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Section I. Basic Immunology

The Immune System: An Overview | 1

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The immune system is an extremely complicated one with a variety of roles in maintaining homeostasis and health. Like the endocrine system, it exerts control within the body by virtue of circulating components capable of acting at sites far removed from their point of origin. The complexity of the system derives from an intricate communications network capable of exerting multiple effects based on a relatively few distinct cell types. The immune regulatory mechanism thus may enormously amplify a given response or markedly diminish it depending on the momentary needs of the organism. A normally functioning immune system is an effective defense against foreign particles such as pathogenic microbial agents and against native cells that have undergone neoplastic transformation. Defective function of the immune system results in disease.

The overview of the immune system presented here emphasizes the immune regulatory mechanisms and how they are genetically controlled. The concepts outlined here are covered in greater detail elsewhere in this text. What I wish to emphasize at the outset is the singular flexibility of response made possible by the complex organization of the cellular and molecular components of the immune system. In almost no instance is the organism limited to one possible pathway in response to an antigenic stimulus.

COMPONENTS OF THE IMMUNE SYSTEM

The genetic, cellular, and molecular components of the immune system are combined in an exquisitely complex communications network. The relationships between these components are reciprocal and circumscribed. Regulatory control of immune mechanisms is a function of their interactions.

Cellular Components of the Immune System

The major cellular components of the immune system are the macrophages and lymphocytes (Chapter 9). Macrophages themselves have a variety of functions in the immune response (Chapter 11). Although macrophages are not currently thought to be specific for any given antigen, their role in concentrating and presenting antigens to lymphocytes is a crucial one. In particular, it is apparently the macrophage that determines which T cells (thymus-derived lymphocytes concerned with cellular immunity; Chapters 9 and 10) will be induced to stimulation and function by various antigens. Moreover, the macrophages secrete several biologically active mediators capable of regulating the type and magnitude of both T and B lymphocyte responses either by enhancing or suppressing cell division or differentiation (Chapter 12). In addition, the macrophage plays a key role in antigen processing, since it is the major phagocytic cell of the monocyte-macrophage system.

Lymphocytes are the antigen-specific cellular components of the immune system, acting via receptors on the surface membrane of every immunocompetent cell (Chapter 1). Each receptor is highly specific, and different clones of lymphocytes express their own unique specificity. The origin of lymphocyte specialization is unclear, and debate continues about whether it is genetically transmitted or induced by somatic mutation (Chapter 4).

The nature of the antigen receptors on the 2 major classes of lymphocytes appears to differ (see below).

Genetic & Molecular Components of the Immune System

A great many genes and molecules have important roles in the immune system (Table 1–1); only those of major importance are noted here. Section I of Table 1–1 summarizes the structural components and functional activities of immunoglobulin genes and immunoglobulin molecules (Chapter 4). The immunoglobulin gene system is the only one yet known in which 2 discrete structural genes participate in the production of a single polypeptide chain.

Each functional immunoglobulin molecule is composed of 4 chains: 2 identical light (L) chains and 2 identical heavy (H) chains. A single chain is formed by the combination of 2 structural genes to form a variable (V) region and a constant (C) region (Fig 4–1). On the various chains comprising an immunoglobulin molecule, therefore, one may designate V_L and V_H genes or regions. Proper integration of these regions to make a competent immunoglobulin molecule is an extremely complex task (Chapter 7B). The genes forming the C region determine the future biologic function of the molecule (eg, whether IgE will bind to

mast cells). The H chains determine the immunoglobulin class of the molecule (IgG, IgA, IgM, IgD, IgE). The immunoglobulin molecule's unique antigen receptor site is determined by the primary structure of the V_L and V_H regions. This site possesses unique antigenic structures called **idiotypes**. Recently, it has become clear that an individual can develop anti-idiotypic responses to the unique combining sites on his or her own immunoglobulin molecules and that such anti-idiotype responses determine, at least in part, the magnitude and duration of antibody production to a given antigen.

In addition to their biologic role as the products of antigen-secreting plasma cells that have differentiated from precursor B cells (Chapter 9), conventional immunoglobulin molecules serve as the antigen-specific receptors on the surface of B lymphocytes. The precise molecular nature of the antigen-specific receptors on T lymphocytes, however, is still unclear. Although the same V-region genes that serve as the antigen-combining sites on conventional immunoglobulin molecules seem to function as the antigen-combining sites on T cells, that portion of the T cell receptor corresponding to the C region of an immunoglobulin molecule has yet to be defined (Chapter 10).

Table 1–1. Genes and molecules of the immune system.

Immunoglobulin genes and molecules
- A. Structure:
  1. Variable *(V)* region (antigen-combining site; idiotypes).
  2. Constant *(C)* region (biological function).
  3. Heavy *(H)* chain—$\mu, \gamma, \alpha, \epsilon, \delta$.
  4. Light *(L)* chain—κ, λ.
- B. Function:
  1. Receptors for antigens on B cells.
  2. *V* region also forms part of T cell antigen receptor (remainder still undefined).
  3. Secretory products of plasma cells (antibodies).

Histocompatibility complex genes and molecules
- A. *I*-region *(HLA-D* in man):
  1. Cell interaction *(CI)* genes and molecules control interactions between T cells, B cells and macrophages.
  2. Immune response *(Ir)* genes determine ability of an individual to respond to a given antigen.
  3. Ia antigens are the major antigens responsible for mixed lymphocyte reactivity and GVH reactions.
  4. Biologically active mediators produced by, and active on, T cells, B cells, and macrophages.
  5. Disease susceptibility; resistance to viruses; allergic and autoimmune diseases (may be related to *CI* or *Ir* gene functions or both).
- B. Other regions:
  1. Major and minor transplantation antigens (graft and tumor rejection).
  2. Interactions with infectious viruses *(K/D)*.
  3. Complement components.

Differentiation genes and molecules
- A. Ly (lymphocyte) antigens:
  1. Lyt-1, 2, 3: Distinguish functional subpopulations of T lymphocytes.
  2. Lyb-3, 5, etc: Differentially expressed on certain B lymphocytes; functional correlations still undefined.
- B. Fc receptors:
  1. FcRγ: Present on B lymphocytes, macrophages, and one subpopulation of T lymphocytes (?suppressor T cells).
  2. FcRμ: Present on certain T lymphocytes (?helper T cells) and macrophages.
- C. Complement receptors: Present on subpopulations of B lymphocytes and T lymphocytes; bind C3b or C3d. Functional significance unclear.

The gene system associated with the histocompatibility complex (Chapters 14 and 15) and its derivative molecules also play a crucial role in the immune system. The system has been studied most thoroughly where the major histocompatibility gene complexes have been designated as HLA and H-2 in humans and in the mouse, respectively. Both complexes have been shown to consist of several distinct genetic regions responsible for distinct functions. The H-2 complex, located in a small segment of mouse chromosome 17, consists of at least 9 regions and subregions (Chapters 10 and 14). Within the complex, *I*-region genes and molecules have been shown to be most versatile with respect to immune responses. In the mouse, 5 *I* subregions have been well defined: *I-A, I-B, I-J, I-E,* and *I-C*. Contained within one or more of these subregions are (1) cell interaction *(CI)* genes that regulate interactions between macrophages, T cells, and B cells; (2) immune response *(Ir)* genes that determine an individual's susceptibility to disease by regulating the capacity to respond to certain antigens and viruses; (3) genes encoding Ia antigens, largely responsible for mixed lymphocyte reactivity and graft-versus-host reactions; (4) genes involved in the synthesis of certain biologically active mediators produced by and active on T cells, B cells, and macrophages; and (5) genes that determine susceptibility to allergic and autoimmune diseases and resistance to certain viruses through processes that may be related to the functions of *CI* or *Ir* genes (or both). It is not established whether distinct genes are responsible for these various functions or whether they are controlled by relatively few genes. Many of these activities, however, are closely related to one another, suggesting multiple gene control. Similar functional distinctions have been assigned to different regions of the HLA gene complex (Chapter 15).

