with one of the $C\kappa$ and $C\lambda$. The VH and CL region genes and the VL and CL region genes are linked closely. The genes for κ , λ , and heavy chains are in three separate unlinked regions. The V and C genes from the same chromosome and the same allele function together. This use of only one of two allelic forms is termed *allelic exclusion* and may be unique to this area. The mechanism used to produce a functional H chain from DNA appears to be rearrangement. Beginning with the amino end there is an L or leader sequence of nucleotides that is followed by a noncoding intervening sequence (intron). The intron is followed by the coding sequence (exon) for the V region. The exon is followed by an intron, then the exon for the J or joining gene. There is another intron, then the exon for the C region. As the maturation from germ line DNA to mRNA of the antibody-producing plasma cell occurs, the sequencing is rearranged to produce the functional polypeptide.²⁶⁶ (See Fig. 1-6.)

The plasma cell is a highly specialized cell. One cell will always secrete only one antibody specificity of one immunoglobulin class, subclass, allotype, and idiotype at a given time. In the maturation of the B cell two membrane-bound immunoglobulins may be expressed at the same time. During maturation to a plasma cell, there is a CH region switch from $C\mu$ to $C\gamma$, requiring a deletion of $C\mu$ and a rearrangement to $C\gamma$.¹⁶⁶ A gene sequence responsible for this switch, and called the S or switch sequence, is theorized. There appears to be only one mRNA molecule for the synthesis of a single light chain or heavy chain. The mRNA travels from the nucleus to the highly developed endoplasmic reticulum. There, translation and peptide synthesis proceed on distinct ribosomes. 144 268