Other immunologically important regions of the H-2 histocompatibility gene complex are the *H-2K* (and *H2L*) and *H-2D* regions on either end of the complex containing the genes responsible for production of the major transplantation antigens (readily detectable with appropriate antibodies on virtually all cells of the organism). The *K, L,* and *D* genes are, in addition, the major antigens attacked by cytotoxic T lymphocytes during rejection of foreign tissue grafts. In recent years, it has also been shown that the products of these genes interact in an undetermined manner with cytopathogenic viruses enhancing recognition of infected cells by cytotoxic T cells. The *S* region, also immunologically active, contains structural genes responsible for the synthesis of certain molecules of the complement system, a highly complex network of component molecules performing distinct biologic and chemical functions (Chapter 8).

Also highlighted in Table 1–1 are selected differentiation genes and molecules prominently associated with distinct immunologic functions (Chapter 10). The Ly antigens constitute a family of cell surface antigenic determinants that are differentially expressed on T lymphocytes (Lyt) and B lymphocytes (Lyb). The Lyt antigens are themselves differentially expressed on distinct functional subpopulations of T lymphocytes; an analogous situation appears to hold true for the Lyb antigens. Receptors on the Fc portion of an immunoglobulin molecule (Chapter 4) have been shown to exist on both T and B lymphocytes as well as on macrophages and are detected by their ability to bind to the Fc regions of aggregated or antigen-complexed immunoglobulin molecules. Certain Fc receptors appear to be specific for IgG molecules (FcRγ) and for the Fc determinants on IgM molecules (FcRμ). FcRγ are present on B lymphocytes, macrophages, and the subpopulation of T lymphocytes that contain suppressor cells (see below). FcRμ are present on macrophages and appear to be differentially expressed on the subpopulation of T lymphocytes containing helper T cells. Receptor molecules capable of binding certain complement components, notably C3b and C3d, exist on certain subpopulations of B lymphocytes, T lymphocytes, and monocytes, although the functional significance of such complement receptors is still unclear. The appearance of these molecules correlates in time with the ontogenic development of the various lymphocyte classes and of the macrophages on which they appear (Chapter 13)—hence their designation as differentiation molecules.

FUNCTIONAL SUBPOPULATIONS OF LYMPHOCYTES

The 2 classes of lymphocytes (Table 1–2) have distinct functional capabilities (Chapters 8 and 10). T lymphocytes neither produce circulating antibodies nor give rise to antibody-secreting cells. The most extensive investigations of these cells have been made in the mouse. Based upon these studies, they can be subdivided into 2 major functional categories: regulatory and effector T lymphocytes.

Table 1–2. Functional subpopulations of lymphocytes.

T lymphocytes
A. Regulatory T lymphocytes:
1. Helper cells.
2. Suppressor cells.
B. Effector T lymphocytes:
1. Delayed hypersensitivity (DTH).
2. Mixed lymphocyte reactivity.
3. Cytotoxic T lymphocyte (CTL or "killer" cells).
B lymphocytes
A. Precursors of antibody-forming cells Bμ, Bγ, Bα, Bϵ.
B. Memory cells.
C. ?Regulatory B lymphocytes.

Regulatory T lymphocytes may amplify (as helper cells) or suppress (as suppressor cells) the responses of other T lymphocytes or of B lymphocytes. Distinct subpopulations of T cells appear to be responsible for these activities. Helper T cells are generally of the Lyt-1+ phenotype; suppressor T cells generally express the Lyt-2,3+ phenotype.

Effector T lymphocytes are responsible for such cell-mediated immune reactions as delayed cutaneous hypersensitivity responses (see Chapter 11), rejection of foreign tissue grafts and tumors, and elimination of virus-infected cells. Cytotoxic T lymphocytes (CTL), commonly referred to as "killer" cells, participate in the latter responses. Rejection of foreign tissues also involves T cells that undergo rapid proliferation in mixed lymphocyte reactions (MLR). These cells can be distinguished by their Lyt phenotypes: the MLR cell is of the Lyt-1+ phenotype, the CTL of the Lyt-2,3+ phenotype. Similarly, CTL (Lyt-2,3+) can be distinguished from delayed cutaneous cells, which are also of the Lyt-1+ phenotype.

Thus, T cells performing helper, delayed cutaneous, and MLR functions are all of the Lyt-1+ phenotype. It remains to be established by other criteria, however, whether these functions are performed by distinct subpopulations (although evidence suggests that helper cells and delayed cutaneous cells are discrete entities). Analogously, although CTL and suppressor cells are both of the Lyt-2,3+ phenotype, functional evidence tends to indicate that they represent distinct subpopulations of T cells.

Functional subpopulations of B lymphocytes may be categorized most readily on the basis of the different classes of immunoglobulin molecules they synthesize (Table 1–2). B lymphocytes give rise to cells that synthesize and secrete all classes of circulating immunoglobulin molecules (IgM, IgG, IgA, and IgE). The respective B cell precursors for these antibody-forming cells are designated Bμ, Bγ, Bα, and Bϵ. Ample evidence now supports the hypothesis that the earliest progenitors of antigen-specific B cells possess receptors of the IgM class; that more mature B cells possess receptors of both IgM and IgD; and that more mature precursor B cells (and perhaps "memory" B cells) express IgG receptors, either alone or in combination with IgD. Although it appears that the B cell precursors of IgM-, IgG-, and IgA-secreting cells may derive from the same subline of B lymphocytes, it is not yet known whether the B cell precursors of IgE-secreting cells derive from that same subline or from a distinct subline. Memory B cells are functionally important for development of rapid secondary (anamnestic) antibody responses upon subsequent antigenic exposure. These cells can be distinguished from "unprimed" B lymphocytes by their distribution in the tissues, size, migratory properties, and surface antigen properties. As yet, there is no hard evidence for the existence of regulatory B lymphocytes functionally analogous to regulatory T lymphocytes, although the future discovery of such cells would not be surprising.

Table 1–3. Genetic control of immune responsiveness.

Cell interaction *(CI)* genes
A. Control most effective macrophage-lymphocyte interactions.
B. Control most effective T-T and T-B lymphocyte interactions.
C. Code for molecules active in enhancing and suppressing immune responses.
D. Control most effective lysis of virus-infected and neoplastic target cells by cytotoxic T lymphocytes.
Immune response *(Ir)* and immune suppression *(Is)* genes
A. *Ir* genes determine ability of an individual to respond to a given antigenic determinant.
B. *Is* genes control stimulation of specific suppressor T lymphocytes.
C. Nature and mechanism(s) of action unknown at present—could be identical to *CI* genes.

The capacity of antibody molecules themselves to specifically regulate immune response by "antibody feedback" is well documented.

GENETIC CONTROL OF IMMUNE RESPONSIVENESS

The control of immune responsiveness exerted by the genes of the major histocompatibility complex is summarized in Table 1–3. Cell interaction *(CI)* genes, the most important regulatory genes of the complex, appear to reside in one or more of the *I* subregions of the *H-2* complex (Chapter 14). The *CI* genes control the most effective cell-cell interactions in the immune system. It has been demonstrated that the interactions between macrophages and T cells and between T cells and B cells involve cell surface molecules, termed cell interaction or CI molecules, whose synthesis is controlled by the *CI* genes located in the *I* region of the *H-2* complex. These genes control the most effective macrophage-lymphocyte interactions and the most effective T-T and T-B lymphocyte interactions. In addition, *CI* genes control the synthesis of biologically active lymphocyte- and macrophage-derived molecules capable of either enhancing or suppressing immune responses. It is not yet known, however, whether the genes responsible for synthesis of these molecules and the *CI* genes controlling the most effective cell-cell interactions are identical or distinct. In addition, *CI* genes located in the *K* or *D* regions of the *H-2* complex control the most effective lysis of virus-infected and neoplastic target cells by cytotoxic T lymphocytes.

Genetic control of immune responsiveness also involves specific immune response *(Ir)* and immune suppression *(Is)* genes. Indeed, the discovery of *Ir* genes represented the first association between the major histocompatibility complex and regulation of immune responsiveness. *Ir* genes, inherited in simple mendelian fashion as autosomal dominant traits, have been found in virtually all species and appear to determine an individual's ability to respond to a given antigen. In certain cases, 2 genes are responsible for the development of an immune response, and the absence of either (or both) results in the inability of the individual to respond to the particular antigen. More recently, investigators have shown that *Is* genes in the *I* region also govern the development of specific suppressor T lymphocytes. In contrast to those cases in which absence of one or more *Ir* genes results in inability of the individual to respond to a particular antigen, the absence of a specific *Is* gene or genes allows an immune response to occur that is essentially dissociated from the regulatory influence of suppressor T cells. Although considerable work has been done in these areas, we still do not understand the nature or the mechanisms of Ir and Is gene activity. In fact, further investigation is needed simply to determine whether these genes are distinct from *CI* genes.

REGULATORY INTERACTIONS IN IMMUNE RESPONSES

The discovery of a complex series of regulatory interactions among components of the immune system has proved to be a major breakthrough in our understanding of the system. Work done in the mid 1960s demonstrated that the development of antibody responses depended upon T cell-B cell interactions (Chapter 10), and our perspective has now widened to reveal the workings of various genes, molecules, and cells in regulation of the immune system (Table 1–4).

We now know that the genes of the system produce (1) antigen-specific receptors on lymphocyte surface membranes; (2) circulating antibodies that perform effector functions and exert feedback regulation; (3) crucial regulatory effects on various cell-cell interactions necessary for normal immunologic homeostasis; and (4) biologically active molecules capable of enhancing or suppressing T cell or B cell activity. The cells of the system are interdependent. The develop-

Table 1–4. Regulatory interactions in immune responses.

Genes and molecules
A. Serve as specific antigen receptors on lymphocyte surface membranes.
B. Circulating antibodies perform effector function and exert feedback regulation.
C. Regulate cell-cell interactions.
D. Biologically active molecules enhance or suppress T cell and/or B cell functions.
Cells
A. Macrophage ↔ T cell interactions; macrophage ↔ B cell interactions.
B. T cell ↔ T cell interactions ↔ cell-mediated immunity.
C. T cell ↔ B cell interactions ↔ antibody production.

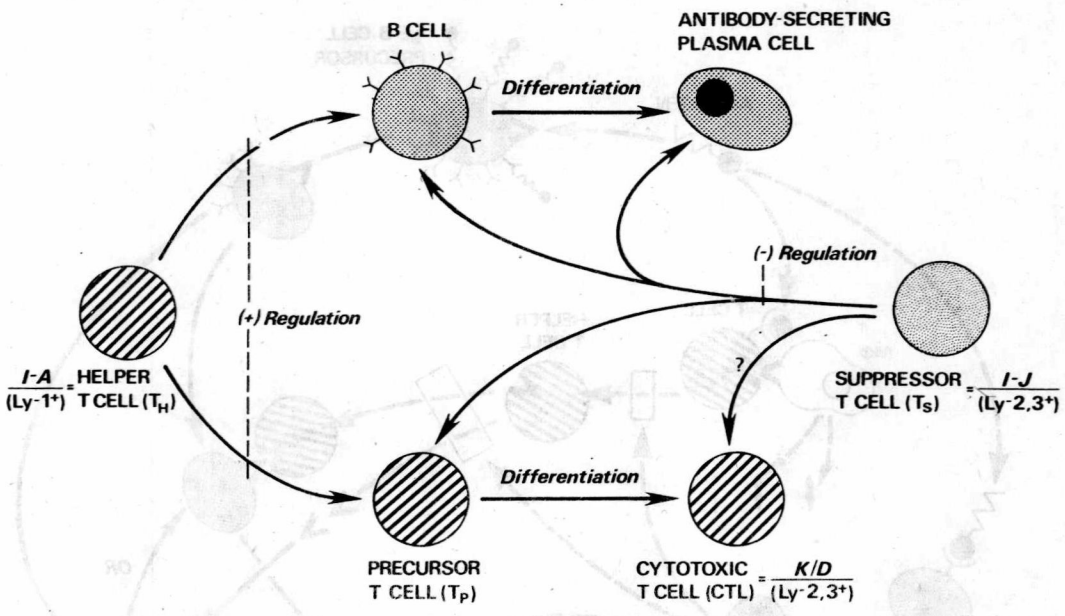

Figure 1–1. Summary of the T lymphocyte regulatory influences in the immune system.

ment of cell-mediated or humoral immunity, therefore, is regulated by a series of essential interactions between macrophages, T cells, and B cells.

Regulatory interactions between constituents of the immune system may be manifested along a spectrum that ranges from enhancement to suppression of immune responses. The qualitative or quantitative response occurring at any given time, however, will reflect the net effect of the extremely dynamic interplay among the system's components.

Fig 1–1 schematically summarizes our current knowledge of T lymphocyte regulatory influences on the immune system. Depicted to the far left is the helper T cell (T_H), with the surface phenotype Lyt-1+, functionally restricted by *CI* genes located in the *I-A* region of the *H-2* complex (see above). These cells are capable of exerting positive regulatory effects on B cells (upper portion of Fig 1–1) and stimulating their differentiation into fully mature antibody-secreting plasma cells. Helper T cells also exert positive regulatory influences on precursors of T cells destined to become CTLs (Lyt-2,3+), restricted in their cytolytic function by *CI* genes located in the *K* or *D* regions of the *H-2* complex (lower portions of Fig 1–1). The second category of regulatory T lymphocytes, known as suppressor cells (T_S), appears at far right. Suppressor T cells (Lyt-2,3+) are genetically restricted by *CI* genes located in the *I-J* region of *H-2*. As indicated, suppressor T cells can exert negative regulatory effects on the differentiation of B lymphocytes or precursors of CTLs by acting directly on such cells or by interfering with the activity of helper T cells that would normally facilitate their development. Moreover, suppressor T cells have been shown to directly inhibit the secretory function of fully matured plasma cells. Whether a similar direct inhibition can be exerted by suppressor T cells on fully mature CTLs is not known.

A schematic illustration of regulatory cell-cell interactions necessary for the development of a normal antibody response is presented in Fig 1–2. Although the figure specifically represents the induction of IgE antibody responses, that process is equally applicable to antibody responses of the other immunoglobulin classes. The antigen is a hapten-carrier conjugate (Chapter 5). Consequently, the carrier determinants are recognized by T cells and haptenic determinants by B cells. Macrophage presentation of the antigen appears to be particularly favorable for induction of helper T cells, which recognize carrier determinants by virtue of determinant specific receptors and interact in a critical way with macrophage-associated CI molecule. In addition, biologically active macrophage-derived soluble factors may play a role in the induction of helper T cells. Once activated, the helper T cells interact with B cells (that have previously interacted with haptenic determinants via their surface immunoglobulin receptors and are, therefore, specific for the hapten), facilitating the differentiation of such B cells into mature antibody-secreting plasma cells or memory cells. These interactions may occur directly or via the mediation of soluble T cell factors. However, suppressor T cell activity, which can be induced by direct antigen binding in the absence of any macrophage presentation, may interfere with these cell-cell interactions in 3 ways (indicated by the broken arrows in Fig 1–2): (1) by preventing the activation of helper T cells; (2) by hindering helper T cell interactions with B lymphocytes; and (3) by directly inhibiting B cell differentiation.

A virtually parallel scheme can be drawn to depict

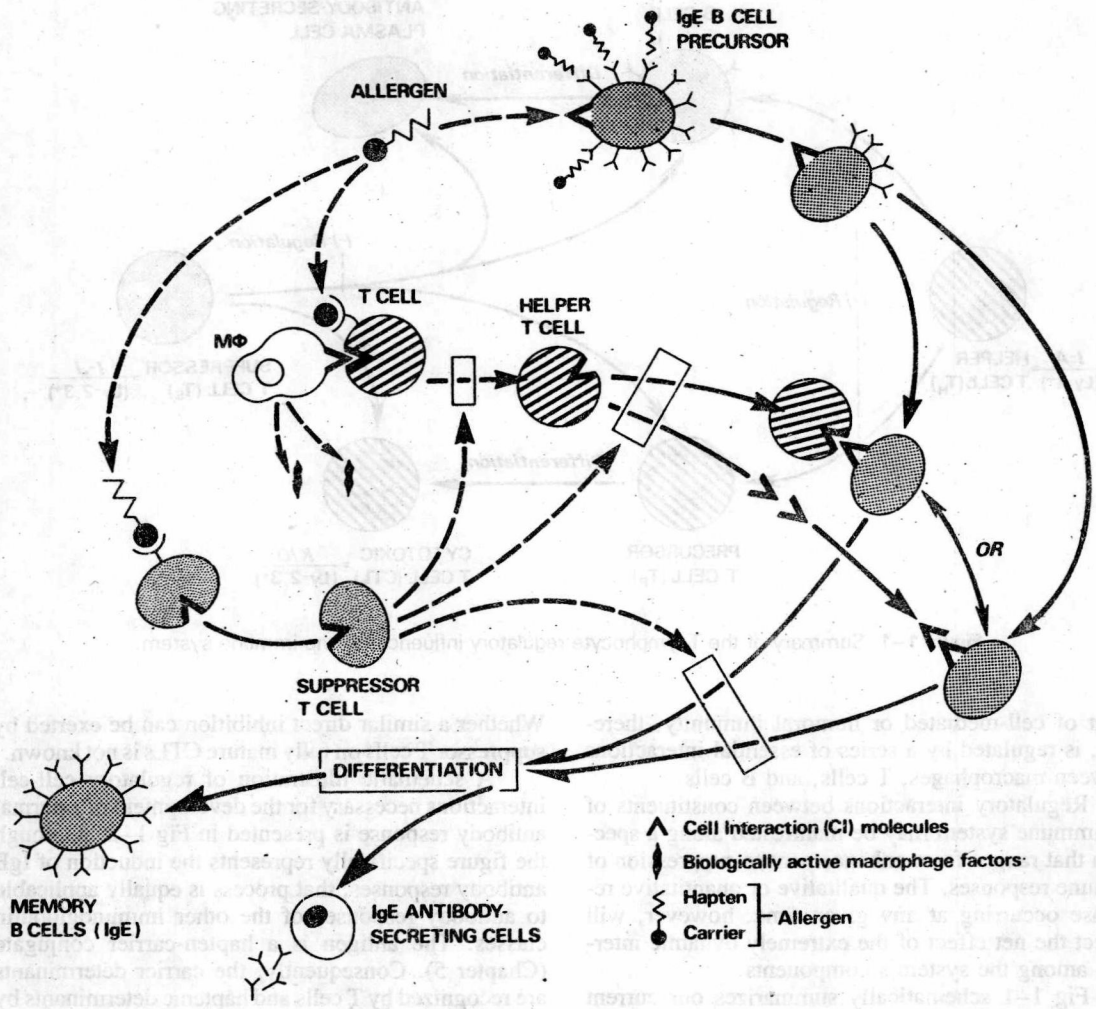

Figure 1–2. The IgE antibody-producing apparatus.

the regulatory cell-cell interactions essential to the development of effector T cells involved in the various types of cell-mediated immune responses.

CLINICAL CIRCUMSTANCES REFLECTING ABERRANT GENETIC & REGULATORY CONTROL OF IMMUNE RESPONSES

There is little doubt that our increasing awareness of the many circumstances in which immune functions may be involved in the pathogenesis of disease has contributed substantially to the enormous growth of immunology over the past 20 years. Progressive advances in our knowledge of the immune system have reflected in part the successes of basic immunologic research and in part the perseverance of clinical immunologists who have explored the immune system's involvement in clinical conditions whose primary causes were theretofore unknown. Perhaps in no other area of biomedical science has the interdependence of basic and clinical research been so fruitful. An important consequence of this partnership has been the unusually rapid progress in the development and application of sophisticated laboratory technics, allowing a more precise examination of the immune system. The earlier, limited technics for evaluating the molecular components of serum protein have now evolved into technologies that make possible more sensitive and specific tests, not only of blood serum protein but also of serum protein fixed to tissue sites in the body (Chapter 26). More recently, the expansion of these technics has permitted analysis of various aspects of cell-mediated immunity (Chapter 27), making possible the construction of immunologic "fingerprints" of a given disease that often reveal a variety of associated abnormalities. The ability to evaluate the association has in certain instances improved the effectiveness of

therapy and promises even greater improvements in the years to come.

The importance of developing immunologic fingerprints of disease is perhaps most apparent in the case of immunodeficiency diseases. Not too many years ago, a patient presenting the typical manifestations of immunodeficiency (eg, chronic or recurring infections with pyogenic organisms) was diagnosed under the broad category of "immunodeficiency disorder." Today, immunologic fingerprints make possible the categorization and subcategorization of immunodeficiency disease in a manner that not only makes the diagnosis more precise but also provides a more rational basis for therapy (Chapter 29). Furthermore, recognizing how variable immunologic fingerprints may be from one immunodeficiency disease to another has substantially enlarged our overall understanding of the interactions between components of the immune system. With increased diagnostic proficiency, it has been possible to broaden our awareness of the primary and secondary involvement of the immune system in various diseases of the hematopoietic (Chapter 31), gastrointestinal (Chapter 33), cardiopulmonary (Chapter 34), endocrine (Chapter 38), nervous (Chapters 39 and 40), and other systems (Chapters 36 and 42). Historically, the rheumatic or autoimmune diseases (Chapter 30) have been the disorders longest under study and, paradoxically, among the most difficult to unravel in terms of pathogenesis. This seems indicative of the enormous complexity of immunologic events underlying such diseases and the manner in which the internal environment of the individual responds to immunologic abnormalities. Nevertheless, great progress has been made in the diagnosis and management of these diseases. For example, in patients with systemic lupus erythematosus, for example, early diagnosis and initiation of therapy are helpful in preventing severe progressive renal disease (Chapter 35), a complication that 20 years ago was responsible for the high mortality rate in patients with this disorder. Furthermore, acute leukemias are now categorized as B, T, pre-B, and null, and these forms differ in prognosis and response to therapy (Chapter 23).

There is at present a long list of diseases in which primary or associated immunologic abnormalities exist. These disorders are discussed in detail in Chapters 29–44. To provide some general clinical perspectives, the remainder of this chapter will consider possible clinical manifestations associated with aberrations in the genetic and regulatory control of immune responses. Some of these associations have been documented; others are of a speculative nature (Table 1–5). This discussion has been divided into 3 sections based on presumed defects in Ir, Is, or CI gene functions, regulatory T cell functions, and B lymphocyte functions. As previously noted, disturbances in Ir, Is, or CI gene function may determine susceptibility to certain bacterial or viral agents and may predispose an individual to development of certain diseases of unknown cause (Table 1–5).

Table 1–5. Clinical circumstances possibly reflecting aberrant genetic and regulatory control of immune responses.

Defects in *Ir, Is (? CI)* gene functions
- A. May determine susceptibility to certain etiologic bacterial or viral agents.
- B. May predispose an individual to development of certain diseases of uncertain etiology such as multiple sclerosis, myasthenia gravis, insulin-dependent diabetes, ankylosing spondylitis.

Defects in regulatory T cell function
- A. Excess suppressor and/or deficient helper cell activity.
  1. Certain forms of acquired hypogammaglobulinemia.
  2. Immunodeficiency of aging.
  3. Immunodeficiency associated with certain neoplastic disorders—eg, Hodgkin's disease.
  4. Congenital thymic deficiencies—eg, DiGeorge syndrome.
  5. Susceptibility to certain diseases of viral etiology.
- B. Deficient suppressor cell activity.
  1. IgE-mediated allergic disorders—eg, ragweed hay fever.
  2. Certain malignancies of lymphoid cell clones—eg, leukemia, plasmacytomas.
- C. Excess or inappropriate helper and/or deficient suppressor cell activity.
  1. Certain autoimmune disease.

Defects in B lymphocyte function
- A. Deficient B cell function.
  1. Certain primary and secondary immunodeficiency diseases.
  2. Immunodeficiency of aging.
- B. Excess B cell function.
  1. Certain autoimmune disorders.

Excessive or deficient regulatory T cell activity may reflect abnormal cellular activity. In either case, normal homeostasis, usually dependent on the proper balance of suppressor and helper T cell activity, is upset. The existence in humans of excessive suppressor T cell activity has been documented in certain forms of acquired hypogammaglobulinemia (Chapter 29). Peripheral blood lymphocytes from a limited number of such patients fail to synthesize and secrete immunoglobulins in tissue culture when stimulated under conditions capable of inducing immunoglobulin synthesis in cultures of normal human lymphocytes. The defect is not intrinsic to the B cells, however, since it has been shown that removal of T lymphocytes from the cultured population enables the isolated B cells to synthesize and secrete immunoglobulin. Moreover, addition of patients' T cells to cultures of normal human lymphocytes inhibits the normal cells from synthesizing and secreting immunoglobulin. Hence, the presence and activity of an aberrant population of suppressor T cells in certain patients is phenotypically expressed as hypogammaglobulinemia. The hypothesis that the progressive immunodeficiency of aging (Chapter 25) reflects, at least in part, a similar excess of suppressor T cell activity is more highly speculative still. This aberrancy, however, may be a relative excess based in part on varying degrees of deficiency in helper T cell activity. Similarly, one might envisage the immunodeficiencies associated

with certain neoplastic diseases as the result of a relative excess in suppressor T cell activity or a relative deficiency in helper T cell activity. The deficiency in T cell-mediated immunity frequently observed in patients with Hodgkin's disease (Chapter 31) may reflect such a situation. Indeed, recent studies have indicated that exposure of peripheral blood lymphocytes of patients with active anergic disease to the anthelmintic drug levamisole in vitro respond to certain phytomitogens known to induce DNA synthesis in T cells. This suggests that anergy in these patients reflects the existence of an inhibitory mechanism that prevents T cell responses in vivo rather than any absolute T cell deficiency. It is possible that suppressor T cells may participate in such a mechanism. A primary deficiency of helper (as well as effector) T cell activity is well documented in such congenital abnormalities as DiGeorge syndrome (Chapter 29). On the more speculative side, although there is experimental support for the association of susceptibility to certain viral diseases with genetic defects that limit the capacity of the immune system to respond to such agents, the relationship of such defects to the development of malignant diseases of possible viral origin remains to be established.

The consequences of deficient suppressor T cell activity are perhaps best exemplified by the IgE-mediated allergic disorders of humans (Chapter 32). Studies have indicated that following exposure, high titers of IgE antibodies develop under conditions of quite low suppressor T cell activity. In the presence of normal suppressor cell activity, however, the converse is true. Recent studies in our own laboratory have suggested the existence of circulating biologically active molecules in the serum of experimental animals capable of selective positive or negative regulation of IgE antibody production. The character of these regulating processes correlates precisely with the magnitude of IgE antibody response following antigen sensitization. The absence or relative deficiency of suppressor T cell activity may be involved in the pathogenesis of certain malignant diseases of lymphoid cell clones (eg, certain leukemias, multiple myeloma), disorders that could well reflect the "escape" of various immune system constituents from normal regulatory controls.

Similar speculation can be entertained about the existence of inappropriate helper T cell activity in the pathogenesis of certain autoimmune diseases (see Chapter 30). If one were to entertain such speculation, one could envision nonspecific or cross-reactive helper cell activity generated by exogenous agents or adjuvants resulting in the loss of normal self-tolerance. Defects in B lymphocyte function can certainly be ascribed to some of the primary and secondary immunodeficiency diseases. Deficient B cell function may be important in the pathogenesis of the immunodeficiency of aging (see Chapter 25). Finally, one might speculate that abnormally excessive B cell activity, alone or in conjunction with abnormal regulatory T cell activity, may play an important role in the pathogenesis of certain autoimmune disorders; indeed, recent evidence supports the existence of hyperactive B cells in experimental animals manifesting spontaneous autoimmune disorders.

CONCLUSIONS

This brief overview of the immune system has stressed the need for a broad understanding of the dynamic interplay among the genes, molecules, and cells of the system that maintain homeostasis between the individual and the external environment. The system is highly complex, and one of the great advantages of this complexity is its inherent flexibility. Because compensatory or alternative routes are available when certain defects, transient or permanent, occur in one or more of the system's components, the immune system can continue to respond to the body's needs. Nevertheless, certain defects, alone or in combination, may result in deleterious primary or secondary consequences. Many of us working in this area are trying to elucidate the nature of these defects and trying to develop therapeutic programs that will restore homeostasis where possible. We believe that this hope can be realized in the near future.

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The Foundations of Immunology | 2

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Immunology became an acknowledged branch of medicine at the end of the 19th century. Since that time it has grown in importance at a steadily increasing rate and has become diversified into special fields such as immunochemistry, immunogenetics, and immunopathology. The current tendency to think of this subject as having become divided into humoral and cellular immunology is probably only a temporary phenomenon.

The growth and diversification of the field are reflected in the increasing number of journals devoted to the publications of immunology research reports. Some of them, such as the *European Journal of Immunology*, the *Scandinavian Journal of Immunology*, and *Annales d'Immunologie*, offer a broad coverage of what is happening in the field. Other journals that have become established since about 1955 confine their interests to special areas of research such as *Immunochemistry*, *Immunogenetics*, and *Cellular Immunology*. Much of the fundamental work in immunology is being published in journals of more general content such as the *Journal of Experimental Medicine*. Thousands of papers reporting the results of new immunologic studies are published each year. It has been estimated that over 10,000 investigators are now at work on immunologic research problems.

The rapid growth of immunology as a special field parallels the development of other fields of modern biology. It has been made possible to a great extent by the development of new technics such as isoelectric focusing, scanning electron microscopy, affinity chromatography, radioisotope labeling, and immunofluorescence microscopy. In other fields of study, 50 years may seem like yesterday or at most the day before. In medicine, the last 50 years have witnessed generations of progress, and immunobiology has been in the forefront of progress in many ways. For example, nothing was known 50 years ago about the role of nucleic acids in protein biosynthesis, the protein nature of antibodies, or the fate of the injected antigen in the recipient organism. These are only a few of the highlights of what has been achieved.

During the years of its beginnings, immunology was regarded as a subtopic of bacteriology because it was known that survivors of bacterial infections were immune to repeated infections (Chapter 3) and that some bacterial infections could be prevented by specific antisera (Chapter 43). The immunologic methods used in this early period were rather primitive, although some were highly sensitive. Bacteriologists at that time, like botanists and zoologists, were concerned chiefly with morphologic problems and with taxonomy. With the advent of cytology, genetics, embryology, and virology, bacteriology became part of a more general area of research that came to be called microbiology. Many departments of bacteriology became departments of microbiology, and some are now called departments of microbiology and immunology.

Microbiology deals with a wide area of problems, many of which are of great interest to the health sciences even though they are not directly connected with clinical immunology. Examples are hygiene and sanitation, food technology, and the study of ecosystems.

CLINICAL IMMUNOLOGY

At present, clinical teaching programs in medical schools are usually organized by organ system. Textbooks of medicine are divided into chapters dealing with the digestive tract, the vascular system and heart, the nervous system, the skin, the genitourinary tract, etc. The "organ system" responsible for the immune response is the lymphoid system, whose cells are widely distributed in the body (Chapter 9), concentrated in many small organs such as the lymph nodes and thymus, in the bone marrow, and in the spleen. Lymphoid cells circulate in the blood in large numbers as white blood cells. Owing to the ubiquity of lymphoid cells, immune reactions can take place in almost any organ. Each local infection in a particular organ leads to local and, frequently, also general immunologic reactions. For all of these reasons, immunology does not fit well into the classic clinical groups of organs or organ systems. Immunology is similar in this respect to neurology, which also deals with a system widely spread throughout many organs of the body. Indeed, we frequently use the term **immunologic memory** when an organism, after **sensitization** by a small amount of antigen, subsequently reacts much more rapidly and more vigorously to a second administration of the same antigen.

HUMORAL & CELLULAR IMMUNE RESPONSES

The methods used in the study of immunology are based essentially on observation of the response that occurs upon combination of an antigen with the antibodies elicited in a living organism or in cultures of lymphoid cells after administration of the same antigen. This statement is strictly valid only for antibodies dissolved in the body fluids, which therefore combine with the added homologous antigen in a more or less easily detectable reaction such as precipitation, agglutination, complement fixation, or neutralization of a toxin (Chapters 3 and 26).

Not all immune reactions occur in solutions containing antigen and antibody. Many individuals suffer from allergies to pollen, milk, eggs, drugs, or certain substances in food (Chapter 32). The body fluids of these sensitized individuals do not contain substantial amounts of IgE antibodies directed against the sensitizing materials, called **allergens.** The reactive IgE antibodies in allergic individuals function in allergic reactions when they are cell-bound and can be detected in vivo by administering traces of allergen to the skin, respiratory tract, or gastrointestinal tract (Chapter 22). Because accurate quantitative methods were not available, very little was known until a few years ago about the detailed mechanisms of cellular immunity, allergy, and other mechanisms of tissue damage. However, with the widespread introduction of new technics, many areas of research in cellular immunology have received great impetus. Basic studies of lymphocyte function and interactions have done much to clarify their biologic roles in such processes as transplantation (Chapter 19), tolerance (Chapters 17 and 18), and tumor immunity (Chapter 23). We are now in the stage of measuring cellular immune function in patients with disease, sometimes as a prelude to specific therapy (Chapters 27 and 29).

ANTIGENS OR IMMUNOGENS

The first antigens used in immunologic research were bacteria, particularly pathogenic bacteria, or cells such as heterologous red cells. Later it became clear that bacteria and cells consist of many different proteins, carbohydrates, lipids, and other body constituents and that many of these molecules could act as antigens. Since they elicit antibody production even if injected in small amounts, we frequently call them immunogens. Although the term **immunogen** is more logical than the term **antigen,** in this chapter the old term antigen is occasionally used because it has been applied in most of the fundamental work on antigen-antibody interactions (Chapter 6).

Generally, one of the prerequisites for immunogenicity is a high molecular weight (at least 10^4) (Chapter 5). Since most proteins are hydrolyzed in the gastrointestinal tract to small peptides and amino acids, many protein antigens lose their immunogenicity if given orally. For such antigens to stimulate antibody production by lymphoid cells, they must be administered subcutaneously, intravenously, intraperitoneally, or by other parenteral technics.

ANTIBODY HETEROGENEITY

When pure crystalline proteins were used as antigens, it was at first assumed that the antibodies formed would also be pure and crystallizable. Until a few years ago, it was impossible to isolate a homogeneous human antibody directed against a pure crystalline protein. The reason for our failure to obtain homogeneous antibodies directed against the typical globular proteins is the presence on the surface of each protein molecule of several determinants or **determinant groups,** each of which is formed by the side chains of a number of adjacent amino acid residues (Chapter 5). Some immunologists prefer the term **epitope** to determinant and have designated the corresponding antibody combining site a **paratope.** Recent analyses by x-ray diffraction have demonstrated many different determinants on the surface of each protein. This diversity of the immunogenic determinants explains why immunization with a pure crystalline protein leads to the production of a heterogeneous mixture of antibodies directed against different facets of the large protein molecule.

Some homogeneous or almost homogeneous preparations of antibodies have been obtained from highly inbred animals when bacterial polysaccharides containing a single repeating type of determinant were used as antigen. However, human individuals are never as highly inbred as laboratory animals, which can be bred rapidly through many generations; therefore, there is little hope that we will encounter many examples of homogeneous human antibodies in clinical immunology. Our knowledge of the chemical composition of human antibodies would indeed be limited had it not been shown that homogeneous immunoglobulins are formed in multiple myeloma, a malignant tumor of plasma cells (Chapter 31).

STRUCTURE OF MYELOMA PROTEINS & OTHER IMMUNOGLOBULINS

Multiple myeloma is a human disease characterized by abnormal proliferation of plasma cells that produce immunoglobulins very similar in structure to some of the normal immunoglobulins (Chapter 4). Myeloma cells, like many other malignant cells, do not

undergo normal differentiation and maturation but continue producing a single type of immunoglobulin. They secrete this immunoglobulin into the plasma, from which it can be separated quite easily in large amounts. Consequently, it has been possible to analyze the myeloma proteins and to determine their amino acid sequences (Chapter 4). Since in a particular case the plasma cells represent the progeny of only a single cell, the cells may be called a **clone** collectively, and their product may also be called a monoclonal protein or a myeloma protein. For these reasons, much of the work on the structure of immunoglobulins has been done with samples of homogeneous myeloma proteins rather than with antibodies directed against the antigens used for immunization (Chapter 31).

Myeloma tumors can be produced easily in selected strains of mice—but not in rabbits—by the injection of mineral oil into the peritoneal cavity. The mouse myelomas grow to very large size and can be maintained by transfer from one mouse to another of the same strain. Myeloma proteins, like the immunoglobulins, generally consist of heavy (H) and light (L) peptide chains. The molecular weights of the H chains are close to 50,000 and those of the L chains close to 23,000. The simplest immunoglobulins of the IgG class are tetramers of the structure L–H–H–L, in which the horizontal lines indicate disulfide bonds (–S-S–). The structure of the different classes of immunoglobulins will be discussed in Chapter 4. Here it should be mentioned only that H chains as well as L chains consist of **domains** of 100–115 amino acid residues and that the N-terminal domains of H and L chains have highly variable amino acid sequences whereas the other domains of the H and L chains have constant amino acid sequences. The variable regions have been designated V_H and V_L domains and the constant regions as C_H and C_L domains. In the IgG immunoglobulins, the H chains consist of the 4 domains $V_H \cdot C_H1 \cdot C_H2 \cdot C_H3$ and the L chains of 2 domains $V_L \cdot C_L$. The 2 chains are linked to each other by disulfide bonds between their constant domains; disulfide bonds also form a bridge between the two H chains (Fig 2–1). All the disulfide bonds are formed by the dehydrogenation of thiol groups (–SH) of the free H and L chains. In many patients suffering from multiple **myeloma**, an abnormal protein, Bence Jones protein, is excreted into the urine; it is a dimer of the L chains. Bence Jones protein is easily detected by its property of being insoluble at approximately 56 C but redissolving when the urine is either heated to boiling temperature or cooled down below 56 C.

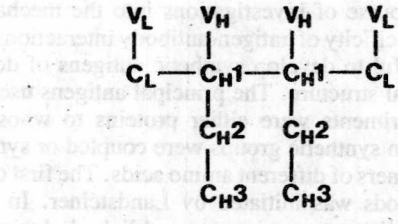

Figure 2–1. Structure of an IgG immunoglobulin. The heavy and light chains are marked by the letters H and L, respectively, and their variable and constant domains by the letters V and C. The vertical lines represent peptide bonds; the horizontal lines, disulfide bonds.

In the last few years, it has been discovered that fusion of myeloma cells with antibody-producing cells yields hybrid cells that in their culture produce not only clones of the myeloma cells but also clones of the antibody-producing cells (Milstein). This has made it possible to produce in cultures large amounts of pure antigen-induced antibody. Analyses of these pure antibodies will probably give us greater insight into the structure of antibodies and of cancer.

It is particularly interesting that some human (and murine) myeloma proteins have the ability to combine specifically with chemically substituted proteins, eg, dinitrophenylated proteins, as if they were antibodies directed against a dinitrophenylated protein. Similarly, other myeloma proteins specifically bind phosphorylcholine or other strongly polar molecules.

IMMUNOGENETICS & IMMUNOCHEMISTRY

It is clear from the foregoing that the immunologic specificity of the antibody molecule is essentially chemical specificity. Even though we do not yet know the complete amino acid sequence of most human antibodies, we know that their structure is transmitted from generation to generation according to mendelian laws. Indeed, the immune response to different antigens depends to a large extent on the genetic characteristics of the individual patient or laboratory animal (Chapter 14). This may partly explain why during major epidemics some individuals become infected whereas others living under the same conditions remain free of symptoms. The close connections between the chemical structure and genetic characteristics of antibodies are of fundamental importance in understanding the mechanism of the immune response. For this reason, some typical examples of the close connections between the structure and genetics of some immunologic systems will be discussed in the following 3 paragraphs. The discussion of these areas of research will also give some insight into the probable pathways future research in immunology can be expected to follow.

Blood Group Substances

It was known in the 19th century that transfusion of blood from one individual to another frequently caused hemolysis, agglutination of red cells, and allergic reactions. These phenomena occur when the red blood cells of the donor and those of the recipient contain blood group substances of different genetic types. In Vienna, Landsteiner discovered in 1900 that

individuals of blood group A have in their blood antibodies that precipitate red blood cells of blood group B and that individuals of blood group B have antibodies against blood group A. This explains why transfusion of blood from individuals with blood group A to individuals with blood group B (or vice versa) causes agglutination of red cells in the recipient. Before transfusion, therefore, it is necessary to determine the blood groups of donor and recipient by mixing a small sample of donor serum with an equally small sample of red blood cells from the recipient and observing for agglutination (Chapter 31). Although blood typing has been used since Landsteiner's discovery, much time elapsed before the chemical nature of the blood group substances was known (Kabat).

In a series of fundamental investigations, W.T.J. Morgan and W.M. Watkins at the Lister Institute in London discovered that the determinant carbohydrate of human blood group substance B consisted of galactose, a simple C6 sugar, whereas the determinant group of blood group substance A consisted of N-acetylgalactosamine. Thus, the only difference between human blood group A and B substances was replacement of an OH– group in B by a $CH_3CO–NH–$ group in A (Chapter 31). The blood group substances are glycolipoproteins with molecular weights close to 300,000; thus, the difference between groups A and B affects only a very small part of the macromolecule—yet it is this small difference that causes the serious and sometimes fatal consequences of transfusion of blood of the wrong type.

This discovery shows impressively that the specificity of immune reactions is determined by the chemical structure of small groups on the surfaces of macromolecules or cells. Only these superficial groups of the antigen can react with the antibody molecules. The above structural studies also reveal that the conversion of blood group substance A into substance B can be catalyzed by specific enzymes found in some microorganisms. Hence, whether the individual's blood is group A or group B probably depends on the absence or presence of similar enzymes in the body, which in turn is determined by the presence or absence of a gene coding for the production of such an enzyme.

The problem of human blood group substances has been discussed here in some detail because it shows convincingly the close connection between immunogenetics and immunochemistry. It also allows us to gain insight into the mechanism of the immune response. It may enable us in the future to synthesize analogs of the blood group substances which would prevent undesirable reactions in random blood transfusions.

Allotypes & Immunoglobulin Structure

Although the presence of different blood group substances was known as a result of Landsteiner's studies, genetically determined differences in antibody molecules were first found in rabbits by Oudin at the Pasteur Institute in Paris. The genetically determined differences have been designated **allotypes** (Chapter 7B). At about the same time, allotypes of human immunoglobulins were investigated and classified by Grubb in Sweden. More than 20 different allotypes, called **Gm** or **Am markers,** have been discovered in the heavy chains of human immunoglobulins and a small number of allotypes in their light chains (Chapter 7B). Certain combinations of the Gm allotypes of IgG are found preferentially in Caucasians; others in blacks; and still others in persons of Asiatic racial origin. There is considerable speculation that certain combinations of Gm allotypes (ie, the phenotype) may be related to susceptibility or resistance to specific infections or other diseases. Convincing evidence to confirm this view has not yet been provided. However, important information concerning the genetic background of an individual can be obtained by asking about the occurrence of genetically determined diseases in parents, grandparents, and siblings.

Since all antibodies are immunoglobulin proteins and since the specificity of all proteins is determined by their amino acid sequence, the question may now be asked, "What are the amino acid sequences of the different human antibodies?" We cannot yet answer this question definitively because human antibodies, for reasons mentioned earlier, are mixtures of antibodies of several similar specificities. Genetic differences in the C regions can be detected by comparing the amino acid sequences of antibodies from different individuals. Thus, determinations of the amino acid sequence in the C region of human L chains of the κ type has revealed that position 191 is occupied by either leucine or valine. The structures of these 2 amino acids are very similar; both have the structure $–NH•CH(R)•CO–$, where R is $–CH_2CH(CH_3)_2$ in leucine and $–CH(CH_3)_2$ in valine. This very small sequence difference was discovered by injecting different human immunoglobulins into rabbits and then using the rabbit immune sera as reagents for the demonstration of human allotypes. In this way, differences in allotypes were demonstrated before anything was known about their chemical structure. The success of this technic clearly confirms the enormous sensitivity of serologic methods. It is often possible, using serologic technics, to detect differences which are not detectable by physical or chemical methods.

Synthetic Antigens

In the course of investigations into the mechanisms and specificity of antigen-antibody interactions, it proved useful to develop synthetic antigens of defined chemical structure. The principal antigens used in such experiments were either proteins to whose surface certain synthetic groups were coupled or synthetic copolymers of different amino acids. The first of these 2 methods was initiated by Landsteiner. In a series of brilliant experiments published during 1922–1940 from the Rockefeller Institute in New York, Landsteiner demonstrated that an experimental animal was able to produce antibodies directed against a large number of synthetic antigenic determinants which do not appear in nature. Landsteiner called these

small determinant groups **haptens** (Chapters 5 and 6). He observed that the chemospecificity of antibodies to individual haptens was very high—sufficiently high to distinguish haptens with **cis** structure from their **trans** isomers and dextrorotatory haptens from their levorotatory isomers. It was also shown that free hapten was bound specifically to its homologous antibody in the absence of a carrier protein. An excess of hapten prevented precipitation of the antibody by the homologous hapten-carrier complex because the hapten competed with the homologous antigen for the specific combining sites of the antibody.

Since many natural antigens are proteins, it seemed particularly appropriate to use proteinlike synthetic antigens. Such substances can be produced relatively easily by the copolymerization of different amino acids. This method was introduced into immunology by Michael Sela of the Weizman Institute in Israel. Antibody production could be elicited by copolymerization of mixtures of several amino acids and by producing branched copolymers (Chapter 5). One of the most important observations to emerge was that when copolymers of amino acids were injected into 2 different strains of highly inbred guinea pigs, they were sometimes immunogenic in one strain but not in the other strain of the same animal species. Evidently, the immunogenicity of an antigen, even though it is a synthetic product, depends on the genetic background of the injected animal. Thus, an animal may be responsive to one amino acid copolymer and unresponsive to another similar copolymer. This responsiveness was shown to be genetically determined and to obey mendelian laws of inheritance. The genes involved in these differences were designated **immune response (Ir)** genes (Chapter 14). This area is one of the most active and important areas in immunology today, but the clinical relevance of immune response genes is not yet completely clarified.

ANTIGEN–ANTIBODY INTERACTIONS

The emphasis on amino acid sequences must not lead to the erroneous conclusion that the specific combination of antigen and homologous antibody is a typical chemical reaction involving cleavage or formation of covalent bonds such as the C–C bond. The combination of an antibody molecule with homologous antigen or with its determinant group is essentially a weak, noncovalent, and usually reversible interaction. Most antigen-antibody complexes are dissociated by lowering the pH or by increasing the temperature. If this is done carefully, the dissociated antigen and antibody molecules may subsequently recombine without any significant loss of immunologic properties or specificity. The forces involved in antigen-antibody interactions are short-range ones, particularly hydrogen bonds, and are efficient over only very short distances. The various factors that influence the interactions between antigen and antibody are outlined in Chapter 6.

PREPARATION OF PURE ANTIBODIES

As mentioned above, the antigen-antibody complex dissociates under favorable conditions into its components. The best available methods for the preparation of pure antibodies are based on adsorption of the antibody to antigen which is rendered insoluble by irreversible attachment to an insoluble resin, usually consisting of polysaccharides. The resin-bound antibody is then desorbed from the immobilized antigen by acidification or by an excess of free hapten. The desorbed antibodies are typical immunoglobulins with heavy and light chains (Chapter 4).

ANTIBODY SPECIFICITY

Antibodies differ from each other and from other immunoglobulins of the same individual particularly in the two V domains, V_H and V_L. It is in these regions that antibody specificity is located. The bulk of antibody produced during prolonged immunization consists of H_2L_2 units. However, in the early stages of immunization, macromolecules of the IgM class antibody containing five H_2L_2 units are found (Chapter 4). The 2 classes IgM and IgG, during a defined immune response, have identical specificity to a particular determinant group.

The "one gene, one peptide" dogma asserts that a polypeptide is synthesized as a single biosynthetic unit originally encoded by a single structural gene which determines the amino acid sequence. In view of the above comments on V and C region domains, there appears to be a situation which is unique to immunoglobulins and is termed the "two genes, one peptide" hypothesis. The H chain and the L chain are each synthesized as single polypeptide units. To satisfy current views on protein synthesis, the V_L and C_L genes for a particular L chain would first combine to permit transcription of the L chain DNA to yield mRNA, whose translation would yield the L chain polypeptide. The situation would be similar for V_H and C_H genes for the H chain. If it is assumed that there are at least 10^2–10^3 different H chains and likewise 10^2–10^3 L chains, their random combination would give 10^4–10^6 different immunoglobulins.

ANTIBODY BIOSYNTHESIS & THE ROLE OF THE ANTIGEN

For more than 20 years, it has been believed that the amino acid sequence of an immunoglobulin, like that of other proteins, reflects strictly the deoxynucleotide sequence of DNA, and that this phase of